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Identification of risk factors for toxicity in patients with hormone receptor-positive advanced breast cancer treated with bevacizumab plus letrozole: A CALGB 40503 (Alliance) correlative study.

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Abstract

Background: In hormone receptor-positive advanced breast cancer, a progression-free survival benefit was reported with addition of bevacizumab to first-line letrozole. However, increased toxicity was observed. We hypothesized that functional age measures could be used to identify

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Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent: Each participant signed an IRB-approved, protocol-specific informed consent document in accordance with federal and institutional guidelines.

Data Availability: The analyzed datasets are available from the corresponding author upon reasonable request.

patients at risk for toxicity while receiving letrozole plus bevacizumab for hormone receptor-positive advanced breast cancer.

Methods: CALGB 40503 was a phase III trial that enrolled patients with hormone receptor-positive advanced breast cancer randomized to letrozole with or without bevacizumab. Patients randomized to bevacizumab were approached to complete a validated assessment tool evaluating physical function, comorbidity, cognition, psychological state, social support, and nutritional status. The relationship between pretreatment assessment measures and the incidence of grade ≥3 (National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0) adverse events was determined.

Results: One hundred thirteen (58%) of 195 patients treated with letrozole plus bevacizumab completed the pretreatment assessment questionnaire. One patient was excluded due to missing adverse event data. The median age of patients was 56. Frequently reported grade ≥3 adverse events were hypertension (26%), pain (20%), and proteinuria (7%). Two hemorrhagic events (one grade 5) and 1 thrombosis event occurred. Age ≥65 years ($p<0.01$), decreased vision ($p=0.04$), and poorer pretreatment physical function measures ($p<0.05$) were found on univariate analysis to be significantly associated with increased incidence of grade ≥3 adverse events. Upon multivariate analysis, age ≥65 years ($p=0.01$) and decreased vision ($p=0.04$) remained significant. Univariable and multivariable logistic regression models demonstrated associations between age, vision, the ability to walk up flights of stairs, and grade ≥3 adverse events.

Conclusions: Age (≥65 years), decreased vision, and impairments in physical function correlated with increased incidence of toxicity in patients receiving first-line letrozole plus bevacizumab. When evaluating therapy likely to increase toxicity, functional assessment measures can identify patients at increased risk for side effects who may benefit from closer monitoring.

Keywords

Breast Cancer; Bevacizumab; Risk Factors; Toxicity

Introduction:

Chronological age alone tells relatively little about an adult's overall functional age. Therefore, the use of pretreatment assessments consisting of validated measures that can capture domains such as functional status, comorbid medical conditions, cognition, psychological status, social functioning and support, and nutritional status, can help to better characterize the overall functional age of an individual [1]. In addition, assessment of these domains has been reported to predict the risk of morbidity and mortality in patients with cancer undergoing systemic therapy [2–9]. This is particularly important because the findings from these assessment measures could be used to identify risk factors for treatment toxicity beyond traditional risk factors such as chronologic age.

Bevacizumab is a recombinant humanized monoclonal antibody against vascular endothelial growth factor receptor (VEGFR) that has been hypothesized to delay the emergence of resistance to endocrine therapy in patients with advanced breast cancer [10]. In the multicenter, phase III clinical trial, Cancer and Leukemia Group B (CALGB) 40503, a progression-free survival benefit was reported in patients with hormone receptor-positive

advanced breast cancer treated with first-line combination bevacizumab and letrozole compared to letrozole alone [11]. However, an increase in bevacizumab-related toxicity, such as hypertension and proteinuria, was also reported with combination therapy and one (0.6%) treatment-related death due to central nervous system (CNS) hemorrhage occurred [11]. Similarly, in the phase III, multicenter letrozole/fulvestrant and avastin (LEA) trial evaluating the addition of bevacizumab to endocrine therapy as first-line treatment for advanced breast cancer, eight (4.2%) treatment-related deaths were reported in the bevacizumab plus endocrine therapy treatment arm [12]. Six of the eight deaths were due to cardiovascular events and six of the eight deaths occurred in patients ≥70 years of age [12]. Based on pooled data from several prior randomized clinical trials investigating the role of bevacizumab combined with chemotherapy, a prior history of arterial thromboembolic events and older age were reported as significant risk factors for toxicity [13]. However, the identification of risk factors for toxicity to bevacizumab treatment combined with endocrine therapy in patients with advanced breast cancer has not been fully investigated.

