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Efficacy and Safety of Dutasteride on Prostate Cancer Risk Reduction in Asian Men: The Results from the REDUCE Study

Hideyuki Akaza[1,*], Hiroshi Kanetake[2], Taiji Tsukamoto[3], Naoto Miyanaga[1], Hideki Sakai[2], Naoya Masumori[3], Hiroomi Nakatsu[4], Kazuyuki Sagiyama[5], Sadaaki Sakamoto[6], Yukihiro Endo[7] and Takayoshi Yamanouchi[7] on behalf of the REDUCE Study Group

[1]Department of Urology, Institute of Clinical Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, [2]Department of Nephro-Urology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, [3]Department of Urology, Sapporo Medical University School of Medicine, Sapporo, [4]Department of Urology, Asahi General Hospital, Chiba, [5]Sagiyama Urology Clinic, Fukuoka, [6]Department of Urology, Nakamura Hospital, Beppu, Oita and [7]Development and Medical Affairs Division, GlaxoSmithKline, Tokyo, Japan

*For reprints and all correspondence: Hideyuki Akaza, Research Center for Advanced Science and Technology, University of Tokyo, 4-6-1 Komaba, Meguro-ku, Tokyo 153-8904, Japan. E-mail: akazah@med.rcast.u-tokyo.ac.jp

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Objective: A *post hoc* analysis of Asian men in the REDUCE study was conducted to investigate whether the outcomes were in line with those of the overall population.
Methods: REDUCE was a 4-year international, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Inclusion criteria were men between 50 and 75 years of age, a serum prostate-specific antigen level of 2.5–10.0 ng/ml (50–60 years) or 3.0–10.0 ng/ml (>60 years), and a single, negative prostate biopsy (6–12 cores) within 6 months before enrollment. The primary endpoint was biopsy-detectable prostate cancer. This *post hoc* analysis included subjects who were recorded as Asian.
Results: A total of 134 Asians, including 57 Japanese, were randomized to the study treatment. During the study period, the incidence of prostate cancer in the placebo and dutasteride groups was 19.6% (11/56) and 9.3% (5/54), respectively (relative risk reduction, 54%; 95% confidence intervals, −27 to 83%, $P = 0.12$), in the Asian subpopulation. Fewer tumors with the Gleason scores of 7–10 and 8–10 were detected among dutasteride-treated men. Although the incidences of drug-related sexual adverse events were higher in the dutasteride group, only in rare occasions did they lead to drug discontinuation.
Conclusions: The incidence of prostate cancer in the dutasteride group was lower than that in the placebo group, although the difference was not significant. These results paralleled those for the overall population and support the value of dutasteride for prostate cancer risk reduction in Asian men with an increased risk of prostate cancer.

Key words: prostate cancer – REDUCE – dutasteride – Asian – Japanese

INTRODUCTION

Prostate cancer is the second most common cancer in men and the third most common cause of male cancer death worldwide (1). It is well known that the incidence of prostate cancer varies worldwide, with higher rates found in North America and Europe, whereas lower rates are observed in Asia (1). African-Americans have the highest incidence, which is ~2.6 times higher than that of Asian Americans (2). Lower prostate cancer rates in Asian countries and among Asian races may be associated not only with genetic susceptibility but also with the lifestyle and environmental factors. Recently, in Asian countries, a trend toward an increased incidence and mortality of prostate cancer has been observed because of globalization of lifestyle, dietary and environmental factors (3).

Because of its high incidence, high mortality and long latency period from histological lesions to clinical disease,

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strategies to reduce the risk of prostate cancer represent a reasonable and promising approach (4,5). To date, only 5-alpha-reductase (5AR) inhibitors have shown a significant prostate cancer risk reduction in appropriately powered and prospective randomized clinical trials. The Prostate Cancer Prevention Trial (PCPT) showed that finasteride, a type-2 5AR inhibitor, reduced the risk of prostate cancer by 24.8%, but with a significantly higher incidence of high-grade tumor in the finasteride group compared with the placebo group (6). Several factors have been suggested as possible explanations for the increase in high-grade tumors observed in the finasteride group, such as a decreased prostate volume (7–9), an increased prostate-specific antigen (PSA) sensitivity for cancer detection (10) and a selective inhibition of low-grade tumors (11). It is now generally accepted that finasteride does not cause high-grade disease or histopathological changes mimicking high-grade disease (11), and American Urological Association/American Society of Clinical Oncology guidelines concluded that 5AR inhibitors may be beneficial mainly based on the PCPT results (12).

Dutasteride inhibits both type-1 and type-2 isoforms of 5AR and almost completely suppresses intraprostatic dihydrotestosterone (13). Type-1 5AR is overexpressed in human prostate cancer tissue compared with benign prostatic tissue, and its expression is greater in more aggressive cancer (14). In Phase III benign prostatic hyperplasia (BPH) trials, the incidence of prostate cancer reported as an adverse event (AE) was reduced by ~50% in the dutasteride group versus the placebo group at 27 months (1.2 and 2.5%, $P = 0.002$) (15). On the basis of these findings, the REduction by DUtasteride of prostate Cancer Events (REDUCE) study was initiated and demonstrated that dutasteride significantly reduced the risk of biopsy-detectable prostate cancer by ~23%, without a significant increase in tumors with the Gleason scores of 7–10 or 8–10 (16). Because both the PCPT and the REDUCE studies included a predominantly Caucasian population, similarly as for many other randomized clinical trials, lack of published data on Asian populations still remains an issue. Considering the recent increasing incidence and mortality of prostate cancer observed in Asian countries (1), evaluating the effect of dutasteride on prostate cancer risk reduction therapies among Asian men is of relevance. The aim of this *post hoc* analysis was to investigate whether the results of Asian subjects were in line with those of the overall REDUCE study population.

