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Safety and Efficacy of First-Line Bevacizumab Plus Chemotherapy in Elderly Patients with Advanced or Recurrent Nonsquamous Non-small Cell Lung Cancer

Safety of Avastin in Lung trial (MO19390)

Janessa Laskin, MD, FRCPC,* Lucio Crinò, MD,† Enriqueta Felip, MD,‡ Fabio Franke, MD,§ Vera Gorbunova, MD,|| Harry Groen, MD, PhD,¶ Guo-liang Jiang, MD, FACR,# Martin Reck, MD, PhD,** and Claus-Peter Schneider, MD††

Introduction: Safety of Avastin in Lung (MO19390) was an international, open-label, single-arm study, which assessed the safety and efficacy of first-line bevacizumab (Avastin®) in combination with standard chemotherapy in patients ($n = 2212$) with advanced or recurrent non-small cell lung cancer (NSCLC). A preplanned subgroup analysis was performed to examine these outcomes in elderly patients older than 65 years.

Methods: Eligible patients with nonsquamous NSCLC received up to six cycles of bevacizumab (7.5 or 15 mg/kg) plus any standard of care chemotherapy. Patients who did not experience disease progression after induction therapy continued bevacizumab therapy until disease progression or unacceptable toxicity. The primary end point was safety; secondary end points included time to disease progression (TTP) and overall survival (OS).

Results: Data were evaluated for 623 patients older than 65 years (mean age 70.6). The majority were Whites (86.2%) with stage IV disease (79.7%) and had adenocarcinoma (83.5%). The incidence of adverse events (AEs) of special interest was similar for elderly and younger patients (any grade bleeding 38.2% versus 38.3%; any

grade hypertension 33.1% versus 30.6%; any grade proteinuria 33.4% versus 29.3%). Most AEs were grade less than or equal to 2. Serious AEs were reported in 45.3 and 34.7% of elderly and younger patients, respectively. Median OS was similar in elderly and younger patients (14.6 months in both age groups), as were TTP (8.2 versus 7.6 months), response rate (49.3% versus 52.4%), and disease control rate (89.3% versus 88.4%). Similar results were seen in a post hoc comparison of the older than 70 years and 70 years or younger subgroups: TTP was 8.6 months versus 7.7 months, respectively; OS was 14.6 months in both subgroups; response rate was 49% and 52%, respectively; incidence of AEs of special interest was comparable.

Conclusion: Patients older than 65 years with nonsquamous NSCLC derive a similar clinical benefit from first-line bevacizumab-based therapy as their younger counterparts and do not experience increased toxicity.

Key Words: Bevacizumab, Vascular endothelial growth factor, Safety, Elderly, Non-small cell lung cancer (NSCLC).

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Platinum doublet chemotherapy has been established as standard first-line therapy for patients with advanced non-small cell lung cancer (NSCLC) on the basis of a meta-analysis and multiple phase III clinical trials,¹ demonstrating that platinum-containing chemotherapy regimens are superior to best supportive care and are associated with median survivals of 8 to 11 months and 1-year survivals of 30% to 45%.^{1–7} However, although it is estimated that about 50% of newly diagnosed cases of NSCLC occur in patients older than 65 years,⁸ there has been a historical reluctance to use platinum compounds in elderly patients because of concerns about toxicity and tolerability.^{9–11}

Treatment restrictions for elderly patients are often based on the assumption that accumulated comorbidities will have led to physiological changes that compromise drug pharmacokinetics and metabolism. Consequently, elderly patients may receive less chemotherapy and are less likely to be enrolled in clinical trials. However, aging is a highly individ-

ual process and the changes that occur cannot be predicted on the basis of chronological age alone. The Elderly Lung Cancer Vinorelbine Italian Study¹² and subsequent Multi-center Italian Lung Cancer in the Elderly Study¹³ were the first trials to show the benefits of single-agent gemcitabine or vinorelbine over best supportive care, in the elderly age group. Although until recently no prospective phase III trials investigating platinum-based chemotherapy had been conducted specifically involving elderly patients, retrospective age-specific subgroup analyses of several phase III trials indicated that clinical outcome does not differ significantly between age groups.^{14–18} In 2010, Quoix et al.¹⁹ presented data from the first prospective, randomized phase III study in patients with NSCLC aged 70 to 89 years with Eastern Cooperative Oncology Group performance status (ECOG PS) 0 to 2. Paclitaxel-carboplatin doublet was shown to significantly extend survival compared with standard single-agent therapy while maintaining an acceptable side effect profile. Thus, there is substantial body of data indicating that chemotherapy provides meaningful clinical benefits in fit elderly patients with advanced NSCLC.