The objective of the current study was to identify whether pre-treatment factors other than chronological age (i.e., functional status and comorbidity) may predict the risk of grade 3 or higher toxicity in patients with advanced, hormone receptor-positive breast cancer enrolled on CALGB/Alliance 40503 receiving treatment with letrozole plus bevacizumab. In addition, an exploratory analysis was performed to identify whether other factors (cognition, psychological state, social support, or nutritional status) either individually or in combination could be used to predict the risk of grade 3 or higher toxicity. Factors to be studied included cognition, pyshcological state, social support, and nutiritonal status as prior studies have demonstrated the ability of these domains to identify the risk of side effects to cancer therapy [14–31].

Patients and Methods:

Patient population

From May 2008 until November 2011, 350 patients were enrolled in the phase III multicenter CALGB 40503 clinical trial evaluating the role of letrozole with or without bevacizumab as first-line therapy for the treatment of postmenopausal women with hormone receptor-positive, locally advanced or metastatic breast cancer [11]. CALGB is now a part of the Alliance for Clinical Trials in Oncology. Eligible patients were postmenopausal (or receiving ovarian suppression with a luteinizing hormone-releasing hormone agonist) women age ≥18 years with hormone receptor-positive (defined as expressing estrogen and/or progesterone receptor ≥1% cells), locally advanced, unresectable or metastatic breast cancer. Patients were required to have Eastern Cooperative Oncology Group performance status ≤1 with adequate bone marrow, hepatic, and renal function, including urine protein dipstick grade of ≤1+ or urine protein: creatinine (UPC) ratio of <1. Key exclusion criteria for study participants included ongoing uncontrolled hypertension (blood pressure: systolic >150 mmHg and/or diastolic >90 mmHg); New York Heart Association grade ≥2 congestive heart failure; history of hypertensive crisis; history (within past 6 months) of myocardial infarction, unstable angina, stroke, abdominal fistula or abscess, or significant bleeding episode; or history of GI perforation within 12 months. The study was approved by the

institutional review board at each participating institution. All participating patients completed the informed consent process.

Study schema and pretreatment patient assessment measures

Patients enrolled onto this clinical trial received treatment consisting of letrozole with or without bevacizumab. Letrozole was administered at 2.5 mg orally once per day and bevacizumab was administered at 15 mg/kg intravenously once every 3 weeks until disease progression or unacceptable toxicity. No dose reductions were permitted for letrozole or bevacizumab. Letrozole was held for grade >3 hepatic dysfunction. Bevacizumab was held for blood pressure >160/100 mmHg, urine protein ≥2 g per 24 hours or UPC ≥2, grade 3 or 4 venous thromboembolic events and for patients requiring surgery. Bevacizumab was permanently discontinued for grade ≥4 hypertension, nephrotic syndrome, reversible posterior leukoencephalopathy syndrome; grade ≥3 hemorrhage/congestive heart failure; grade ≥2 arterial thromboembolic events; any grade gastrointestinal (GI) perforation, leak, or fistula; for wound dehiscence requiring intervention; or grade ≥3 or 4 unspecified bevacizumab-related adverse events.

As part of an amendment to the clinical trial, a correlative study was added in which patients in the letrozole plus bevacizumab treatment arm of the study were asked to complete a pretreatment patient assessment questionnaire. The primary objective of this correlative study was to identify factors other than chronological age that predict the risk of grade 3, 4, or 5 toxicity in patients receiving letrozole plus bevacizumab (CONSORT diagram, Figure 1), including validated measures of functional status and comorbidity: Older Americans Resources and Services Scale (OARS)—Instrumental Activities of Daily Living [32], Medical Outcomes Study Physical Function [33], Karnofsky Performance Status Rated Health Care Professional [14], Timed “Up and Go” [15], and OARS Physical Health Section [32]. The secondary objective was to perform an exploratory analysis of whether other factors included in the patient assessments either individually or in combination predicted the risk of grade 3, 4, or 5 toxicity. These other factors included validated measures of cognition (the Blessed Orientation-Memory-Concentration [BOMC] Test [16]), psychological status [6,27], social functioning [33] and support [34], and nutritional status [30].