PATIENTS AND METHODS

Study Design and Population

The study design and population of the REDUCE study have previously been reported (17). This study was an international, multicenter, randomized, double-blind, placebo-controlled, parallel-group study with 42 participating countries including Japan. Men considered to be at high risk of prostate cancer were enrolled. Inclusion criteria were men between 50 and 75 years of age, a serum PSA level of 2.5–10.0 ng/ml (50–60 years) or 3.0–10.0 ng/ml (>60 years), and a single, negative prostate biopsy (6–12 cores) within 6 months before enrollment. Men with more than one prostate biopsy, the presence of high-grade prostatic intraepithelial neoplasia (HG-PIN) or atypical small acinar proliferation (ASAP) in the baseline biopsy, history of prostate cancer, prostate volume >80 ml; or International Prostate Symptom Score of 25 or higher, or 20 or higher in the case of men taking α-blockers were excluded from the study. The REDUCE protocol was approved by Institutional Review Boards at each study site. The study was conducted in accordance with the Helsinki Declaration, and all participants signed informed consent forms.

After a 4-week placebo-based run-in period, eligible subjects were randomized to receive dutasteride 0.5 mg or placebo once daily for 4 years. Ten-core transrectal ultrasound-guided 'protocol-dependent' biopsies were conducted at 2 and 4 years. The investigator was allowed to perform 'protocol-independent' (for-cause) biopsies whenever clinically necessary. Baseline biopsies before enrollment (obtained independently of the study), protocol-mandated biopsies and for-cause biopsies were reviewed centrally (Bostwick Laboratories, Richmond, VA, USA). All positive biopsies were also reviewed centrally to confirm the diagnosis and the Gleason score.

Study Endpoints

The primary endpoint was biopsy-detectable prostate cancer at years 2 and 4. For-cause biopsies conducted between months 19 and 24 and between months 43 and 48 counted as protocol-mandated biopsies at years 2 and 4, respectively. Biopsies between months 1 and 18 and between months 25 and 42 were considered 'protocol-independent' biopsies. Key secondary endpoints included the Gleason score, amount of cancer and occurrence of HG-PIN and ASAP.

Statistical Analysis

The efficacy population consisted of subjects who received the study medication at least once and had had a negative biopsy before the study. The safety population included all randomized subjects. The results of these *post hoc* analyses included subjects who were recorded as Asian by self-report. Statistical analysis for the primary endpoint was performed using the Mantel-Cox test stratified by the time period. The Mantel-Haenszel estimate of the relative risk and associated confidence intervals (CIs) were calculated. In this *post hoc* analysis, a restricted crude rate approach (men with at least one post-baseline biopsy) was used. For the secondary

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endpoints and safety variables, summary statistics were calculated.

RESULTS

Subject Demographics and Disposition

Subject demographics and disposition are shown in Table 1 and Fig. 1. A total of 134 Asian men enrolled in Argentina, Australia, Brazil, Canada, Germany, Japan, Mexico, the Netherlands, New Zealand, Slovenia, South Africa, the UK and the USA were randomized into a double-blind phase. Of these, 57 were Japanese men enrolled at the sites in Japan. The efficacy population consisted of 133 (99%) Asian subjects, of which 56 (98%) were Japanese. A total of 110 (83%) Asians including 52 (93%) Japanese men underwent at least one biopsy during the double-blind phase.

The baseline characteristics were consistent with those of a population considered to be at an increased risk of prostate cancer based on an elevated PSA. Asian and Japanese baseline characteristics—age, family history of prostate cancer and PSA—were generally similar to those of the overall REDUCE study population, but their prostate volume was slightly lower.

Primary Endpoint

Over the 4-year study period, the incidence of biopsy-detectable prostate cancer in the placebo and dutasteride groups was 19.6% (11/56) and 9.3% (5/54), respectively (relative risk reduction, 54%; 95% CI, −27 to 83%, $P = 0.12$), in the Asian subpopulation. Among Japanese, the incidence was 21.4% (6/28) in the placebo group and 8.3% (2/24) in the dutasteride group (relative risk reduction, 62%; 95% CI, −75 to 92%, $P = 0.20$). Similar risk reduction was observed in years 1–2 and years 3–4 in both Asian and Japanese men (Fig. 2). Only 1 out of the 16 biopsy-detected prostate cancers was diagnosed in a protocol-independent biopsy.

Pathologic Endpoints

Gleason Scores

The Gleason score distributions are shown in Table 2. In the Asian subpopulation, there were seven (12.5%) and three (5.6%) tumors with the Gleason scores of 5–6 in the placebo and dutasteride groups, respectively. The number of tumors with the Gleason scores of 5–6 was two (7.1%) in the placebo group and one (4.2%) in the dutasteride group in Japanese subjects. Compared with the placebo group, a numerically smaller number of tumors with the Gleason scores of 7–10 were observed in the dutasteride group. Regarding the Gleason score 8–10 tumors, one case in the placebo group was identified (Gleason score 8), whereas no case was observed in the dutasteride group.

Biopsy Cancer Measurements

In the Asian subpopulation, the mean number of positive cores, percentage of cores with cancer and tumor volume for the placebo and dutasteride groups, respectively, were 1.8 and 1.6, 17.2 and 16.4%, and 0.00222 and 0.00287 ml. In the Japanese subjects, these were 2.2 and 1.5, 11.6 and 10.0%, and 0.00221 and 0.00216 ml, respectively.

High-grade Prostatic Intraepithelial Neoplasia and Atypical Small Acinar Proliferation

In the Asian subpopulation, the rates of HG-PIN (without ASAP or prostate cancer) and ASAP (without prostate

Table 1. Baseline demographics and patient characteristics (safety population)

	Total population ($n = 8231$)	Asian ($n = 134$)		Japanese ($n = 57$)	
	Total ($n = 8231$)	Placebo ($n = 67$)	Dutasteride ($n = 67$)	Placebo ($n = 30$)	Dutasteride ($n = 27$)
Age (years)	62.8 ± 6.06	62.6 ± 6.73	62.0 ± 6.75	64.3 ± 5.91	62.9 ± 6.63
Range	48–77	50–75	51–75	51–74	51–74
Body mass index (kg/m^2)	27.4 ± 4.05	25.3 ± 3.24	24.6 ± 3.05	25.3 ± 3.19	23.4 ± 2.68
Family history of prostate cancer, no. (%)	1066 (13)	6 (9)	7 (10)	3 (10)	2 (7)
Total PSA (ng/ml)	5.9 ± 1.98	5.8 ± 2.06	6.0 ± 2.31	5.6 ± 1.97	5.9 ± 1.95
Free PSA (%)	16.7 ± 6.21	16.5 ± 5.03	16.0 ± 6.28	16.3 ± 4.94	14.9 ± 5.85
Prostate volume (ml)	45.7 ± 18.49	38.5 ± 13.76	36.4 ± 14.99	35.4 ± 11.53	33.5 ± 13.68
PSA density (ng/ml/ml)	0.15 ± 0.092	0.16 ± 0.076	0.18 ± 0.079	0.17 ± 0.083	0.19 ± 0.066
Cores at baseline biopsy (no.)	8.8 ± 2.46	9.0 ± 2.20	8.2 ± 2.11	8.6 ± 2.25	8.3 ± 2.07
International Prostate Symptom Score	8.7 ± 5.66	9.9 ± 5.84	8.6 ± 6.84	9.3 ± 5.88	8.7 ± 6.04

Plus–minus values are means ± standard deviation. PSA, prostate-specific antigen.

