Sarcopenia During Androgen-Deprivation Therapy for Prostate Cancer

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ABSTRACT

Purpose

To characterize changes in lean body mass (LBM) in men with prostate cancer receiving androgen-deprivation therapy (ADT).

Patients and Methods

We prospectively evaluated LBM in a prespecified substudy of a randomized controlled trial of denosumab to prevent fractures in men receiving ADT for nonmetastatic prostate cancer. LBM was measured by total-body dual-energy x-ray absorptiometry at study baseline and at 12, 24, and 36 months. The analyses included 252 patients (132, denosumab; 120, placebo) with a baseline and at least one on-study LBM assessment. Patients were stratified by age (< 70 v ≥ 70 years) and by ADT duration (≤ 6 v > 6 months).

Results

Median ADT duration was 20.4 months at study baseline. Mean LBM decreased significantly from baseline, by 1.0% at month 12 (95% CI, 0.4% to 1.5%; $P < .001$; $n = 248$), by 2.1% at month 24 (95% CI, 1.5% to 2.7%; $P < .001$; $n = 205$), and by 2.4% at month 36 (95% CI, 1.6% to 3.2%; $P < .001$; $n = 168$). Men age ≥ 70 years ($n = 127$) had significantly greater changes in LBM at all measured time points than younger men. At 36 months, LBM decreased by 2.8% in men age ≥ 70 years and by 0.9% in younger men ($P = .035$). Men with ≤ 6 months of ADT at study entry ($n = 36$) had a greater rate of decrease in LBM compared with men who had received more than 6 months of ADT at study entry (3.7% v 2.0%; $P = .0645$).

Conclusion

In men receiving ADT, LBM decreased significantly after 12, 24, and 36 months.

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INTRODUCTION

Sarcopenia refers to a decrease in skeletal muscle or lean body mass (LBM).¹ Sarcopenia is associated with mobility disorders, increased risk of falls and fractures, impaired ability to perform activities of daily living, disabilities, loss of independence, and increased mortality.^{2,3} In addition to aging, multiple factors may contribute to sarcopenia, including poor nutrition, sedentary lifestyle, chronic diseases, and certain medications.^{4,5} The loss of LBM in men receiving androgen-deprivation therapy (ADT) is often associated with an increase in fat mass, a combination referred to as sarcopenic obesity.^{6,7} Definitions of sarcopenia have evolved over time; whereas early definitions focused on the effects of aging on LBM, later definitions incorporate the concepts of loss of strength or mobility.⁸ Of note, modest proportional changes in LBM have been found to be associated with larger proportional changes in strength.⁹ In addition to locomotion and strength,

lean body tissue performs other functions, including cardiac output, respiratory function, glucose and insulin management, and drug metabolism⁸; for that reason, it is important to separate the variables involved in sarcopenia and to characterize the factors that affect LBM in various patient populations.

Androgens are important determinants of LBM in men. Serum testosterone concentrations correlate positively with LBM in men.¹⁰ Testosterone replacement therapy increases LBM in men with hypogonadism due to aging,¹¹ HIV infection,^{12,13} and other chronic diseases.¹⁴

Prospective studies have reported that gonadotropin-releasing hormone agonists decrease LBM in men with prostate cancer. In a single-center study¹⁵ of 32 men initiating ADT for prostate cancer, LBM significantly decreased by 2.7% from baseline to month 12. In another study¹⁶ of 79 men receiving ADT for prostate cancer, LBM decreased by 3.8% from baseline to month 12. The long-term effects of ADT on LBM and patient characteristics

associated with LBM changes in men with prostate cancer are not well characterized. Dual-energy x-ray absorptiometry (DXA) scanning, which is commonly used to measure bone density, is also used in research settings to measure LBM.^{1,17,18}

In a recently reported 3-year randomized, placebo-controlled phase III study¹⁹ of men receiving ADT for nonmetastatic prostate cancer (n = 1,468), denosumab significantly increased bone mineral density (BMD) and decreased new vertebral fractures. In this report, we describe the results of a prespecified substudy to better characterize the long-term change in LBM in prostate cancer survivors receiving ADT.