Bevacizumab is the first and only antivasculature endothelial growth factor therapy for the first-line treatment of nonsquamous NSCLC approved for use in North America (US Food and Drug Administration and Health Canada) and Europe (European Medicines Agency). The phase III ECOG 4599 study²⁰ demonstrated a 2-month difference in median survival with the addition of bevacizumab to carboplatin-paclitaxel (hazard ratio 0.79; $p = 0.003$), leading to its approval in the United States and the general acceptance of this regimen as the standard of care. Subsequently, the results of the Avastin in Lung (AVAIL) study of first-line bevacizumab with cisplatin plus gemcitabine demonstrated a significant improvement in progression-free survival (PFS); overall survival (OS) was numerically longer with the addition of bevacizumab although the difference was not statistically significant.^{21,22}

The phase IV Safety of Avastin in Lung (SAiL [MO19390]) study was conducted to determine the safety and efficacy of first-line bevacizumab combined with a range of standard chemotherapy regimens in a broad patient population.²³ Here, we report a preplanned analysis of the SAiL study undertaken to determine the safety profile and clinical benefits of this therapy in elderly patients with advanced or recurrent nonsquamous NSCLC. Elderly was defined as age older than 65 years, which has previously been reported in the oncology literature,²⁴ and is defined in the National Comprehensive Cancer Network Senior Adult Oncology guidelines as an accepted societal age cutoff for the definition of elderly.²⁵ Use of an older cutoff age, such as 70 years, is increasingly common, however, and an additional post hoc analysis was conducted using this cutoff.

PATIENTS AND METHODS

Study Design and Objectives

The SAiL study was a phase IV, open-label, multicenter, single-arm study conducted in a general patient population, including elderly patients, those receiving concomi-

tant medications, and those with ECOG PS 2. Known central nervous system (CNS) metastases were not allowed, but patients were not screened for subclinical CNS metastases before enrolment. The primary objective was to assess the safety profile of bevacizumab in combination with chemotherapy as first-line treatment of advanced or recurrent nonsquamous NSCLC. Secondary objectives included assessment of efficacy of these combinations as measured by time to disease progression (TTP) and OS and assessment of safety in patients who developed CNS metastases during and up to 6 months after the treatment period. Overall response rates (ORR) and disease control rates (DCR; ORR plus stable disease) were assessed according to the treating physicians' routine clinical practice. The study protocol did not specify an evaluation method or the frequency of assessment; this was done according to the local practice standard of care. No centralized independent assessment of response was done.

Patients

Full details of the inclusion and exclusion criteria have been published previously.²³ A total of 2212 patients were recruited between August 2006 and June 2008 from 40 countries across six continents. Eligible patients had histologically or cytologically documented, inoperable, locally advanced (stage IIIB with supraclavicular lymph node metastases or malignant pleural or pericardial effusion), metastatic (stage IV), or recurrent nonsquamous NSCLC.

Treatment

Patients received up to six cycles of bevacizumab (7.5 or 15 mg/kg on day 1 and then every 3 weeks) in combination with standard-of-care first-line chemotherapy (bevacizumab dose and chemotherapy regimen at investigators' discretion). The study protocol permitted the use of nonplatinum doublets and single-agent chemotherapy regimens if the center had experience with an established regimen, or for patients who were elderly or had an ECOG PS of 2. After a maximum of six cycles of chemotherapy plus bevacizumab, nonprogressing patients continued to receive bevacizumab therapy alone until disease progression or unacceptable toxicity.

Assessments

All reported serious adverse events (SAEs) and non-SAEs associated with bevacizumab or chemotherapy were used to assess the safety profile of the bevacizumab combinations. The incidence of adverse events (AEs) of special interest (AESIs) for bevacizumab, namely hypertension, proteinuria, wound-healing complications, gastrointestinal perforations, arterial and venous thromboembolic events, hemoptysis, CNS bleeding, other hemorrhages, and congestive heart failure, was also assessed. AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3. All AEs occurring up to 28 days after the last bevacizumab infusion were recorded. AESIs were reported up to 6 months after the last bevacizumab infusion, and SAEs associated with bevacizumab were reported for the duration of the study. Information on existing medical conditions other than NSCLC was also recorded, as

were concomitant medications at baseline. Disease response was determined according to standard clinical practice.

Statistical Analysis

The intention to treat (ITT) population ($n = 2212$) was the primary analysis population; it included all patients with at least one valid postbaseline tumor assessment. All demographics and safety and efficacy analyses were based on the ITT population. The data reported here are from preplanned analyses of safety and efficacy data recorded for patients older than 65 years or 65 years or younger, which is a widely accepted age cutoff point for the definition of elderly. The age cutoff of 65 years was selected for consistency with previous analyses of elderly patients with NSCLC.²⁶ In addition, as a practical consideration, using a higher age cutoff would result in a significant imbalance between the sizes of the elderly and nonelderly subgroups as only 266 (12.0%) patients were older than 70 years of age. All SAEs and AESIs (all occurrences irrespective of severity and relationship to bevacizumab) were summarized by incidence rates and 95% Pearson-Clopper confidence intervals (CIs).

RESULTS

Baseline Patient and Disease Characteristics

Out of the total 2212 patients in the ITT population, 623 were older than 65 years. The mean age of the ITT population was 58.8 years (standard deviation, 10.3; range, 24–86), while the mean age in the older than 65 years subgroup was 70.6 years (range 66–86 years). Within the older than 65 years population, most patients were Whites (86.2%), with stage IV disease (79.7%) and had adenocarcinoma (83.5%). Baseline patient and disease characteristics of elderly and younger patients are shown in Table 1. The elderly patient cohort included smaller proportions of current smokers than younger patients (16.9% versus 26.9%) and patients with a good performance status (ECOG PS 0: 31.6% versus 39.4%).

