Non-Interventional Study (NIS) Report	
NIS Name/Code	NIS-OKR-CAS-2010/1
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One year comparison of bone mineral loss between GnRH agonist alone vs. GnRH agonist plus anti-androgen combination treated prostate cancer patients – A non interventional study

Study dates	First Subject In: 27 April 2011 Last Subject Last Visit: 24 February 2014

[STUDY SUMMARY]

Sponsor:	AstraZeneca Korea Ltd.
Study Title:	One year comparison of bone mineral loss between GnRH agonist alone vs. GnRH agonist plus anti-androgen combination treated prostate cancer patients – A non interventional study
Study Number:	NIS-OKR-CAS-2010/1
Study Sites and Investigators:	[redacted]
Publication(s): Planned	
Study Period: 34 months (2 years 10 months) **First Subject In:** 27 April 2011 **Last Subject Last Visit:** 24 February 2014	**Study Phase:** Observational Study
Study Objectives: Primary objective: To observe the change in bone mineral density (BMD) over 1 year period after initiation of either GnRH agonist monotherapy or the combination therapy of gonadotropin-releasing hormone (GnRH) agonist with anti-androgen drug (combined androgen blockade, CAB) in patients with prostate cancer Secondary objectives:	

- To identify the underlying factor(s) affecting BMD
- To estimate the 10-year probability of major fractures

Methodology:

This is a multi-centre, non-interventional, prospective study which collected information of the patients who were eligible for study enrolment based on the inclusion/exclusion criteria.

The target population of this study was the prostate cancer patients who had been undergoing either GnRH agonist monotherapy or CAB therapy prescribed by his doctor prior to the study participation, and, as a non-interventional study (NIS), it was conducted in the routine clinical practice without affecting the patients' treatment.

The BMD measurements at baseline (just before the treatment initiation) were collected from medical records, and those at Month 12 (after 12^{th} month from the treatment initiation) were collected at study site.

Number of Subjects:

1) Planned: 250 subjects per group, a total of 500 subjects
2) Analysed: 234 subjects in CAB group, 70 subjects in GnRH group, a total of 304 subjects

	CAB group	GnRH group
Enrolled (N=312)	242	70
Analysis Set (N=304)	234	70
Study Completed (N=253)	196	57

Target Population:

Prostate cancer patients receiving hormone (either CAB or GnRH agonist) therapy

Selection Criteria:

Inclusion criteria:

1) Pathologically diagnosed Korean prostate cancer patients aged ≥ 50
2) Patients who have been receiving either CAB therapy or GnRH agonist monotherapy within 6 months prior to the study participation
3) Patients with BMD measurement just before the above hormone therapy

Exclusion criteria:

1) Patients who required treatment with bisphosphonate for lowered T-score ≤ -3.0 or who are receiving any medications other than calcium and Vitamin D to treat osteoporosis
2) Patients with difficulties in interpretation of BMD due to other bone disease(s)
3) Patients with difficulties in interpretation of BMD due to severe disorders in other organ(s)
4) Patients with difficulties in anlaysis of the result due to insufficient medical records, at the study investigator's discretion
5) Patients already enrolled in this study

Observation Period: 12 months

Study Endpoints:

Primary endpoint:

Change in BMD score from baseline to Month 12 from the initiation of CAB therapy compared to GnRH agonist monotherapy

Secondary endpoints:

1) Factor analysis to identify underlying elements affecting change in BMD
2) Fracture Risk Assessment Tool (FRAX®) scores at baseline, Month 12 and change from baseline to Month 12 by treatment groups

Statistical Analysis:

Primary endpoint:

Summary statistics (number of subjects (n), mean, standard deviation (SD), median, range (minimum, maximum)) of the specified primary endpoint were provided along with baseline, Month 12 and the change from baseline to Month 12 by treatment groups. The changes from baseline to Month 12 were evaluated by paired *t*-test, and the difference between the treatment groups was evaluated by two sample *t*-test.

The limit of non-inferiority for the percentage change in total BMD score of lumbar spine (L-spine) was specified as -1.5% in advance, and the 95% confidence interval of difference between groups (CAB group – GnRH group) was provided.

Additionally, the number and proportion of subjects with osteopenia or osteoporosis were provided and analysed by Pearson's chi-square test.

Secondary endpoints:

The underlying factors affecting the change in BMD (BMD score, T-score, Z-score) from baseline to Month 12 were identified by multiple regression analysis with treatment group, age, weight, and history of smoking and alcohol drinking as independent variables.