PATIENTS AND METHODS

Patients

This report describes a prespecified body composition substudy embedded in a global randomized controlled trial. The substudy includes patients from 38 centers in North America who had total-body DXA scans to evaluate LBM. The analyses include patients with baseline and at least one on-study total-body DXA scan. Patients were invited to participate in the substudy after enrollment in the main study. As previously reported,¹⁹ the randomized, placebo-controlled trial included men with histologically confirmed prostate cancer who were receiving ADT with an expected duration of on-study treatment ≥ 12 months. Men were ≥ 70 years old or, if younger than age 70, they were required to have either a low baseline BMD test (T-score at the lumbar spine, total hip, or femoral neck < -1.0) or a history of an osteoporotic fracture. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2. Key exclusion criteria included concurrent antineoplastic therapy or radiotherapy and prostate-specific antigen more than 5 ng/mL after receiving ADT for more than 1 month. Patients were also excluded if they had a BMD T-score less than -4.0 at lumbar spine, total hip, or femoral neck, or were currently receiving treatment for osteoporosis.

Patients were randomly assigned to receive subcutaneous injections of 60 mg denosumab, a fully human monoclonal antibody against receptor activator of nuclear factor kappa B ligand (RANKL), or matching placebo every 6 months. Randomization was stratified by duration of prior ADT (≤ 6 v > 6 months) and age (< 70 v ≥ 70 years). All patients were instructed to take calcium (1 g per day) and vitamin D (≥ 400 IU per day). Patients were not provided specific instructions about nutrition or exercise; guidance about diet and exercise was provided at the discretion of the treating physician. Institutional review boards at each center approved the protocol. All patients provided written informed consent before participating.

Study Outcomes

The primary outcome measured in this substudy was change from baseline in LBM, measured by DXA at baseline and at months 12, 24, and 36 by using Hologic (Hologic, Bedford, MA) or Lunar (General Electric Lunar, Madison, WI) densitometers. All DXA results were assessed in a blinded fashion by a central reader (Synarc, San Francisco, CA). Serum testosterone was measured at baseline and every 6 months by using a validated radioimmunoassay (ICON Laboratories, Farmingdale, NY).

Statistical Analyses

Analyses were based on patients pooled from both treatment arms, because no differences in LBM were expected or observed due to treatment with denosumab. Analyses of percentage change from baseline in LBM through 36 months used a mixed effects model for repeated measures²⁰ that included baseline LBM, machine type (Lunar v Hologic), baseline LBM-by-machine type interaction, and visit (month 12, 24, or 36) as fixed effects. An unstructured within-patient variance-covariance matrix was used in the model. Patients who had a baseline and at least one postbaseline LBM measurement were included. Subgroup analyses for age group (< 70 v ≥ 70 years), ADT duration at study entry (≤ 6 v > 6 months), and baseline body mass index (BMI) used the same mixed effects model. Two-sided *P* values are

Fig 1. CONSORT diagram.

reported, and a *P* value less than .05 was considered statistically significant with no adjustment for multiplicity.

RESULTS

Patient Characteristics

A total of 309 patients were enrolled in the substudy; of these, 252 were eligible for analysis with baseline LBM data and at least one

Table 1. Study Baseline Characteristics (N = 252)

Characteristic	No.	%	Mean	SD
Age, years			74.9	7.5
Race				
White	167	66.3		
Black	17	6.7		
Hispanic	63	25.0		
Other	5	2.0		
Median ADT duration at study entry, months	20.4			
BMI, kg/m ²			28.1	4.2
< 25	58	23.0		
25-29.9	129	51.2		
≥ 30	65	25.8		
Lean body mass, kg			51.3	7.0
Serum testosterone, nmol/L				
Median		0.24		
Q1, Q3		0.14, 0.42		
Serum testosterone, g/dL (Q1, Q3)				
Median		6.9		
Q1, Q3		4.0, 12.1		