The most common comorbidity in elderly patients at baseline was hypertension, occurring in 39.6% of elderly versus 22.0% of younger patients. Concomitant medication at baseline was more frequent in elderly patients than younger patients (82.3% versus 69.9%); cardiovascular drugs were the most common concomitant medications (48.2% in elderly patients versus 25.1% in younger patients; Table 1), particularly ACE inhibitors (18.9% versus 8.2%, respectively). Among younger patients, the most common type of concomitant medication was analgesia (37.8% versus 34.7% in elderly patients), particularly opioids (20.5% versus 17.3% in elderly patients). Concomitant antiplatelet therapy was used in 11.4% of elderly and 5.2% of younger patients, and low-dose anticoagulant therapy in 5.5% of elderly and 3.1% of younger patients. Cisplatin doublet therapy was less frequently used in elderly patients than younger patients (29.7% versus 40.5%), but there was little difference in the use of carboplatin doublet therapy between elderly (54.4%) and younger (47.1%) patients.

Treatment Exposure

Median bevacizumab treatment duration was 17.3 and 22.4 weeks for elderly and younger patients, respectively. The median number of administered bevacizumab cycles was six in elderly patients and eight in younger patients. A greater proportion of younger patients received bevacizumab maintenance (57.8%), after four to six cycles of chemotherapy treatment, than elderly patients (46.2%; maintenance therapy comprises continued 3-weekly cycles of bevacizumab alone until disease progression or unacceptable toxicity). Median duration of chemotherapy treatment and median number of cycles was 12.1 weeks and four cycles for elderly patients, and 15.1 weeks and six cycles for younger patients. Table 2 summarizes the chemotherapy regimens and bevacizumab doses received by elderly and younger patients during the study.

Safety

SAEs were reported in 45.3% and 34.7% of elderly and younger patients, respectively, with neutropenia representing the most frequently documented SAE in both groups (4.5% in elderly patients and 3.5% in younger patients). Grade more than or equal to 3 febrile neutropenia was observed in 29 patients (1.8%) in the younger subgroup and 20 patients (3.2%) in the elderly subgroup.

AESIs were reported by 441 patients (70.8%) and 1085 patients (68.3%) in the elderly and younger patient subgroups, respectively. The majority of AESIs were classified as grade less than or equal to 2 in both age cohorts (Table 3), and the rate of grade more than or equal to 3 events was similar for both age groups (14.8% versus 14.1% for the elderly and younger patients, respectively). The most frequently reported AESIs were bleeding events (most commonly epistaxis), which were reported for 238 (38.2%) elderly patients and 608 (38.3%) younger patients. Pulmonary hemorrhage was reported in 52 (8.3%) elderly patients and in 134 (8.4%) younger patients. Hypertension events were recorded for 206 (33.1%) and 487 (30.6%) elderly and younger patients, respectively. The only other AESI reported in more than 5% of patients was proteinuria, and this occurred in 208 (33.4%) elderly patients and 465 (29.3%) younger patients.

AESIs were most frequently reported in association with carboplatin doublet chemotherapy in both elderly and younger patients (all grades 72.6 and 69.1%, respectively; grade more than or equal to 3, 18.6 and 17.2%, respectively), followed by nonplatinum doublet chemotherapy (all grades 57.1% versus 83.3%; grade more than or equal to 3 28.6% versus 16.7%), cisplatin doublet chemotherapy (all grades 71.4% versus 68.5%; grade more than or equal to 3 23.8% versus 21.4%), and monotherapy (all grades 70.4% versus 60.0%; grade more than or equal to 3 29.6% versus 26.7%). Bleeding events were the most frequently reported AESIs and were generally observed with similar frequency in elderly and younger patients in each of the chemotherapy categories (Tables 4 and 5).

AESIs necessitating treatment interruption or discontinuation are shown in Table 6. Wound-healing complications were the most common AESI requiring treatment interruption in both elderly and younger patients: 3 of 13 events (23.1%) and 5 of 18 events (27.8%) led to treatment interruption, respectively. Gastrointestinal perforation was the most frequent AESI requiring

TABLE 1. Summary of Patient Demographics and Baseline Characteristics

Parameter	Patients 65 yr and Younger (n = 1589)	Patients Older than 65 yr (n = 623)	ITT Population (n = 2212)
Mean age, yr (range)	54.2 (24–65)	70.6 (66–86)	58.8 (24–86)
Male (%)	59.0	62.8	60.1
Stage (%)			
IIIB	19.5	20.3	19.7
IV	80.5	79.7	80.3
ECOG PS (%)			
0	39.4	31.6	37.2
1	54.7	61.3	56.6
2	5.9	7.1	6.2
Smoking status (%)			
Never	29.6	32.1	30.3
Former	43.5	51.0	45.7
Current	26.9	16.9	24.1
Ethnicity (%)			
Whites	78.6	86.2	80.7
Afro-Caribbean	0.8	0.3	0.6
Asian	16.7	9.6	14.7
Hispanic	2.8	3.2	2.9
Other	1.1	0.6	1.0
Metastatic disease (%) ^{a,b}			
Bone	38.4	35.3	37.6
Lung	56.5	59.2	57.3
Liver	15.1	12.7	14.4
Brain	0.1	0.0	0.1
Other	41.9	38.6	40.9
Pathology (%) ^c			
Adenocarcinoma	86.9	83.5	86.0
Bronchoalveolar carcinoma	2.3	2.8	2.4
Large cell carcinoma	6.3	8.5	6.9
Mixed cell type (>50% nonsquamous)	0.4	1.2	0.6
Other	4.1	4.0	4.1
Centrally located lung tumor (%)	27.1	23.8	26.1
Tumor cavitated (%)	2.9	1.6	2.5
Receiving baseline medication (%)	69.9	82.3	73.4
Antihypertensive/cardiovascular	25.1	48.2	31.6
Anticoagulants (prophylactic)	3.1	5.5	3.8