Patients were followed during treatment with combination bevacizumab and letrozole. Grade ≥3 AEs as defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 were reported. The relationship between pretreatment patient assessment measures and the incidence of AEs was determined.

Statistical analysis

Descriptive analyses were performed to summarize patient, tumor, and treatment characteristics and pretreatment assessment results. The incidence of specific categories of NCI CTCAE grade 3, 4, or 5 toxicities were calculated. Chi square or Fisher’s exact tests [35,36], as appropriate, were used to compare baseline characteristics and incidence of AEs between patients completing the baseline assessment questionnaire versus patients with no baseline assessment questionnaire. Chi square or Fisher’s exact tests (as appropriate)

[35,36], and univariable logistic regression were used to examine univariable association between the presence of grade ≥3 AEs and pretreatment assessment variables. Multivariable logistic regression was performed to determine the association of each variable in the presence of other variables. Results of the logistic models were summarized with odds radios (ORs), corresponding 95% confidence intervals (CIs), and c-statistic. All tests were two-sided, and p-values less than 0.05 were considered to be statistically significant. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center. Analyses were performed using SAS version 9.3 (SAS Institute INC., Cary, NC). Data were frozen on April 15, 2015. Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson following Alliance policies.

Results:

Patient characteristics

This substudy cohort consisted of 195 patients with locally advanced or metastatic, hormone receptor-positive, breast cancer treated with first-line combination letrozole and bevacizumab. Of the 195 patients, 112 (57%) patients completed the pretreatment patient assessment questionnaire and had adverse event toxicity data available for analysis. One additional patient completed the pretreatment patient assessment questionnaire but did not have adverse event toxicity data available and was therefore excluded from these analyses. The CONSORT diagram for this study is found in Figure 1. There were no significant differences between patients completing the pretreatment assessment questionnaire compared to those who did not in terms of age, race, performance status, hormone receptor status, and incidence of grade ≥3 adverse events (data not shown). The baseline patient characteristics of the 112 patients completing the pretreatment assessment questionnaire are shown in Tables 1 and 2. The median age of participants was 56 years (range: 25–85) and 22% of patients were age 65 years or older. Sixty-three (56%) patients reported a Karnofsky performance status of 100. Seventy-six (68%) patients reported having no comorbid medical conditions and being completely independent in their instrumental activities of daily living. The median activities of daily living score (Medical Outcomes Study physical functioning) was 90 (range: 5–100). Ninety-nine (88%) patients had excellent or good vision. Only 1 patient had an abnormal BOMC Cognition Score and no patients reported greater than 5% weight loss in the past 6 months.

Factors associated with treatment toxicity to combination letrozole and bevacizumab

As previously reported with the main results of CALGB/Alliance 40503[11], treatment with bevacizumab in addition to letrozole was associated with an increase in grade ≥3 toxicities compared to treatment with letrozole alone. In the current substudy of 112 patients who completed the pretreatment assessment questionnaire and were treated with combination letrozole and bevacizumab, treatment-related grade 3 or grade 4 adverse events occurred in 55 (49%) and 5 (4%) patients, respectively. One treatment-related death also occurred as a result of CNS hemorrhage. Notable grade ≥3 adverse events occurring in this study population likely related to bevacizumab treatment include hypertension (26%), pain (20%), proteinuria (7%), syncope (3%), cardiac ischemia (1%), hemorrhage (2%), and thrombosis (1%). Additional grade ≥3 adverse events are shown in Table 3.

In order to identify potential risk factors for toxicity to combination treatment with letrozole and bevacizumab, univariate analyses were conducted to examine the association between patient characteristics, pretreatment assessment variables, and any grade 3–5 toxicity (See Table 4). Age ($p<0.01$), decreased vision ($p=0.04$), lower instrumental activities of daily living scores (OARS IADL) ($p=0.02$), and lower activities of daily living scores (MOS physical functioning) ($p=0.02$) were associated with grade ≥3 toxicity to treatment with letrozole and bevacizumab. In addition, specific measures such as needing help getting to places out of walking distance ($p=0.02$), limitation in climbing one ($p=0.04$) or multiple ($p=0.02$) flights of stairs, and limitation with walking more than one mile ($p=0.04$) were also associated with grade ≥3 toxicity. In multivariate analysis, factors that remained associated with grade 3 or more toxicity included age ≥65 years ($p=0.01$) and decreased vision ($p=0.04$).