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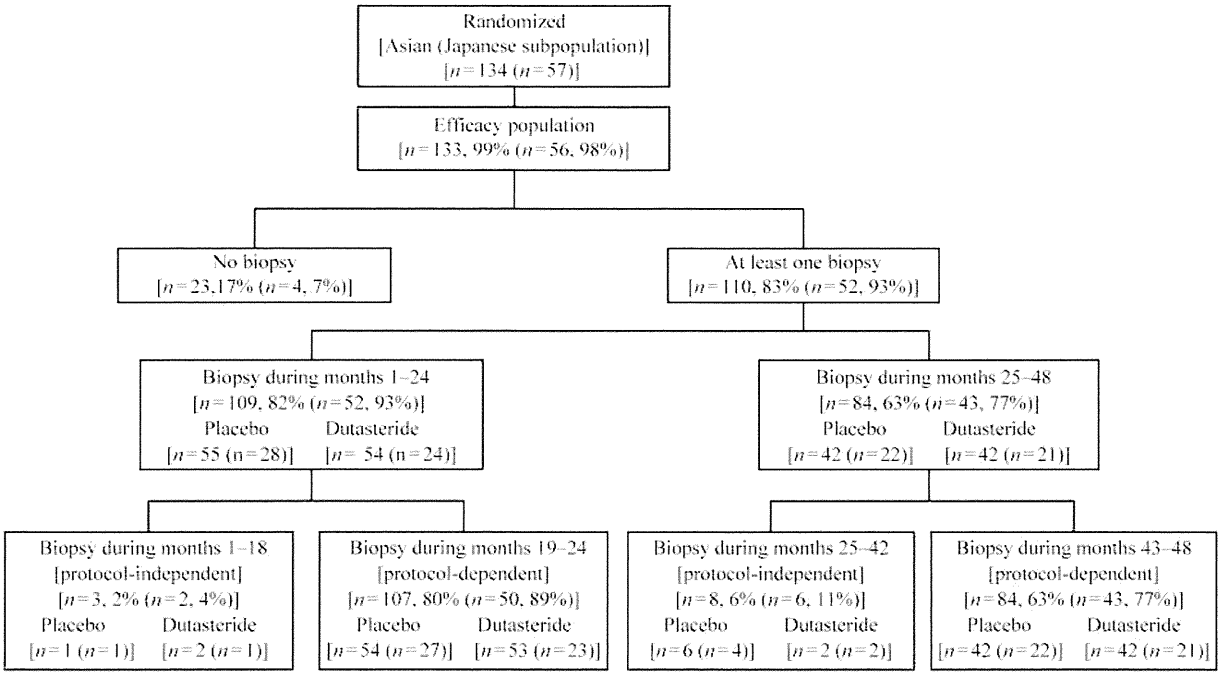

Figure 1. Subject disposition in the Asian subpopulation. Subjects were allowed to undergo a protocol-independent biopsy and have a subsequent protocol-dependent biopsy. The numbers of Asian and Japanese subjects are shown on the left and right, respectively, e.g. 'Randomized: $n = 134$ ($n = 57$)' means the number of Asian subjects was 134, and of those, 57 were Japanese.

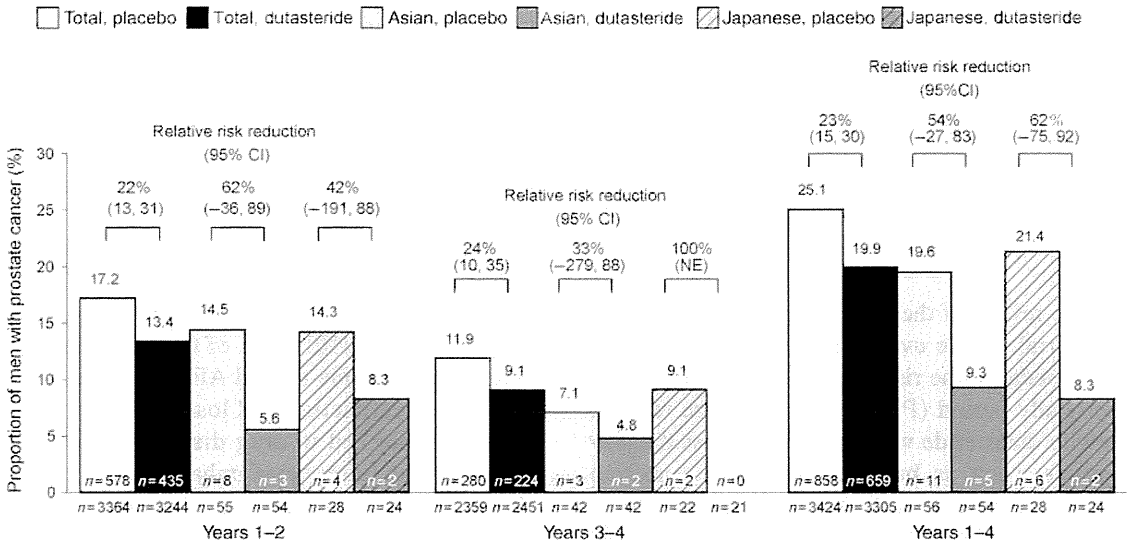

Figure 2. Proportions of men with a biopsy-detectable prostate cancer by the treatment period and the treatment group in the efficacy population. The occurrence of biopsy-detectable prostate cancer was calculated by using a restricted crude rate approach (men with at least one post-baseline biopsy). The numbers in and under the bars are the numbers of subjects. CI, confidence interval; NE, not estimable.

cancer; with or without HG-PIN) were numerically lower in the dutasteride group compared with the placebo group (9 and 7%, and 7 and 2%, respectively). Among the Japanese subjects, these rates were 4 and 0%, and 7 and 4%.