^a Percentage based on total number of patients with metastatic disease.
^b Multiple metastatic sites were possible.
^c Percentage based on total number of patients with tumor sample taken.
ITT, intention to treat; ECOG PS, Eastern Cooperative Oncology Group performance status.

treatment discontinuation in both elderly and younger patients (8 of 9 events [88.9%] in elderly patients and 18 of 21 events [85.7%] in younger patients). The majority of AESIs resolved or improved after treatment interruption/discontinuation in both elderly and younger patients (Table 7). Mortality rates linked to AESIs were 2.9 and 2.5% for the elderly and younger patients, respectively. The most common AESI causes of death were thromboembolism, documented in 8 (1.3%) elderly and 18 (1.1%) younger patients, and bleeding in 4 (0.6%) elderly and 13 (0.8%) younger patients.

The safety profile in a post hoc analysis of patients older than 70 versus those 70 years and younger was similar

to that reported for patients older than 65 versus 65 years or younger (Table 8). In particular, the incidence of AESIs was similar regardless of the cutoff used, and no new safety signals were apparent.

Efficacy

At the time of the efficacy evaluation (July 24, 2009), 31.5% of elderly and 33.2% of younger patients were still alive, and of these, 61.5% of elderly and 71.9% of younger patients had progressive disease. Mean follow-up time was 12.5 months.

For elderly patients, the median TTP was 8.2 months (95% CI, 7.5–8.7) and for younger patients was 7.6 months (95% CI, 7.3–8.0) (Figure 1A). Median OS was 14.6 months for both elderly (95% CI, 13.0–15.4) and younger patients (95% CI, 13.7–15.7) (Figure 1B). ORR was 49.3% and 52.4% for elderly and younger patients, respectively, and complete response was documented for 2.7% of elderly and 3.4% of younger patients. DCR (ORR + stable disease) was 89.3% for elderly patients and 88.4% for younger patients. Similar efficacy outcomes were seen in a post hoc analysis of patients older than 70 years versus those 70 years or younger (Table 8). Median OS was the same in both the older than 70 years and 70 years or younger groups (14.6 months), while median TTP was slightly higher in the older than 70 years group (8.6 months) versus the 70 years or younger group (7.7 months).

DISCUSSION

Although mortality attributed to lung cancer has decreased in younger patients (50 years or younger), increasing

lung cancer mortality rates have been documented for older patients (older than 70 years).²⁷ This finding may be attributable, at least in part, to lower use of any treatment, particularly chemotherapy, in elderly compared with younger patients; little more than 20% of elderly patients with advanced lung cancer ever receive chemotherapy.^{9–11,28}

It is commonly perceived that outcomes observed in clinical trials may not be achieved in a real-world setting because patients may be older and have less favorable health characteristics. Consequently, physicians may be wary of using chemotherapy in populations that are under-represented in clinical trials. Indeed, despite the increasing population of elderly patients with cancer, their representation in clinical trials evaluating new anticancer agents remains poor.^{29–31}

There may also be a belief among physicians that antiangiogenic agents may be less well tolerated by elderly patients and they may consequently be more inclined to discontinue treatment in elderly patients at earlier grades of toxicity than they would in younger patients.

The SAiL study of bevacizumab in combination with chemotherapy followed by bevacizumab monotherapy for the management of patients with advanced NSCLC aimed to address questions on the utility of this regimen in routine clinical practice. This analysis of the SAiL study was undertaken to determine the effect of age on outcomes of bevacizumab in combination with chemotherapy followed by bevacizumab monotherapy, including patients receiving concomitant medications and those with an ECOG PS of 2. Given the under-representation of patients older than 65 years in the clinical trials that establish clinical practice for patients with advanced NSCLC, 65 years of age was selected as the criterion for the subgroup analysis by age in the SAiL study. The definition of elderly as older than 65 years used in this preplanned analysis has previously been used in the oncology literature,²⁴ although a cutoff age of older than 70 years is sometimes used.³² When the SAiL study started, both age cutoffs were considered to be acceptable definitions of elderly. The use of 65 years as the definition of elderly in our preplanned analysis allowed for sufficient patient numbers to be included in the elderly subgroup to allow meaningful

TABLE 2. Summary of Treatment Regimens

Treatment Regimen, n (%)	Patients 65 yr and Younger (n = 1589)	Patients Older than 65 yr (n = 623)	ITT Population (n = 2212)
Platinum doublet	1392 (88)	524 (84)	1916 (87)
Cisplatin doublet	644 (41)	185 (30)	829 (37)
Carboplatin doublet	748 (47)	339 (54)	1087 (49)
Nonplatinum doublet	6 (<1)	7 (1)	13 (1)
Single agent ^a	15 (1)	27 (4)	42 (2)
Other ^b	8 (<1)	2 (<1)	10 (<1)
Bevacizumab			
7.5 mg/kg	181 (11)	79 (13)	260 (12)
15 mg/kg	1403 (88)	541 (87)	1944 (88)
Switched dose	5 (<1)	3 (<1)	8 (<1)

^a Carboplatin, cisplatin, docetaxel, gemcitabine, paclitaxel, pemetrexed, and vinorelbine.
^b Triplet and quadruplet chemotherapy regimens.
 ITT, intention to treat; NA, not available.