The associations between various model variables were also performed to assess the relationship between different pretreatment assessment measures of interest with age (See Table 5). Univariable models were then developed and limitations in climbing flights of stairs (OR 3.14, c-statistic=0.635) and walking more than one mile (OR 2.67, c-statistic 0.617) were found to be more strongly associated with toxicity than age (OR 3.93, c-statistic 0.597) as a risk factor for development of grade ≥3 adverse events to treatment with letrozole and bevacizumab (See Table 6). Multivariable models with age were then performed and the addition of decreased vision and functional variables such as needing help getting to places out of walking distance, limitation in climbing flights of stairs, and limitation in walking more than one mile, all improved the model's ability to predict grade ≥3 adverse event risk to treatment with letrozole and bevacizumab compared to age alone (See Table 7).

Discussion:

The current study identified patient characteristics that may predict for grade 3 or higher toxicity in postmenopausal patients with advanced, hormone receptor-positive breast cancer receiving first-line treatment with letrozole plus bevacizumab. In addition to chronologic age alone, this study demonstrated that decreased vision and decreased physical functioning measures such as lower OARS IADL or lower MOS physical functioning scores were associated with increased grade ≥3 toxicity to treatment with letrozole and bevacizumab on univariate analysis. On multivariate analysis, only increased age and decreased vision remained associated with grade ≥3 toxicity to treatment with letrozole and bevacizumab. However, on multivariable modeling, the addition of functional variables to age was able to improve the model's ability to predict grade ≥3 adverse event risk to treatment with letrozole and bevacizumab.

Prior research focused on identifying potential risk factors for increased toxicity to treatment with bevacizumab has been limited. In patients with various malignancies treated with chemotherapy plus bevacizumab, reported risk factors for bevacizumab treatment-related toxicity included older age, history of uncontrolled hypertension, significant cardiac disease, a history of bleeding, and a history of arterial thrombotic events [37–41]. However, chronologic age alone is often insufficient to fully describe the overall potential

vulnerabilities of an individual receiving cancer therapy. The use of comprehensive assessments that include an evaluation of functional status, comorbid medical conditions, cognitive function, nutritional status, social support and psychological state can help to identify additional risk factors other than chronological age that may predict for toxicity to cancer treatments. For example, Repetto et al. demonstrated that use of comprehensive assessments can uncover problems not detected by the routine history and physical examination performed by a treating physician at time of an initial consultation or follow-up care [42]. Furthermore, the use of comprehensive assessments has also been shown to predict toxicity to chemotherapy [43,44] and survival [2].

Mohile et al. performed an analysis of the relationship between a similar pretreatment assessment questionnaire as used in the current study (consisting of domains measuring functional status, comorbid medical conditions, cognition, psychological status, social functioning and support, and nutritional status) and grade 3–5 toxicity specifically in older adults ≥65 years of age with advanced stage colorectal cancer and non-small cell lung cancer treated with chemotherapy and bevacizumab [45]. Interestingly, age was not associated with toxicity in that study and none of the additional pretreatment assessment variables were found to be specifically associated with grade 3–5 toxicity in bivariate and multivariate analysis [45]. In contrast to prior studies and the Mohile et al. study, our study focused on patients with advanced breast cancer undergoing treatment with letrozole plus bevacizumab and found that in addition to increased chronologic age, pretreatment assessment measures such as decreased vision and limitation in physical function measures were associated with increased risk of grade ≥3 toxicity. Decreased vision in this study was self-reported. Other studies based on self-reported measures found that decreased vision is likely to be associated with other comorbidities including difficulty breathing, depression, diabetes, and heart problems [46–48]. Furthermore, in a cross-sectional study, visual impairment was shown to be characterized by more medical comorbidities in comparison to non-visually impaired controls and these differences were not accounted for by age alone [49]. Therefore, it is likely that self-reported decreased vision is associated with additional medical comorbidities that increase the susceptibility for treatment-related toxicity. To our knowledge, our study is unique in that it is the first study to identify potential risk factors beyond traditional variables such as chronological age alone in predicting toxicity for patients with advanced breast cancer receiving first-line letrozole plus bevacizumab.