Abbreviations: ADT, androgen-deprivation therapy; BMI, body mass index; Q, quartile; SD, standard deviation.

postbaseline LBM measurement (Fig 1). Table 1 summarizes baseline characteristics for the 252 patients included in these analyses. Most men were white or Hispanic. Mean age was 74.9 years (standard deviation [SD], 7.5 years). Median ADT duration at study baseline was 20.4 months. More than three quarters of men were overweight or obese. One-hundred ninety-eight patients (64.1%) completed the 36-month study, a proportion similar to that in the overall study. The most common reason for discontinuation was withdrawal of consent (15%; Fig 1); in most cases, this occurred when the blinded period of the study was extended from 2 years to 3 years.¹⁹

Gonadal Steroids

At study baseline, median serum testosterone was 6.9 ng/mL (0.24 nmol/L). Median serum testosterone levels remained in the castrate range (< 50 ng/mL) throughout the 36-month study (Fig 2).

LBM

Mean LBM decreased significantly from study baseline to months 12, 24, and 36 (Fig 3A). From baseline to month 12, mean LBM decreased by 1.0% (95% CI, 0.4% to 1.5%; $P < .001$; $n = 248$). From baseline to months 24 and 36, mean LBM decreased by 2.1% (95% CI, 1.5% to 2.7%; $P < .001$; $n = 205$) and 2.4% (95% CI, 1.6% to 3.2%; $P < .001$; $n = 168$), respectively.

Changes in LBM differed according to patients' age and duration of ADT at study entry (Figs 3B and 3C). Men age ≥ 70 years had significantly greater changes in LBM at all measured time points. At 36 months, LBM decreased by 2.8% in men age ≥ 70 years ($n = 127$) compared with a decrease of 0.9% in younger men ($P = .035$). Men with ≤ 6 months of ADT at study entry ($n = 36$) had a greater rate of decrease in LBM at 36 months compared with men who had received more than 6 months of ADT at study entry (3.7% v 2.0%; $P = .0645$); similar results were obtained in analyses adjusted for age.

Waterfall plots summarize the individual LBM changes according to patients' age and ADT duration at study entry (Fig 4). Consistent with the results of subset analyses (Figs 3B and 3C), older patients and those with short ADT duration at study entry tended to have greater decreases in LBM. From study baseline to month 12, for example, LBM decreased in 48.2% of men younger than 70 years and in 58.8% of men older than 70 years. LBM decreased in 68.8% of patients with less than

Fig 2. Median serum testosterone levels from study baseline to month 36 among all randomly assigned patients in substudy ($n = 309$). Q, quartile.

Fig 3. (A) Mean changes in lean body mass from study baseline to month 36 for the overall study population ($*P < .001$ v baseline); (B) according to patients' age ($*P < .001$ v baseline; $†P < .05$ v < 70 years); and (C) according to androgen-deprivation therapy (ADT) duration at study entry ($*P < .01$ v baseline; $†P < .05$ v baseline; $‡P < .05$ v > 6 months).

6 months of prior ADT and in 55.1% of patients with more than 6 months of prior ADT at baseline.

Mean overall change from study baseline in BMI was 1% (95% CI, 0.3% to 1.6%) at month 12, 0.6% (95% CI, -0.1% to 1.4%) at month 24, and 0.3% (95% CI, -0.5% to 1.2%) at month 36. The mean decreases in LBM from baseline to months 12, 24, and 36 were statistically significant for patients with a baseline BMI less than 25 mg/kg² or 25 to 29 mg/kg² (Fig 5), but not for patients with a baseline BMI ≥ 30 mg/kg². Mean differences in LBM change between the patients with baseline BMI less than 25 mg/kg² and those with baseline scores of 25 to 29 mg/kg² or ≥ 30 mg/kg² were not statistically significant.

Fig 4. (A, B) Waterfall plots for changes in lean body mass from study baseline to month 12 according to patients' age and (C, D) androgen-deprivation therapy (ADT) duration at study entry.