TABLE 3. AEs of Special Interest

Patients with at Least One Event, n (%)	Patients 65 yr and Younger (n = 1589)				Patients Older than 65 yr (n = 623)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Overall bleeding	573 (36.1)	31 (2.0)	3 (0.2)	13 (0.8)	218 (35.0)	25 (4.0)	5 (0.8)	4 (0.6)
Epistaxis	426 (26.8)	12 (0.8)	0	0	156 (25.0)	14 (2.2)	3 (0.5)	0
Pulmonary hemorrhage ^a	124 (7.8)	4 (0.3)	0	7 (0.4)	49 (7.9)	1 (0.2)	2 (0.3)	1 (0.2)
CNS bleeding ^b	3 (0.2)	1 (0.1)	0	0	2 (0.3)	0	0	1 (0.2)
Hypertension	421 (26.5)	86 (5.4)	5 (0.3)	0	180 (28.9)	34 (5.5)	1 (0.2)	0
Proteinuria	433 (27.2)	41 (2.6)	6 (0.4)	0	194 (31.1)	15 (2.4)	5 (0.8)	0
Thromboembolism	77 (4.8)	79 (5.0)	39 (2.5)	18 (1.1)	38 (6.1)	25 (4.0)	15 (2.4)	8 (1.3)
Gastrointestinal perforation	3 (0.2)	10 (0.6)	4 (0.3)	4 (0.3)	0	3 (0.5)	2 (0.3)	4 (0.6)
Wound-healing complications	14 (0.9)	1 (0.1)	1 (0.1)	0	10 (1.6)	0	0	0
Congestive heart failure	1 (0.1)	2 (0.1)	0	4 (0.3)	5 (0.8)	1 (0.2)	2 (0.3)	2 (0.3)

^a Pulmonary hemorrhage/hemoptysis.

^b Cerebral hemorrhage/hematoma.

AEs, adverse events; CNS, central nervous system.

TABLE 4. Incidence of AEs of Special Interest (All Grades) By Chemotherapy Regimen—Younger Patients

Patients with at Least One Event, n (%)	Patients 65 yr and Younger (n = 1589)											
	Carboplatin Doublets n = 748		Cisplatin Doublets n = 644		Nonplatinum Doublets n = 6		Monotherapy n = 15		Other Combinations n = 8		Switched Chemotherapy n = 168	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
AESI (any grade)	517 (69.1)		441 (68.5)		5 (83.3)		9 (60.0)		0		113 (67.3)	
Overall bleeding	307 (41.0)	20 (2.7)	226 (35.1)	21 (3.3)	2 (33.3)	1 (16.7)	4 (26.7)	1 (6.7)	0	0	69 (41.1)	4 (2.4)
Epistaxis	217 (29.0)	3 (0.4)	164 (25.5)	8 (1.2)	1 (16.7)	0	2 (13.3)	0	0	0	50 (29.8)	1 (0.6)
Pulmonary hemorrhage ^a	81 (10.8)	5 (0.7)	44 (6.8)	4 (0.6)	0	0	2 (13.3)	1 (6.7)	0	0	7 (4.2)	1 (0.6)
CNS bleeding ^b	2 (0.3)	0	1 (0.2)	1 (0.2)	0	0	0	0	0	0	1 (0.6)	0
Hypertension	199 (26.6)	30 (4.0)	232 (36.0)	49 (7.6)	0	0	5 (33.3)	1 (6.7)	0	0	51 (30.4)	10 (6.0)
Proteinuria	238 (31.8)	26 (3.5)	173 (26.9)	13 (2.0)	3 (50.0)	0	3 (20.0)	1 (6.7)	0	0	48 (28.6)	7 (4.2)
Thromboembolism	70 (9.4)	48 (6.4)	100 (15.5)	64 (9.9)	0	0	1 (6.7)	0	0	0	25 (14.9)	14 (8.3)
Gastrointestinal perforation	11 (1.5)	11 (1.5)	5 (0.8)	4 (0.6)	0	0	0	0	0	0	5 (3.0)	3 (1.8)
Wound-healing complications	6 (0.8)	1 (0.1)	8 (1.2)	1 (0.2)	1 (16.7)	0	0	0	0	0	1 (0.6)	0
Congestive heart failure	4 (0.5)	3 (0.4)	2 (0.3)	2 (0.3)	0	0	1 (6.7)	1 (6.7)	0	0	0	0

^a Pulmonary hemorrhage/hemoptysis.^b Cerebral hemorrhage/hematoma.