Summary statistics (n, mean, SD, median, range (minimum, maximum)) of the FRAX® scores were provided along with baseline, Month 12 and the change from baseline to Month 12 by treatment groups, and evaluated by paired *t*-test. The difference between the treatment groups was evaluated by two sample *t*-test.

Results:

Demographics and other baseline characteristics:

When the change in BMD over 12 months was observed in 304 patients with prostate cancer, a total of 253 subjects (196 in CAB group and 57 in GnRH group) completed the study. The mean age was 70.70±7.83 years in CAB group and 72.24±8.63 years in GnRH group. The proportion of current smokers at the time of study enrolment was 10.26% (24/234 subjects) and 12.86% (9/70 subjects) in CAB group and GnRH group, respectively. The proportion of subjects with history of alcohol drinking was 54.70% (128/234 subjects) in CAB group, 62.86% (44/70 subjects) in GnRH group, and, of those

subjects, 40.63% (52/128 subjects) and 22.73% (10/44 subjects) had a mean daily alcohol consumption about 2 units or more, respectively. 8.12% (19/234 subjects) in CAB group and 7.14% (5/70 subjects) in GnRH group had fracture histories, and 1 subject in CAB group (0.43%) had family history of hip fracture. The proportion of subjects with bone-related concurrent disease(s) was 1.28% (3/234 subjects) in CAB group and 1.43% (1/70 subjects) in GnRH group, and that with history of osteoporosis-related disease(s) was 30.77% (72/234 subjects) and 17.24% (19/70 subjects), respectively.

The mean Gleason score was 7.76±1.06 in CAB group and 7.77±1.20 in GnRH group, and the median prostate volume was statistically significantly greater in CAB group (p=0.0017) with 44.00 cc than in GnRH group with 35.00 cc. In accordance with the Tumour-Nodule-Metastasis (TNM) clinical staging of prostate cancer, the disease status was relatively advanced in CAB group compared to GnRH group, however, the serum prostate specific antigen (PSA) levels were not siginicantly different between groups (p=0.1573). In CAB group and GnRH group, 39.22% (91/219 subjects) and 48.57% (34/67 subjects) received prostatectomy, and 8.62% (20/219 subjects) and 2.86% (2/67 subjects) received radiation therapy, respectively.

Primary Endpoint:

The results have shown a statistically significant decrease in L-spine total BMD score in both groups with 2.61±13.11% in CAB group and 4.37±5.04% in GnRH group, respectively (CAB group: p=0.0090, GnRH group: p<0.0001).

The change in total BMD score of L-spine was 1.77% smaller in CAB group compared to GnRH group with the 95% confidence interval of [-2.04%, 5.57%]. The non-inferiority of CAB group was not determined with the lower limit of 95% confident interval less than -1.5%, however, the difference between the groups was not statistically significant (p=0.1518). Likewise, the BMD of total femur and femur neck were significantly decreased from baseline to Month 12 in both groups, but there was no significant difference between the groups.

Through investigation regarding osteopenia or osteoporosis, 51.28% (120/234 subjects) of CAB group was normal, 39.32% (92/234 subjects) had osteopenia and 9.40% (22/234 subjects) had osteoporosis at baseline, whereas 50.00% (35/70 subjects) of GnRH group was normal, 41.43% (29/70 subjects) had osteopenia and 8.57% (6/70 subjects) had osteoporosis at baseline. After 12th month from the treatment initiation, the proportion of the subjects with osteopenia or osteoporosis was slightly increased, but the difference between the groups was not significant (p=0.3688).

Secondary Endpoints:

The factor analysis performed to identify the underlying elements affecting the change in BMD has shown that the treatment group is not a significant factor. For L-spine BMD, there were no factors affecting either T-score or Z-score. Despite the age was identified to affect the change in BMD score (p=0.0285), the clinical effect was insignificant when considering the regression estimate (e=0.002). For total femur, similar to L-spine, the age was identified as a factor affecting the change in BMD (BMD score: p=0.0445, T-score; p=0.0372, Z-score: p=0.0267), however, the clinical effect was insignificant when considering the regression estimate (BMD score: e=0.001, T-score: e=0.007, Z-score: e=0.009). On the other hand, there were no factors affecting the change in BMD (BMD score,

T-score, Z-score) for femur neck.

When the 10-year probability of major fractures was estimated using FRAX®, the 10-year probability of major osteoporotic fracture was not significantly changed from baseline to Month 12 in both groups, with no significant difference between the groups. Though the 10-year probability of hip fracture was increased by 0.20±1.16% with statistical siagificance (*p*=0.0231) in CAB group, while there was no statistically significant change over 12 months in GnRH group, there was no difference between the groups (*p*=0.5531).

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