DISCUSSION

In this prespecified analysis of a large, multicenter prospective study, we observed that LBM significantly decreased after 1, 2, and 3 years in men receiving ADT for prostate cancer. As shown by the waterfall plots for individual response at 12 months, the majority of patients experienced muscle loss. Decreases in LBM were greatest in older men and those with short ADT duration before study entry.

The observation that LBM decreased during ADT is consistent with the results of several prior reports.^{15,16,21-23} In two small prospective studies^{15,16} of men initiating ADT for prostate cancer, LBM significantly decreased by 2.7% to 3.8% from baseline to month 12. In a single-center prospective study²³ of men receiving ADT for prostate

cancer, LBM decreased from baseline to 24 months in men with short-term (< 6 months) and long-term (≥ 6 months) prior ADT duration. Smaller decreases in LBM were observed during longer follow-up, although the authors noted that evidence for ongoing treatment-related muscle loss was lacking in their study because of limited outcome data after 1 year. In contrast to earlier reports, this study was multicentered, larger, had a longer follow-up (up to 36 months), and included racially diverse patients. To the best of our knowledge, this is the first study to determine that older men have greater LBM declines during ADT and to convincingly demonstrate that LBM continues to decline with long-term treatment. ADT is also associated with fatigue, loss of energy, emotional distress, and lower overall quality of life.²⁴⁻²⁶ Sarcopenia may contribute to the adverse effects of ADT on self-reported and objective physical function and quality of life.²⁷ The potential impact of ADT on LBM and other health outcomes should be considered in individual decisions about the timing and duration of ADT, particularly in settings in which there is no documented survival benefit.

ADT increases the risk for clinical fractures in men with prostate cancer.^{28,29} ADT also decreases BMD,³⁰⁻³³ an important determinant of fracture risk. Decreases in LBM in men during ADT may contribute to frailty and greater risk for falls.^{1,34} Thus, ADT may increase fracture risk by decreasing both BMD and LBM. Notably, older age is independently associated with fractures in men with prostate cancer.^{28,29} Our observation that treatment-related muscle loss was greatest in older men raises particular concern about potential adverse effects of ADT in a vulnerable elderly population.

Serum testosterone levels decline by more than 90% to the castrate range (< 50 ng/dL) within the first month after initiation of ADT and then remain in the castrate range during chronic treatment. Commensurate with the initial marked decline in testosterone, we observed

Fig 5. Mean changes in lean body mass from study baseline to month 36 according to body mass index at each visit (* $P < .01$ for change from baseline; † $P < .001$ for change from baseline).

that decreases in LBM were greater in men who recently initiated ADT. Notably, changes in BMD during ADT appear to follow a similar pattern with early brisk decline followed by slower decline during chronic therapy.³⁵ Our study may have underestimated the magnitude of LBM change during long-term therapy because it included men who initiated ADT before study entry; in fact, the mean duration of ADT at study entry was 20.4 months.

In the general population, age-related sarcopenia is attributed to alterations in systemic and cellular factors, other medical conditions, and behavioral changes.³⁶ Age-related alterations in systemic and cellular properties contribute to muscle atrophy and/or muscle fiber loss. Medical conditions that accompany aging, including diabetes, peripheral vascular disease, and kidney disease, are associated with sarcopenia. Poor nutrition and inactivity accelerate muscle loss in older individuals. We observed that decreases in LBM during ADT were greater in older men. The higher rates of muscle loss in older patients may reflect a combination of age-related differences in muscle metabolism, greater prevalence and severity of other medical conditions, and maladaptive patient behaviors.

Our study did not control for exercise or diet, and data about physical activity and nutrition were not collected. Several studies suggest that resistance exercise training may mitigate or reverse some of the adverse effects of ADT on body composition.³⁷⁻³⁹ Additional studies are needed to determine the effects of other forms of exercise and diet on LBM in prostate cancer survivors.