AEs, adverse events; AESI, adverse events of special interest; CNS, central nervous system.

TABLE 5. Incidence of AEs of Special Interest (All Grades) by Chemotherapy Regimen—Elderly Patients

Patients with at Least One Event, n (%)	Patients Older than 65 yr (n = 623)											
	Carboplatin Doublets n = 339		Cisplatin Doublets n = 185		Nonplatinum Doublets n = 7		Monotherapy n = 27		Other Combinations n = 2		Switched Chemotherapy n = 63	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
AESI (any grade)	246 (72.6)		132 (71.4)		4 (57.1)		19 (70.4)		1 (50.0)		39 (61.9)	
Overall bleeding	143 (42.2)	19 (5.6)	65 (35.1)	10 (5.4)	3 (42.9)	1 (14.3)	7 (25.9)	1 (3.7)	0	0	20 (31.7)	2 (3.2)
Epistaxis	101 (29.8)	10 (2.9)	48 (25.9)	4 (2.2)	2 (28.6)	0	3 (11.1)	1 (3.7)	0	0	13 (20.6)	1 (1.6)
Pulmonary hemorrhage ^a	32 (9.4)	3 (0.9)	12 (6.5)	1 (0.5)	0	0	3 (11.1)	0	0	0	5 (7.9)	0
CNS bleeding ^b	2 (0.6)	0	0	0	1 (14.3)	1 (14.3)	0	0	0	0	0	0
Hypertension	111 (32.7)	13 (3.8)	63 (34.1)	12 (6.5)	2 (28.6)	1 (14.3)	6 (22.2)	2 (7.4)	1 (50.0)	1 (50.0)	23 (36.5)	6 (9.5)
Proteinuria	117 (34.5)	10 (2.9)	59 (31.9)	4 (2.2)	0	0	10 (37.0)	1 (3.7)	1 (50.0)	0	21 (33.3)	5 (7.9)
Thromboembolism	34 (10.0)	19 (5.6)	37 (20.0)	22 (11.9)	0	0	2 (7.4)	2 (7.4)	0	0	6 (9.5)	3 (4.8)
Gastrointestinal perforation	5 (1.5)	5 (1.5)	3 (1.6)	3 (1.6)	0	0	0	0	0	0	1 (1.6)	1 (1.6)
Wound-healing complications	8 (2.4)	0	1 (0.5)	0	0	0	1 (3.7)	0	0	0	0	0
Congestive heart failure	2 (0.6)	1 (0.3)	4 (2.2)	2 (1.1)	0	0	3 (11.1)	2 (7.4)	0	0	1 (1.6)	0

^a Pulmonary hemorrhage/hemoptysis.^b Cerebral hemorrhage/hematoma.

AEs, adverse events; AESI, adverse events of special interest; CNS, central nervous system.

comparison with the younger patients. Our post hoc analysis using a cutoff age of 70 years showed similar efficacy and safety to the 65-year-old analysis.

As expected, elderly patients tended to have a poorer performance status than their younger counterparts, and comor-

bidity were more common in the elderly subgroup, notably hypertension. These findings are consistent with previous studies.¹³ Furthermore, the use of concomitant medication was substantially greater in elderly than in younger patients; this was largely due to greater use of cardiovascular medications.

TABLE 6. AEs of Special Interest Leading to Temporary Interruption or Permanent Discontinuation of Bevacizumab

AEs, n (%) ^a	Patients 65 yr and Younger (n = 1589)		Patients Older than 65 yr (n = 623)	
	Temporary Interruption	Permanent Discontinuation	Temporary Interruption	Permanent Discontinuation
Overall bleeding	18 (1.1)	78 (4.9)	10 (1.6)	32 (5.1)
Hypertension	55 (3.5)	23 (1.4)	17 (2.7)	17 (2.7)
Proteinuria	25 (1.6)	19 (1.2)	13 (2.1)	12 (1.9)
Thromboembolism	26 (1.6)	97 (6.1)	8 (1.3)	43 (6.9)
Gastrointestinal perforation	0	18 (1.1)	0	8 (1.3)
Wound-healing complications	5 (0.3)	1 (0.1)	3 (0.5)	0
Congestive heart failure	1 (0.1)	4 (0.3)	1 (0.2)	5 (0.8)

^a Percentages are based on total number of patients within each age category. AEs, adverse events.

TABLE 7. Outcomes of AEs of Special Interest after Treatment Interruption/Discontinuation

AEs, n (%) ^a	Patients 65 yr and Younger (n = 1589)					Patients Older than 65 yr (n = 623)				
	n	Resolved	Improved	Persistent	Led to Death	n	Resolved	Improved	Persistent	Led to Death
Overall bleeding	976	833 (85.3)	25 (2.6)	105 (10.8)	13 (1.3)	371	321 (86.5)	14 (3.8)	32 (8.6)	4 (1.1)
Hypertension	727	548 (75.4)	63 (8.7)	116 (16.0)	0	298	230 (77.2)	31 (10.4)	37 (12.4)	0
Proteinuria	734	502 (68.4)	71 (9.7)	161 (21.9)	0	312	215 (68.9)	31 (9.9)	66 (21.2)	0
Thromboembolism	233	108 (46.4)	40 (17.2)	67 (28.8)	18 (7.7)	91	48 (52.7)	17 (18.7)	18 (19.8)	8 (8.8)
Gastrointestinal perforation	21	13 (61.9)	3 (14.3)	1 (4.8)	4 (19.0)	9	5 (55.6)	0	0	4 (44.4)
Wound-healing complications	18	12 (66.7)	1 (5.6)	5 (27.8)	0	13	10 (76.9)	1 (7.7)	2 (15.4)	0
Congestive heart failure	7	1 (14.3)	1 (14.3)	1 (14.3)	4 (57.1)	11	5 (45.5)	1 (9.1)	3 (27.3)	2 (18.2)

^a Percentages are based on total number of AEs within each AE category. AEs, adverse events.