There were several limitations to this study. First, this was a relatively young, selective group of patients with a median age of 56, and only 25 (22%) patients were age 65 years or older. In addition, due to trial eligibility criteria, most patients had a good performance status, with over 87% of patients having a KPS ≥90. Furthermore, 68% of patients did not have any comorbid medical conditions. Therefore, the use of a pretreatment assessment questionnaire typically aimed at identifying vulnerabilities in a more diverse older adult population may not have been able to differentiate the subtle differences in patient characteristics in this relatively young, healthy, homogeneous study population. The incidence of grade ≥3 toxicity in patients treated with combination letrozole plus bevacizumab on CALGB/Alliance 40503 was also modest, consisting mainly of hypertension and proteinuria. Only 1 episode of hemorrhage, 1 episode of thrombosis, and 1 treatment-related death occurred. This is in sharp contrast to the 8 treatment-related deaths

that occurred in the LEA study, which consisted of an older patient population with a median age of 64 [including 89 (47%) patients ≥65 years] treated with endocrine therapy plus bevacizumab [12]. Interestingly, 6 of the 8 patients who died in the LEA study were older adults with several comorbidities [12]. Therefore, application of a pretreatment assessment questionnaire in a more vulnerable older adult patient population such as the LEA study could potentially have been able to identify possible additional risk factors of toxicity to combination treatment with endocrine therapy and bevacizumab. Finally, in the current study many of the pretreatment assessment variables were found to be strongly associated with age, causing difficulty in building a comprehensive multivariable model. This was an exploratory analysis and larger studies in other tumor types evaluating the role of pretreatment patient assessment measures to identify risk factors for toxicity in patients undergoing treatment with combination therapy with bevacizumab will be needed in the future.

Despite these limitations, our current study further adds to the body of literature by identifying additional potential risk factors of toxicity for patients undergoing treatment with bevacizumab, which had not been previously well described. The current study demonstrated through both univariable and multivariable models that the addition of functional variables to age improved the model's ability to predict grade ≥3 adverse event risk to treatment with letrozole and bevacizumab compared to age alone even in this relatively young, healthy, homogenous study population. This suggests that incorporation of functional age assessment measures can be used to identify potential patients at serious risk of toxicity and should potentially be considered for inclusion in future studies.

In conclusion, older age, decreased vision, and impairment in physical function correlate with increased incidence of toxicity in postmenopausal, advanced, hormone receptor-positive, breast cancer patients receiving first-line treatment with letrozole plus bevacizumab. When evaluating therapy likely to increase toxicity, functional assessment measures can be used to further identify patients at increased risk for side effects who may benefit from closer monitoring.

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Compliance with Ethical Standards

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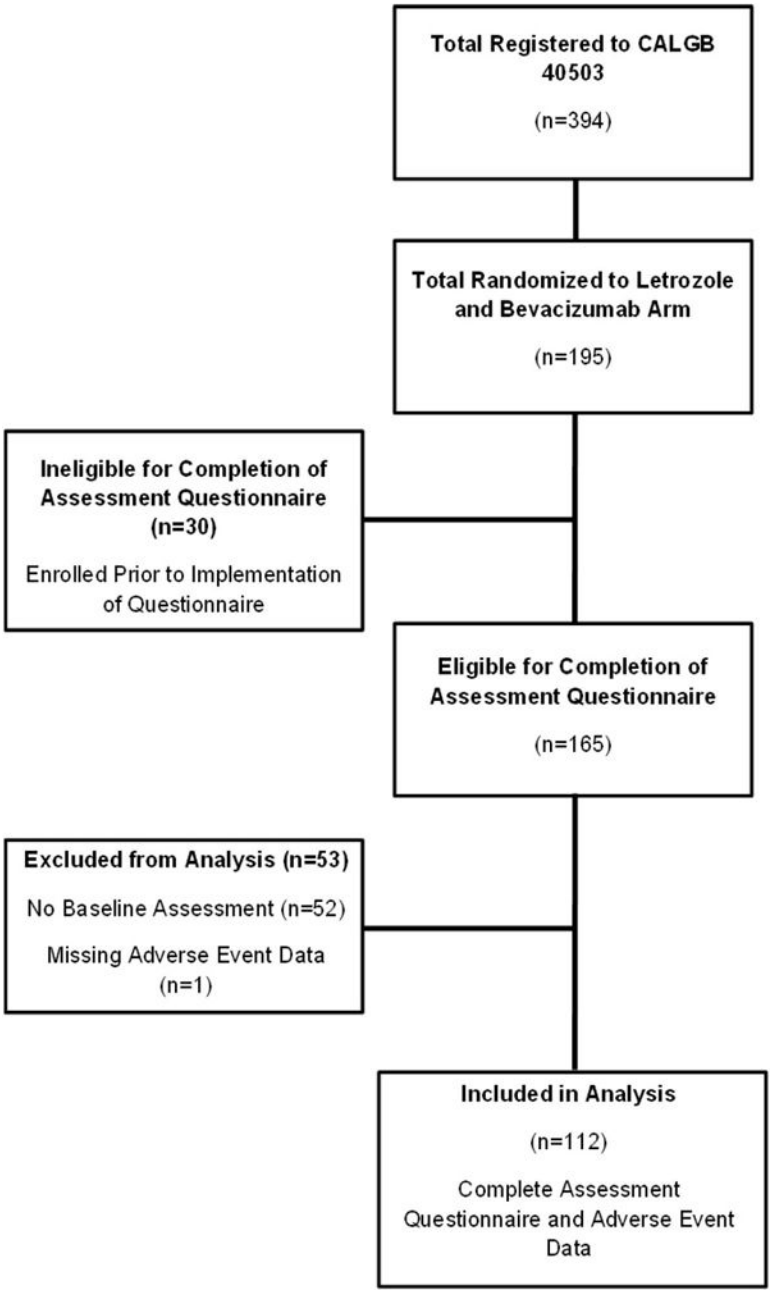