Prostate Cancer Stage and Overall Survival

The majority of biopsy-detected prostate cancers were T1 or T2. One T3a case was reported in the placebo group. There were no cases of metastatic disease. No deaths were reported in the Asian subjects.

Safety and Tolerability

A summary of AEs is presented in Table 3. Overall, slightly higher rates of AEs, drug-related AEs and serious AEs were observed with dutasteride among the Asian and Japanese subjects; however, the majority of AEs were mild or

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Table 2. Numbers and proportions of men with prostate cancer by the Gleason score and treatment in the biopsied population.

Gleason grade and score	Asian (years 1–4)		Japanese (years 1–4)	
	Placebo ($n = 56$)	Dutasteride ($n = 54$)	Placebo ($n = 28$)	Dutasteride ($n = 24$)
All tumors	11 (19.6%)	5 (9.3%)	6 (21.4%)	2 (8.3%)
5	0	0	0	0
6	7 (12.5%)	3 (5.6%)	2 (7.1%)	1 (4.2%)
5–6	7 (12.5%)	3 (5.6%)	2 (7.1%)	1 (4.2%)
7	3 (5.4%)	2 (3.7%)	3 (10.7%)	1 (4.2%)
7: 3 + 4	3 (5.4%)	2 (3.7%)	3 (10.7%)	1 (4.2%)
7: 4 + 3	0	0	0	0
8	1 (1.8%)	0	1 (3.6%)	0
9	0	0	0	0
10	0	0	0	0
7–10	4 (7.1%)	2 (3.7%)	4 (14.3%)	1 (4.2%)
8–10	1 (1.8%)	0	1 (3.6%)	0

The Gleason score is the sum of the two most common histological patterns or grades (each graded 1–5, with 5 being the most cytologically aggressive) in a prostate cancer.

Table 3. Summary of adverse events (safety population)

	Asian		Japanese	
	Placebo ($n = 67$)	Dutasteride ($n = 67$)	Placebo ($n = 30$)	Dutasteride ($n = 27$)
Any adverse event	87%	79%	93%	100%
Any serious adverse event	13%	15%	13%	19%
Any drug-related adverse event	16%	28%	33%	37%
Any drug-related adverse event leading to drug discontinuation	4%	6%	10%	4%
Fatal adverse events	0	0	0	0
Drug-related adverse events occurring in ≥2 subjects in any treatment group				
Erectile dysfunction	3 (4%)	8 (12%)	3 (10%)	3 (11%)
Loss of libido	1 (1%)	2 (3%)	1 (3%)	1 (4%)

The safety population consists of all randomized subjects.

moderate in intensity and on rare occasions led to drug discontinuation. Sexual AEs (erectile dysfunction and loss of libido) were the most common drug-related AEs in both treatment groups, with higher rates observed in the dutasteride group.

DISCUSSION

We report here the results of the Asian subjects participating in the REDUCE trial. In the overall REDUCE study population, dutasteride reduced the risk of prostate cancer by 23% over the 4-year study period ($P < 0.001$) (16). The relative risk reduction with dutasteride was consistent across the predefined subgroups, such as baseline age, PSA, prostate volume and family history. Similar trends in prostate cancer risk reduction were observed with less prostate cancer detected in dutasteride-treated men compared with placebo-treated men in the Asian subgroup. Among the 134 Asian men, 57 (43%) subjects were residents of Japan, and the remaining 77 (57%) subjects were residents of non-Asian countries. The incidence of prostate cancer in the dutasteride group was also lower than that in the placebo group among Japanese subjects. In the overall REDUCE study population, ~70% of the prostate cancers detected were tumors with the Gleason scores of 5–6, and dutasteride significantly reduced the risk of low-grade cancer, with no significant increase in tumors with the Gleason scores of 7–10 or 8–10 ($P = 0.81$ and 0.15, respectively) (16). Among the Asian subpopulation, tumors with the Gleason scores of 5–6 accounted for the majority of tumors, and less prostate cancers were detected in the dutasteride group across all the Gleason score categories. Although fewer tumors with the Gleason scores of 7–10 or 8–10 were seen in the dutasteride group in the *post hoc* analysis, the number of tumors in the Asian subpopulation was too small to draw any conclusions regarding the difference in high-grade tumors between Asians and the overall REDUCE population.

No new safety issue with dutasteride treatment was identified during the 4-year treatment period among Asian men, and the safety and tolerability results of these subpopulations were consistent with those of the overall population. Most common dutasteride-related AEs were of sexual nature, such as erectile dysfunction and loss of libido; however, on rare occasions they led to drug discontinuation. In the overall population, an unexpected imbalance in a composite term of cardiac failure was observed (16); however, no cardiac failure events were reported in the Asian subpopulation. The safety and tolerability profile of dutasteride in this Asian population at an increased risk of prostate cancer was also consistent with that observed in Asian BPH populations (18,19).

Although this study was not designed to compare the differences between the Asian subpopulation and the overall population, baseline characteristics of the Asian subjects were generally similar to those observed in the overall REDUCE study populations, except for a slightly lower prostate volume in Asian men. This observation is consistent with previous reports that compared prostate volume between Caucasian and Japanese men (20–22). On the other hand, baseline PSA was similar between the Asian subjects and the overall population. Similar PSA

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levels with lower prostate volume have been reported in Asian men compared with Caucasians (23,24), including a recent Asian subanalysis of the CombAT BPH study (18). The prostate cancer incidence in the placebo-treated men during the 4-year period in the Asian and Japanese subjects (19.6 and 21.4%, respectively) approached that of the overall population (25.1%), although slightly lower rates of biopsy-detectable prostate cancer were observed in both Asian and Japanese men. This observation may be caused by study population because we enrolled subjects who had an elevated PSA in the study. This is consistent with the previous report, suggesting that the risk of developing prostate cancer is generally similar between Japanese men and European men who had the same baseline PSA levels (25).

This *post hoc* analysis has several limitations. First, the REDUCE study was not designed for treatment comparisons among the Asian subpopulations, and second, the treatment outcomes are based on a limited number of Asian participants. However, risk reduction with dutasteride among Asian men was consistent with the trends observed for the overall population.