TABLE 8. Comparison of Efficacy and Safety Outcomes for Different Elderly Cutoffs (Older than 65 yr Versus Older than 70 yr)

Efficacy Outcomes	65 yr or Younger (n = 1589)			Older than 65 yr (n = 623)			70 yr or Younger (n = 1946)			Older than 70 yr (n = 266)		
TTP, months (95% CI)	7.6 (7.3–8.0)			8.2 (7.5–8.7)			7.7 (7.4–8.1)			8.6 (7.3–9.2)		
OS, months (95% CI)	14.6 (13.7–15.7)			14.6 (13.0–15.4)			14.6 (13.8–15.4)			14.6 (11.0–17.1)		
RR (%)	52			49			52			49		
DCR (%)	88			89			88			90		
AESIs (%)	65 yr or Younger			Older than 65 yr			70 yr or Younger			Older than 70 yr		
	Gr 3	Gr 4	Gr 5	Gr 3	Gr 4	Gr 5	Gr 3	Gr 4	Gr 5	Gr 3	Gr 4	Gr 5
Overall bleeding	2.0	0.2	0.8	4.0	0.8	0.6	2.4	0.3	0.8	3.4	1.1	0.8
Epistaxis	0.8	0	0	2.2	0.5	0	1.2	0.1	0	1.1	0.8	0
Pulmonary hemorrhage	0.3	0	0.4	0.2	0.3	0.2	0.1	0	0.1	0	0.4	0
CNS bleeding	0.1	0	0	0	0	0.2	0.1	0	0.1	0	0	0
Hypertension	5.4	0.3	0	5.5	0.2	0	5.5	0.2	0	4.5	0	0
Proteinuria	2.6	0.4	0	2.4	0.8	0	2.7	0.5	0	1.5	0.4	0
Thromboembolism	5.0	2.5	1.1	4.0	2.4	1.3	4.8	2.5	1.2	4.1	2.3	0.8
Gastrointestinal perforation	0.6	0.3	0.3	0.5	0.3	0.6	0.7	0.3	0.4	0	0.4	0.4
Wound-healing complications	0.1	0.1	0	0	0	0	0.1	0.1	0	0	0	0
Congestive heart failure	0.1	0	0.3	0.2	0.3	0.3	0.2	0.1	0.3	0	0.4	0.4

It is perhaps then not surprising that the median number of cycles, duration of chemotherapy, and total time on bevacizumab in this study were shorter in elderly than in younger patients. However, the rates of AESIs were comparable in

elderly and younger patients and the majority of events were grade less than or equal to 2 in both cohorts. There were remarkable similarities between the two age cohorts with respect to specific AESIs, including bleeding, hypertension,

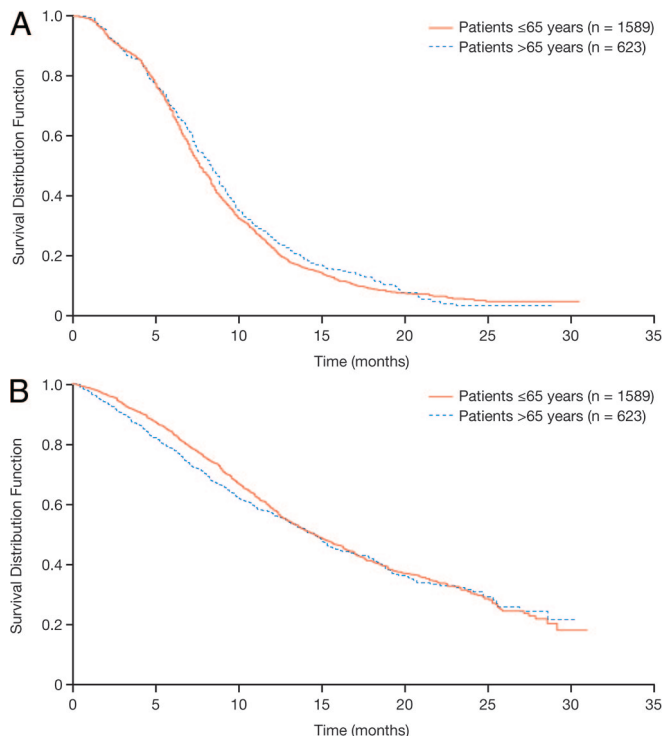


FIGURE 1. Kaplan-Meier curves of (A) median time to progression for nonelderly and elderly patients; (B) median overall survival for nonelderly and elderly patients.

proteinuria, and thromboembolism. Furthermore, AEs requiring treatment interruption or discontinuation occurred with similar frequency in elderly and younger patients, and the majority of AEs resolved or improved during the study. Mortality attributed to treatment-related AEs was similarly low in both age cohorts. No effect of age was apparent with regard to the rates of AEs across patients who received different chemotherapy regimens; admittedly some of the chemotherapy regimens were only given in small numbers.