Fig. 1:
CONSORT Diagram for Letrozole and Bevacizumab Arm of CALGB 40503

Table 1

Characteristics of Patients Treated with Bevacizumab Plus Letrozole

Characteristic		Patients Treated with Bevacizumab Plus Letrozole (n=112)
Median Age – year (range)		56 (25–85)
Age- no. (%)	<65	87 (77.7%)
	≥65	25 (22.3%)
Race- no. (%)	White	103 (92.0%)
	Other	6 (5.4%)
	Unknown	3 (2.7%)
Ethnicity- no. (%)	Hispanic or Latino	1 (0.9%)
	Not Hispanic or Latino	92 (82.1%)
	Unknown/Not reported	19 (17.0%)
Karnofsky Performance Status- no. (%)	100	63 (56.3%)
	90	35 (31.3%)
	80	10 (8.9%)
	70	4 (3.6%)
Hormone Receptor Status- no. (%)	ER+	112 (100.0%)
	PR+	89 (79.5%)
	HER2+	2 (1.8%)

Table 2

Assessment Variables Reported in Pretreatment Questionnaire

Pretreatment assessment Variable		Patients Treated with Bevacizumab Plus Letrozole (n=112)		
		# of Patients (%)	Mean ± Standard Deviation	Median (Range)
OARS IADL[a]	Completely Independent	76 (67.9%)	13.2 ± 1.5	32 (6–32)
OARS Comorbidity	0 1 2 or more	76 (67.9%) 19 (17.0%) 17 (15.2%)		
MOS[b]	Activities of Daily Living		76.8 ± 26.5	90 (5–100)
	Social Activity		47.9 ± 9.6	50 (25–75)
Timed Up and Go	Seconds		13.0 ± 9.2	10 (2–60)
Falls in past 6 months	None 1 or more Unavailable	88 (78.6%) 22 (19.6%) 2 (1.8%)		
Hearing	Excellent/Good Fair/Poor/Deaf Unavailable	97 (86.6%) 14 (12.5%) 1 (0.9%)		
Vision	Excellent/Good Fair/Poor/Blind Unavailable	99 (88.4%) 12 (10.7%) 1 (0.9%)		
MHI[c]	Depression and Anxiety		78.3 ± 33.0	81 (21–100)
BOMC[d] Cognition Score	<11 ≥11 Unavailable	108 (96.4%) 1 (0.9%) 3 (2.7%)		
BMI (kg/m²)[e]	<22 ≥30 Unavailable	17 (15.2%) 46 (41.1%) 49 (43.7%)		
Weight Loss	Greater than 5% in the last 6 months	0 (0.0%)		

a: Older Americans Resources and Services Scale—Instrumental Activities of Daily Living

b: Medical Outcomes Study

c: Mental Health Inventory

d: Blessed Orientation-Memory-Concentration

e: Body Mass Index (kilogram/meter squared)