In the USA, most men diagnosed with prostate cancer having low-risk features will receive aggressive treatment (26–28). Although in Japan, primary androgen deprivation therapy is the most commonly provided treatment for men with low-stage prostate cancer, similar trends of potential overtreatment have also been reported (29). Thus, reducing the number of indolent prostate cancer diagnoses, and as a consequence reducing the number of cancer interventions, is an important strategy for the Asian region as well. Risk reduction by dutasteride could be considered as a treatment option for Asian men at an increased risk of prostate cancer.

In conclusion, in the REDUCE study, the results of the Asian subpopulations were in line with those of the overall population. In Asian subjects, the incidence of prostate cancer in dutasteride-treated men was lower than that of placebo-treated men. Fewer high-grade tumors were diagnosed in the dutasteride group among Asian subjects. Dutasteride safety and tolerability profile in Asian subjects was consistent with that seen in the overall REDUCE study population and in previous dutasteride studies in Asian BPH populations. No new safety issue emerged throughout the 4-year treatment. These results support the value of dutasteride for prostate cancer risk reduction in Asian men at an increased risk of prostate cancer.

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Conflict of interest statement

Hideyuki Akaza received consulting or advisory fees from GlaxoSmithKline. Taiji Tsukamoto, Naoya Masumori and Hideki Sakai received lecture fees from GlaxoSmithKline. Yukihiro Endo and Takayoshi Yamanouchi are employees of GlaxoSmithKline.

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IV.　附　　厚生労働科学研究費補助金事業実績報告書　　（様式A6）

様式Ａ（６）

厚生労働科学研究費補助金事業実績報告書抜粋

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厚生労働大臣　殿

住　　所　〒160-0023　新宿区西新宿 3-15-5-10
フリカ゛ナ　アカザ　ヒデユキ
研究者　氏　　名　赤座　英之　印
生年月日　１９４６年　４　月　１７日生

平成２３　年度厚生労働科学研究費補助金（　**医療技術実用化総合**　研究事業）の事業実績報告書について

平成２３年８月２９日厚生労働省発医政０８２９第４号をもって交付の決定を受けた標記の事業を完了したので、関係書類を添えて報告する。

研究課題名（課題番号）：**癌治療薬の市販後全例調査資料の有効利用によるエビデンス創出に関する研究**（Ｈ２３-臨研推-指定-０１２）

６．研究結果の概要

本研究は、図1に示すように、より有効な薬剤の risk management plan (RMP) の策定に寄与する研究である。現在、社会保障改革に関する集中検討会議や医療イノベーション会議、厚生科学審議会医薬品等制度改正検討部会等において、医療上必要な医薬品等の患者への迅速な提供や早期のドラッグラグの解消が求められているところである。このため、平成24年4月1日付で、医薬品リスク管理指針が、厚生労働省医薬食品局安全対策課長・審査管理課長の連名通知として出されている。この2課長通知には、RMPの策定には、Risk/ Benefit バランス評価の重要性が指摘されている（図２）。本研究の目的は、製薬企業に義務付けられている新規抗悪性腫瘍薬の市販後全例調査（使用成績調査）を如何に有効に利用できるかを検討することである。研究成果により、患者の病態に合わせた最適の薬物療法の確立や適応拡大に関する十分なエビデンスが創出できるようになれば、根拠に基づいた適切な治療ガイドラインの策定及びドラッグラグの解消に貢献するものとなる。検討は、腎細胞癌の新規分子標的薬2種（Sorafenib, Sunitinib）の全例調査をモデルとして行った。調査項目に、従来の主目的である副作用に関する項目以外に有効性、すなわち抗腫瘍効果、progression free survival (PFS),および, overall survival (OS)を加えることにより、以下のことが解析可能であることが明らかになった。　その結果、これら新薬に関する有効なRMP策定に寄与できると考えられた。
(1) 副作用の患者背景因子ごとの特徴、(2) 各副作用の程度と発現時期に関する一定のpattern,
(3) 日本人患者特有の副作用・効果の発現のpattern, (4) 薬剤の投与量・投与期間と副作用、
および、効果の関係、(5) 患者の背景因子（PS, 転移数、転移部位、前治療の有無、種類、性別、年齢、
等）とPFS, OSの関係。これらは、有効なRMP策定の重要な要素である Benefit/Risk の検討に不可欠
のものである（図3-12）。

一方、次の点が、問題点として明らかになった。

(1) 承認直後の新薬を用いた臨床試験としての全例調査の義務は、米国のFDAにも無く、日本独自のシステムである。従って、製薬企業、特に外資系、から見れば、大きな負担となっている。(2) この義務は、単に企業側に負担をかけるのみでなく臨床現場にも負担をかけるところである。(3) 調査項目であるが、副作用と効果の判定で、治験では、義務付けられているCTC評価基準やRECIST判定基準が義務付けられておらず、データの質が必ずしも上質とは言えず、国内外の治験データとの比較性が損なわれる。(4) データモニタリング等、試験の管理が治験ほど厳格でなく、得られた結果の保証に問題が残る。(5) 従って、正確なデータを得るためには、臨床現場との協調が不可欠であるが、その体制が確立されているとは言い難い。

以上のことから、新規抗悪性腫瘍薬開発企業に課せられた市販後全例調査は、いくつかの問題を解決することにより、日本独自のすぐれたシステムにすることが出来ると考えられた。

7．研究により得られた成果の今後の活用・提供

研究により得られた成果の今後の活用・提供については、以下に箇条書きする。

1. 今回検討した2種類の進行腎細胞癌にたいする分子標的薬に関する全例調査（使用成績調査）は、PFSやOSを含む効果の検討もされており、効果予測因子や予後予測因子の日本人患者独自の検討が可能である。副作用に関する情報に加えてこれ等の情報を論文化して発表する。すでに、RMPの一環として必要な部分は各企業からホームページ等にて公表されているが、SorafenibとSunitinib両薬剤を比較しつつ学術誌に発表することによりアカデミカルにも貴重な情報となる。