This study evaluated the prespecified covariates of age and duration of ADT therapy because these were stratification factors in the original randomization for this study and because they are of wide interest. We also evaluated the effect of BMI on changes in LBM. Additional studies might also be useful for considering other questions related to the effects of ADT. Because all the men in this study received ADT, it is not possible to separate the effects of aging from those of ADT on sarcopenia. Further studies are warranted, addressing functional outcomes as well as measurement of LBM. It might also be of interest to consider whether sarcopenia is related to either the efficacy or toxicity of ADT; however, the efficacy and toxicity of ADT were not within the scope of this study. We did not evaluate disease

progression or ADT-related toxicity. In addition, other variables such as race might be worthy of analysis; such an analysis would require a larger population than was represented in this study.

In summary, LBM decreased significantly after 1, 2, and 3 years in men with prostate cancer who were receiving ADT. Decreases in LBM were greatest in older men and those with initial ADT.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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REFERENCES

- Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al: Sarcopenia: European consensus on definition and diagnosis—Report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 39:412-423, 2010
- Cawthon PM, Marshall LM, Michael Y, et al: Frailty in older men: Prevalence, progression, and relationship with mortality. *J Am Geriatr Soc* 55:1216-1223, 2007
- Lauretani F, Russo CR, Bandinelli S, et al: Age-associated changes in skeletal muscles and their effect on mobility: An operational diagnosis of sarcopenia. *J Appl Physiol* 95:1851-1860, 2003
- Rolland Y, Czerwinski S, Abellan Van Kan G, et al: Sarcopenia: Its assessment, etiology, pathogenesis, consequences and future perspectives. *J Nutr Health Aging* 12:433-450, 2008
- Sayer AA, Syddall H, Martin H, et al: The developmental origins of sarcopenia. *J Nutr Health Aging* 12:427-432, 2008
- Saylor PJ, Smith MR: Metabolic complications of androgen deprivation therapy for prostate cancer. *J Urol* 181:1998-2006; discussion 2007-2008, 2009
- Zamboni M, Mazzali G, Fantin F, et al: Sarcopenic obesity: A new category of obesity in the elderly. *Nutr Metab Cardiovasc Dis* 18:388-395, 2008
- Cederholm TE, Bauer JM, Boirie Y, et al: Toward a definition of sarcopenia. *Clin Geriatr Med* 27:341-353, 2011
- Sattler F, Bhasin S, He J, et al: Testosterone threshold levels and lean tissue mass targets needed to enhance skeletal muscle strength and function: The HORMA trial. *J Gerontol A Biol Sci Med Sci* 66:122-129, 2011
- Vermeulen A, Goemaere S, Kaufman JM: Testosterone, body composition and aging. *J Endocrinol Invest* 22:110-116, 1999
- Snyder PJ, Peachey H, Berlin JA, et al: Effects of testosterone replacement in hypogonadal men. *J Clin Endocrinol Metab* 85:2670-2677, 2000
- Bhasin S, Storer TW, Javanbakht M, et al: Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. *JAMA* 283:763-770, 2000
- Grinspoon S, Corcoran C, Stanley T, et al: Effects of hypogonadism and testosterone administration on depression indices in HIV-infected men. *J Clin Endocrinol Metab* 85:60-65, 2000
- Reid IR, Wattie DJ, Evans MC, et al: Testosterone therapy in glucocorticoid-treated men. *Arch Intern Med* 156:1173-1177, 1996
- Smith MR, Finkelstein JS, McGovern FJ, et al: Changes in body composition during androgen deprivation therapy for prostate cancer. *J Clin Endocrinol Metab* 87:599-603, 2002
- Smith MR: Changes in fat and lean body mass during androgen-deprivation therapy for prostate cancer. *Urology* 63:742-745, 2004
- Chen Z, Wang Z, Lohman T, et al: Dual-energy X-ray absorptiometry is a valid tool for assessing skeletal muscle mass in older women. *J Nutr* 137:2775-2780, 2007
- Visser M, Fuerst T, Lang T, et al: Validity of fan-beam dual-energy X-ray absorptiometry for measuring fat-free mass and leg muscle mass: Health, Aging, and Body Composition Study—Dual-Energy X-ray Absorptiometry and Body Composition Working Group. *J Appl Physiol* 87:1513-1520, 1999