Table 3

Frequent and Notable Grade ≥3 Adverse Events

Type of Adverse Event	Incidence (%)		
	Grade 3	Grade 4	Grade 5
Hypertension	27 (24%)	2 (2%)	0 (0%)
Pain	22 (20%)	0 (0%)	0 (0%)
Proteinuria	8 (7%)	0 (0%)	0 (0%)
Nausea	5 (4%)	0 (0%)	0 (0%)
Syncope	3 (3%)	0 (0%)	0 (0%)
Cardiac Ischemia	1 (1%)	0 (0%)	0 (0%)
Hemorrhage	1 (1%)	0 (0%)	1 (1%)
Thrombosis	1 (1%)	0 (0%)	0 (0%)
Hypocalcemia	0 (0%)	1 (1%)	0 (0%)
Neutropenia	0 (0%)	1 (1%)	0 (0%)
Other Neurologic Event	0 (0%)	1 (1%)	0 (0%)

Table 4

Significant Baseline Risk Factors for Grade ≥3 Toxicity: Univariable Analysis

Risk Factors	p-value
Age	<0.01
Decreased Vision	0.04
Lower Instrumental Activities of Daily Living Scores (OARS IADL[a])	0.02
Lower Activities of Daily Living Scores (MOS[b])	0.02
Needing help getting to places out of walking distance *	0.02
Limitation in climbing flights of stairs **	0.02
Limitation climbing one flight of stairs **	0.04
Limitation walking more than one mile **	0.04

a: Older Americans Resources and Services Scale—Instrumental Activities of Daily Living

b: Medical Outcomes Study

**:* Individual item of OARS IADL

***:* Individual Items of MOS

Table 5

Association Between Model Variables of Interest

	Age	Vision	Needing help getting to places out of walking distance[a]	Limitation in climbing several flights of stairs[b]	Needing help to take medications[a]	Limitation in walking more than one mile[b]
Age	-	0.82	<0.01	0.02	0.05	<0.01
Vision		-	0.03	<0.01	0.60	<0.01
Needing help getting to places out of walking distance[a]			-	<0.01	<0.01	<0.01
Limitation in climbing several flights of stairs[b]				-	0.02	<0.01
Needing help to take medication[a]					-	0.06
Limitation in walking more than one mile[b]						-

a: Question from Older Americans Resources and Services Scale—Instrumental Activities of Daily Living (OARS-IADL)

b: Questions from Medical Outcomes Study

Table 6

Univariable Models

Risk Factors for Grade ≥3 Toxicity	OR (95% CI)	p-value	c-statistic
Age (≥65)	3.93 (1.24–9.31)	0.02	0.597
Vision (fair or worse)	4.70 (0.98–22.58)	0.05	0.562
Needing help getting to places out of walking distance[a]	5.28 (1.11–25.06)	0.04	0.570
Limitation in climbing several flights of stairs[b]	3.32 (1.41–6.99)	< 0.01	0.635
Limitation in walking more than one mile[b]	2.67 (1.21–5.87)	0.01	0.617

a: Question from Older Americans Resources and Services Scale—Instrumental Activities of Daily Living (OARS-IADL)

b: Questions from Medical Outcomes Study

Table 7

Multivariable Models with Age

Risk Factors for Grade ≥3 Toxicity	OR (95% CI)	p-value	c-statistic
Age (≥65) Vision (fair or worse)	3.62 (1.30 – 10.09) 5.36 (1.10 – 26.29)	0.01 0.04	0.646
Age (≥65) Needing help getting to places out of walking distance[a]	2.71 (0.96 – 7.69) 4.00 (0.81 – 19.74)	0.06 0.09	0.632
Age (≥65) Limitation in climbing flights of stairs[b]	2.88 (1.02 – 8.16) 2.80 (1.24 – 6.35)	0.05 0.01	0.670
Age (≥65) Limitation in walking more than one mile[b]	2.82 (1.00 – 7.97) 2.28 (1.01 – 5.32)	0.05 0.05	0.659

a: Instrumental Activities of Daily Living

b: Medical Outcomes Study