2. 平成24年度のRegulatory Science学会において、成果の一部を発表して、全例調査の有効利用のための提言をする。

3. 第13回抗悪性腫瘍開発フォーラム（今回の組織委員長；赤座）の課題は，“Revisiting Japan- 全例調査“である。ここで全例調査の現状を米国FDAとの比較において議論する中で、全例調査の意義と課題を論じ、今回の研究成果についても報告する。そして、開発フォーラムとして、日本における市販後調査の意義と課題に関する提言をまとめる際の一資料として今回の研究成果を活用する。

4. 今回の研究結果から、市販後全例調査（使用成績調査）の重要性は、明らかであるが、同時に解決、改善されなければならない課題も少なくないことが判明した。これらを勘案しつつ、今後、市販後全例調査のシステムを有効に活用することで、現在も依然として解消されていない “Drug lag” の解消の一助となるような提言を様々な機会を通して行っていく。たとえば、米国FDA では、早期承認の条件として、市販後義務調査（Post Marketing Requirements: PMR）の法規制を設けているが、市販後全例調査をPMRと位置付け、その変わり承認申請に必要な治験データとその評価期間を単純、短縮すれば、承認（仮承認）までの期間を大幅に短縮できる可能性が期待される。

5. 効果に関する調査も重視したことでBenefit/Risk バランスに関する的確な議論が可能となるため、
よりよいRMPを提供できることが期待される。

８．研究の実施経過

1. 進行腎細胞癌にたいする分子標的薬であるSorafenib,および、 Sunitinib の全例調査計画書作成の段階
で、臨床側（赤座が、医学専門家として関与した。）から積極的に協調することにより、特に効果に関する
調査項目について従来の全例調査とは異なる改善を加えることができた。
2. 同時に、共同研究者の一人（河原）が、米国FDAに調査に出向き、FDAにおける抗悪性腫瘍薬の市販後
調査の実体をまとめた。
3. Sorafenib, Sunitinib全例調査（使用成績調査）データの解析が、一定症例集積ごとに進められたが、
この際に、臨床側の医学専門家の意見、助言が取り入れられた。
4. 全共同研究者と2剤の開発企業担当者が一堂に会し（2012年1月19日）、上記1, 2, 3に関する情報を
共有し、全例調査の解析方法とまとめ方について議論を交わし、データの有効利用の方法をまとめた。
5. Sorafenib, Sunitinib に関する使用調査最終報告書が、それぞれ公表された。
6. それぞれの学術誌投稿用原稿が準備中である。
7. さらに、その二つの論文を基に、全例調査の有効利用に関する論文を、RMP の観点からまとめる予定で
ある。特に、新規抗悪性腫瘍薬については、Benefit/Risk の評価が重要であり、そのためには、副作用
のみの調査では十分でなく効果の調査があってこそ、Benefit/Risk が解析されることを強調する。
8. さらに、Regulatory Science 学会等で、今回の成果を発表するなど、積極的に成果の発表を行う。

RCC 厚生労働省科学研究費　報告書
付図集

赤座　英之

図 1 研究の流れ

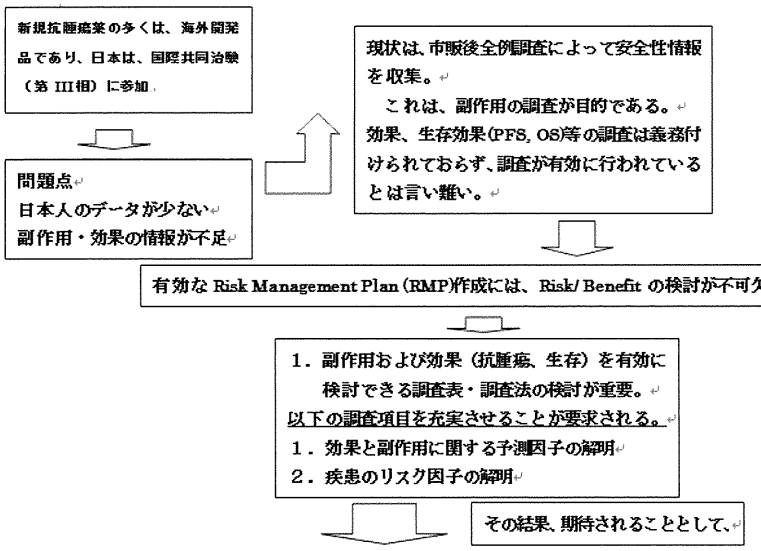

新規抗腫瘍薬の多くは、海外開発品であり、日本は、国際共同治験（第 III相）に参加
問題点
日本人のデータが少ない
副作用・効果の情報が不足
現状は、市販後全例調査によって安全性情報を収集。
これは、副作用の調査が目的である。
効果、生存効果(PFS, OS)等の調査は義務付けられておらず、調査が有効に行われているとは言い難い。
有効な Risk Management Plan (RMP)作成には、Risk/ Benefit の検討が不可欠
1．副作用および効果（抗腫瘍、生存）を有効に検討できる調査表・調査法の検討が重要。
以下の調査項目を充実させることが要求される。
1．効果と副作用に関する予測因子の解明
2．疾患のリスク因子の解明
その結果、期待されることとして、
新薬の有効な Risk Management Plan (RPM)の策定と実行に寄与することができる。
① 学際研究のモデルとなり得る
② 開発新薬の安全性のみならず、効果についても重要なエビデンスが得られる
③ 質の高い臨床研究結果が公開できる
④ 治療のテーラーメイド化を推進することができる
⑤ 医療費の有効利用
⑥ 同じ人種であるアジア諸国に対する情報発信ができる