19. Smith MR, Egerdie B, Hernández Toriz N, et al: Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med* 361:745-755, 2009
20. Longford NT: *Random Coefficient Models*. New York, NY, Oxford University Press, 1993
21. Tayek JA, Heber D, Byerley LO, et al: Nutritional and metabolic effects of gonadotropin-releasing hormone agonist treatment for prostate cancer. *Metabolism* 39:1314-1319, 1990
22. Berruti A, Dogliotti L, Terrone C, et al: Changes in bone mineral density, lean body mass and fat content as measured by dual energy x-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. *J Urol* 167:2361-2367, 2002; discussion 2367
23. van Londen GJ, Levy ME, Perera S, et al: Body composition changes during androgen deprivation therapy for prostate cancer: A 2-year prospective study. *Crit Rev Oncol Hematol* 68:172-177, 2008
24. Herr HW, O'Sullivan M: Quality of life of asymptomatic men with nonmetastatic prostate cancer on androgen deprivation therapy. *J Urol* 163:1743-1746, 2000
25. Potosky AL, Knopf K, Clegg LX, et al: Quality-of-life outcomes after primary androgen deprivation therapy: Results from the Prostate Cancer Outcomes Study. *J Clin Oncol* 19:3750-3757, 2001
26. Stone P, Hardy J, Huddart R, et al: Fatigue in patients with prostate cancer receiving hormone therapy. *Eur J Cancer* 36:1134-1141, 2000
27. Alibhai SM, Breunis H, Timilshina N, et al: Impact of androgen-deprivation therapy on physical function and quality of life in men with nonmetastatic prostate cancer. *J Clin Oncol* 28:5038-5045, 2010
28. Shahinian VB, Kuo YF, Freeman JL, et al: Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med* 352:154-164, 2005
29. Smith MR, Lee WC, Brandman J, et al: Gonadotropin-releasing hormone agonists and fracture risk: A claims-based cohort study of men with nonmetastatic prostate cancer. *J Clin Oncol* 23:7897-7903, 2005
30. Diamond T, Campbell J, Bryant C, et al: The effect of combined androgen blockade on bone turnover and bone mineral densities in men treated for prostate carcinoma: Longitudinal evaluation and response to intermittent cyclic etidronate therapy. *Cancer* 83:1561-1566, 1998
31. Eriksson S, Eriksson A, Stege R, et al: Bone mineral density in patients with prostatic cancer treated with orchidectomy and with estrogens. *Calcif Tissue Int* 57:97-99, 1995
32. Maillefert JF, Sibilia J, Michel F, et al: Bone mineral density in men treated with synthetic gonadotropin-releasing hormone agonists for prostatic carcinoma. *J Urol* 161:1219-1222, 1999
33. Smith MR, McGovern FJ, Zietman AL, et al: Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. *N Engl J Med* 345:948-955, 2001
34. Fried LP, Tangen CM, Walston J, et al: Frailty in older adults: Evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 56:M146-M156, 2001
35. Greenspan SL, Coates P, Sereika SM, et al: Bone loss after initiation of androgen deprivation therapy in patients with prostate cancer. *J Clin Endocrinol Metab* 90:6410-6417, 2005
36. Buford TW, Anton SD, Judge AR, et al: Models of accelerated sarcopenia: Critical pieces for solving the puzzle of age-related muscle atrophy. *Ageing Res Rev* 9:369-383, 2010
37. Segal RJ, Reid RD, Courneya KS, et al: Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *J Clin Oncol* 21:1653-1659, 2003
38. Galvão DA, Taaffe DR, Spry N, et al: Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: A randomized controlled trial. *J Clin Oncol* 28:340-347, 2010
39. Segal RJ, Reid RD, Courneya KS, et al: Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. *J Clin Oncol* 27:344-351, 2009