図2

医薬品リスク管理計画指針；平成24年4月11日付け；厚生労働省医薬食品局安全対策課長・審査管理課長連名通知

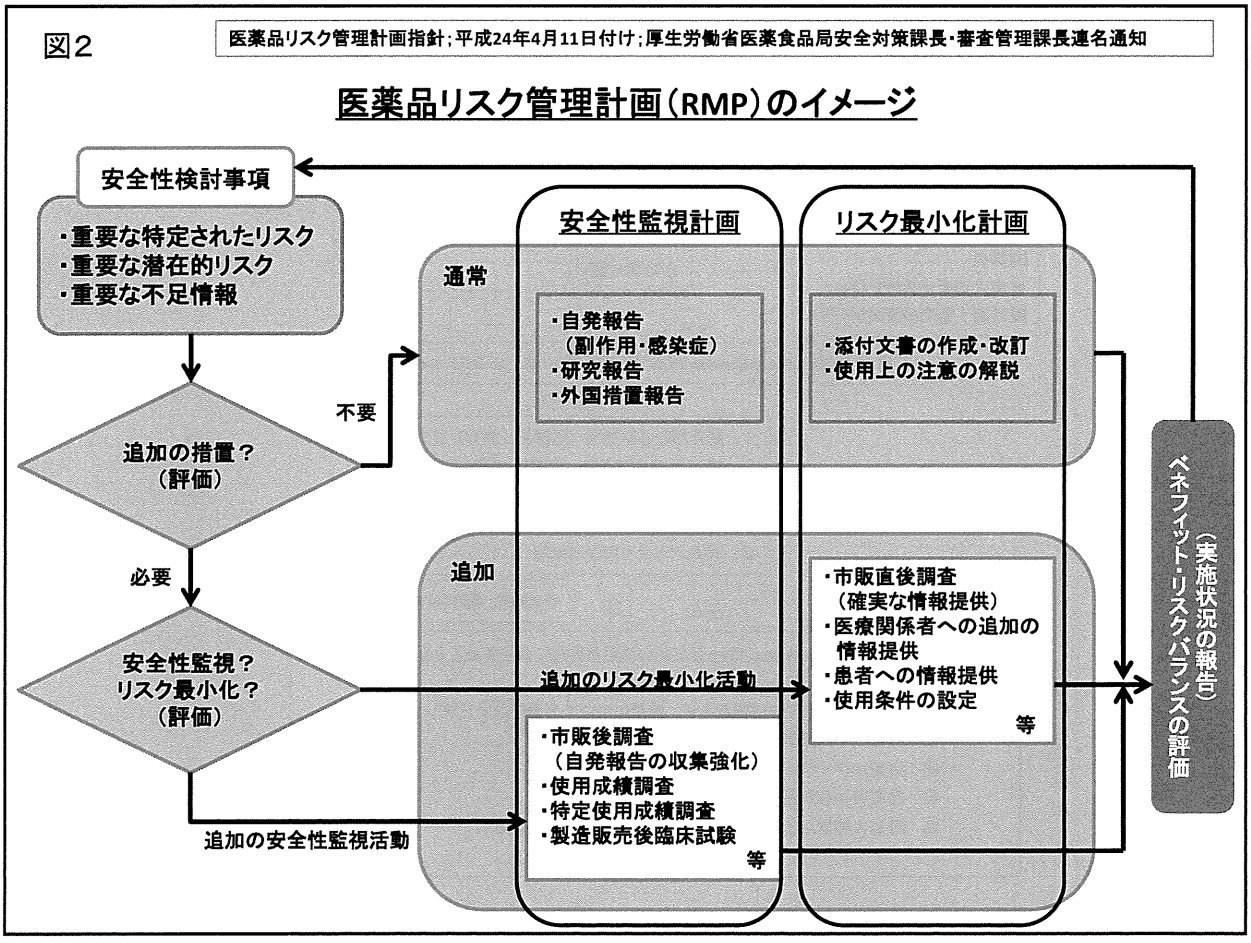


図3; Sorafenib

Dose Intensity（平均値）

$$\text{Dose Intensity [\%]} = \frac{\text{実投与量の総計 [mg]}}{\text{投与期間*[日] x 800 [mg/日]}} \times 100$$

*投与開始から投与中止まで，休薬期間を含む

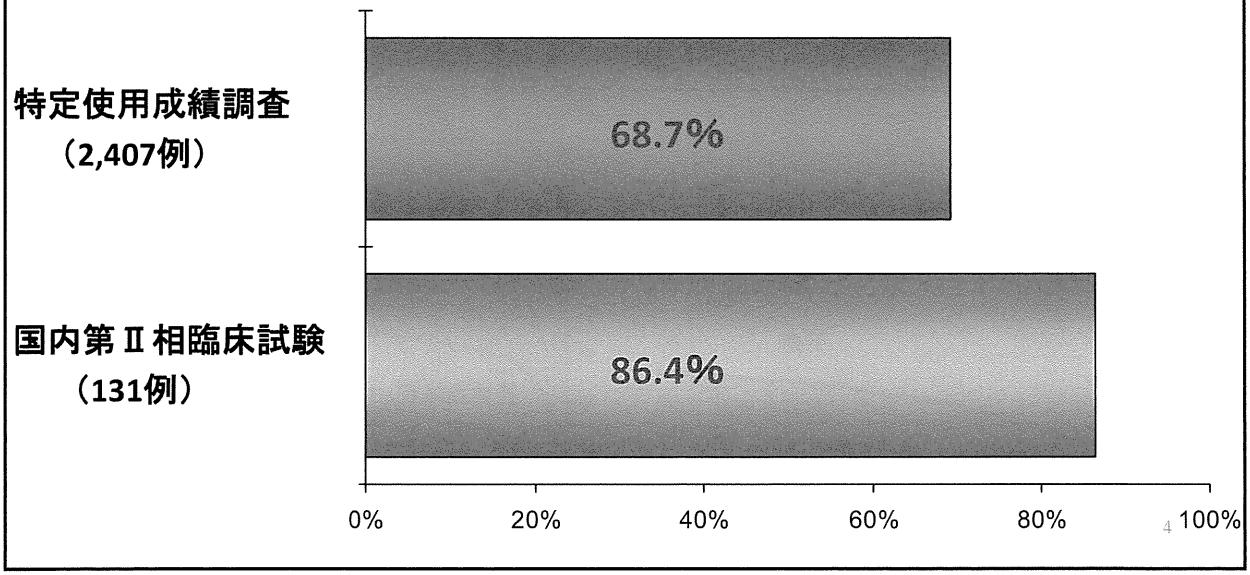
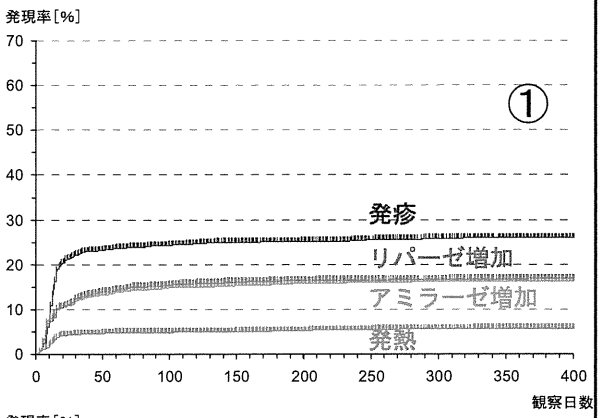
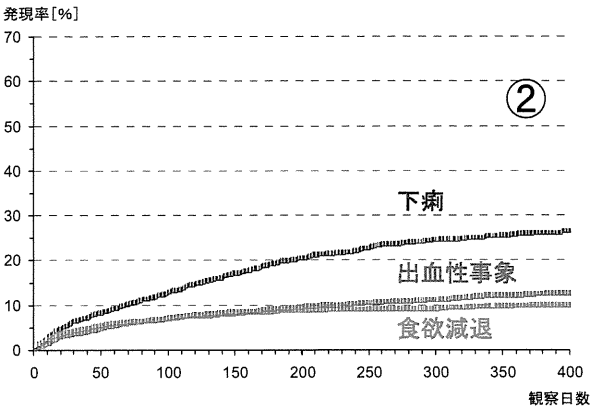


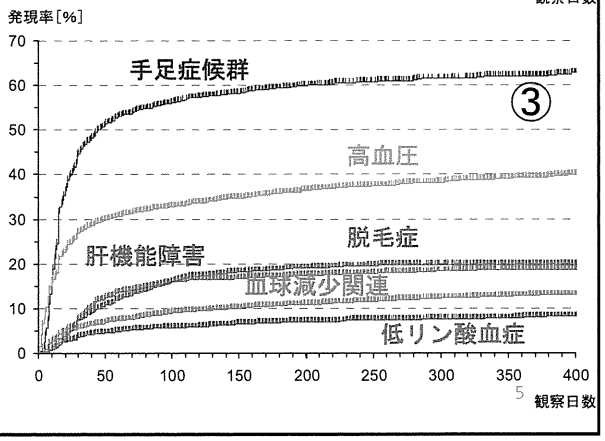
図4; Sorafenib

副作用発現時期（カプランマイヤー法による）

投与初期に発現	◆ 発疹 ◆ アミラーゼ増加 ◆ リパーゼ増加 ◆ 発熱	①
観察期間を問わず発現	◆ 下痢 ◆ 出血性事象 ◆ 食欲減退	②
主として投与初期＋その後も発現	◆ 手足症候群 ◆ 高血圧 ◆ 肝機能障害 ◆ 血球減少関連 ◆ 低リン酸血症 ◆ 脱毛症	③





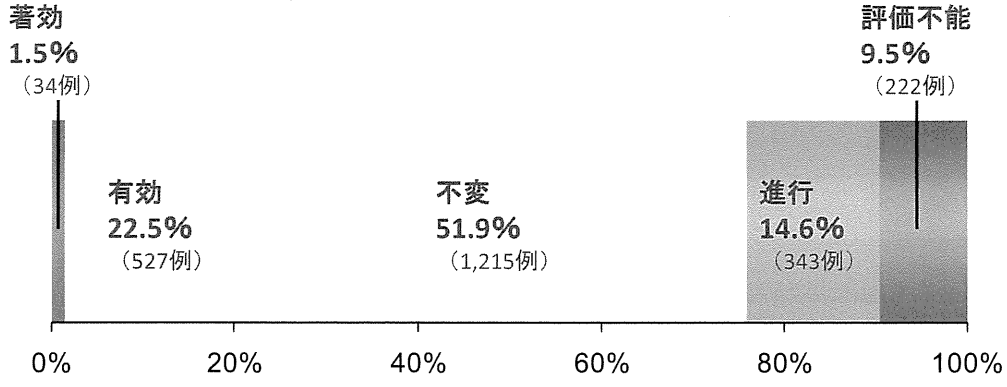


5

図5; Sorafenib

抗腫瘍効果

- 情報が得られた2,341例における検討※
  - 奏効率(著効＋有効) : 24.0%
  - 著効＋有効＋不変 : 75.9%



※ 腎癌取扱い規約，非観血的治療効果判定基準

6

図6; Sorafenib

奏効に至るまでの期間／奏効している期間

- 著効または有効を示した561例における検討

奏効に至るまでの期間	中央値	**53.0日**	（7.6週）
	25%位値	33日	
	75%位値	101日	
奏効に至るまでの平均1日投与量	中央値	**650.0 mg**	
	25%位値	404 mg	
	75%位値	800 mg	
奏効している期間	中央値	**171日**	（24.4週）
	25%位値	84日	
	75%位値	280日	

7

図7; Sunitinib

Relative Dose Intensity

観察期間	症例数	平均総投与量(mg)	Dose intensity(%)
投与開始～6週	1618	1016.19	72.59
投与開始7週～12週	1340	943.08	67.36
投与開始13週～18週	1110	882.84	63.06
投与開始19週～24週	951	834.36	59.60

観察期間6週とした理論上の総投与量1400mgに対して、観察期間毎の実際の総投与量の割合を示した

8

図8; Sunitinib

奏効率

	最良総合評価					合計	奏効率	95%両側信頼区間
	CR	PR	SD	PD	判定不能			
臨床効果	8	304	578	383	162	1435	312	19.6-24.0
	(0.6)	(21.2)	(40.3)	(26.7)	(11.3)		(21.7)	

背景因子		有効症例数(%)	症例数	検定結果
登録時期	2008/6/3～2008/12/4	70 (19.7)	356	p=0.235 [1)]
	2008/12/5～2009/5/27	94 (20.5)	458	p=0.105 [4)]
	2009/5/28～2009/11/17	148 (23.8)	621	
前治療薬	[IFN-α]	81 (27.1)	299	p=0.024 *[1)]
	[IFN-α][IL-2]	28 (27.7)	101	
	[IFN-α][IL-2][NEX]	37 (21.1)	175	
	[IFN-α][NEX]	30 (14.0)	214	
	[IL-2]	3 (17.6)	17	
	[IL-2][NEX]	1 (9.1)	11	
	[NEX]	14 (16.9)	83	
	その他	7 (17.5)	40	
	無	111 (22.4)	495	

※ 1) χ2検定 4)C-A検定 ** : p<0.01, * : p<0.05

9