The AVAiL and ECOG 4599 phase III studies evaluated first-line bevacizumab with gemcitabine-cisplatin and paclitaxel-carboplatin, respectively. Both trials met their primary end points. AVAiL demonstrated significant improvements in PFS^{21,22} and ECOG 4599 demonstrated a significant OS benefit in patients receiving bevacizumab.²⁰ In the SAiL study, there was an absence of a notable effect of age on the tolerability of bevacizumab-based therapy which is consistent with the findings of the AVAiL study: a retrospective subgroup analysis of 304 elderly (65 years or older) patients in AVAiL identified no new safety signals in elderly patients and similar rates of grade more than or equal to 3 toxicities between treatment arms (bevacizumab 7.5 mg/kg, 15 mg/kg, and placebo: 84, 80, and 80%, respectively).²⁶ However, a retrospective subgroup analysis of older (70 years or older) patients ($n = 224$) in the ECOG 4599 study demonstrated that the addition of bevacizumab to chemotherapy led to a significant increase in the incidence of grade more than or equal to 3 toxicities versus paclitaxel-carboplatin alone (87% versus 61%; $p < 0.001$); seven treatment-related deaths occurred

among elderly patients who received bevacizumab versus two deaths in the chemotherapy alone arm.³³ Furthermore, grade more than or equal to 3 neutropenia, bleeding, and proteinuria were reported more frequently with bevacizumab in elderly than younger patients.³³ The discrepant age effects in the ECOG trial compared with the AVAiL and SAiL trials with respect to toxicity may be due, at least in part, to a difference between the age criterion used in the analyses (65 years in AVAiL and SAiL and 70 years in the ECOG 4599 study) and also in the proportions of patients who were very elderly (i.e., older than 75 years) in the different arms. The difference in the chemotherapy backbone used could also account for these differences, but the broad patient selection criteria and diversity of chemotherapies in SAiL suggest that this is less likely to be the case. In this subgroup analysis of the SAiL study, response rates were similar in elderly and younger patients, as were disease control rates, TTP, and OS. These findings are compatible with the retrospective analyses of AVAiL and ECOG 4599 showing that the PFS benefit with bevacizumab is maintained in elderly patients²⁶ and age is not a negative prognostic factor for survival ($p = 0.34$).³³ Median OS results for bevacizumab eligible patients included in SAiL (14.6 months),²³ are similar to survival results for bevacizumab-treated patients in more rigorously controlled phase III trials such as AVAiL (13.6 and 13.4 months with bevacizumab 7.5 and 15 mg/kg, respectively)²² and ECOG 4599 (12.3 months).²⁰

Given the large number of older patients enrolled in the SAiL study, this dataset provides a valuable resource for evaluating safety, tolerability, and efficacy of bevacizumab-based therapy in the elderly and is in accord with the findings for elderly patients from the AVAiL trial in terms of efficacy and lack of any additional toxicities being reported. This analysis according to age provides reassurance that elderly patients can tolerate first-line bevacizumab in combination with appropriate chemotherapy regimens and derive a similar benefit as younger patients.

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REFERENCES

- Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92–98.
- Non-small Cell Lung Cancer Collaborative Group: Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. *BMJ* 2005;331:899–909.
- Pfister DG, Johnson DH, Azzoli CG, et al. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. *J Clin Oncol* 2004;22:330–353.

4. D'Addario G, Felip E. Non-small-cell lung cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2008;19 (Suppl 2):ii39–ii40.
5. Kelly K, Crowley J, Bunn PA, et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small cell lung cancer: a southwest oncology group trial. *J Clin Oncol* 2001;19:3210–3218.
6. Scagliotti GV, De Marinis F, Rinaldi M, et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small cell lung cancer. *J Clin Oncol* 2002;20:4285–4291.
7. Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. *J Clin Oncol* 2003;21:3016–3024.
8. Gridelli C, Perrone F, Monfardini S. Lung cancer in the elderly. *Eur J Cancer* 1997;33:2313–2314.
9. Ramsey SD, Howlader N, Etzioni RD, et al. Chemotherapy use, outcomes, and costs for older persons with advanced non-small-cell lung cancer: evidence from surveillance, epidemiology and end results-medicare. *J Clin Oncol* 2004;22:4971–4978.
10. Owonikoko TK, Ragin CC, Belani CP, et al. Lung cancer in elderly patients: an analysis of the surveillance, epidemiology, and end results database. *J Clin Oncol* 2007;25:5570–5577.
11. Townsley C, Pond GR, Pelozo B, et al. Analysis of treatment practices for elderly cancer patients in Ontario, Canada. *J Clin Oncol* 2005;23:3802–3810.
12. Gridelli C. The ELVIS trial: a phase III study of single-agent vinorelbine as first-line treatment in elderly patients with advanced non-small cell lung cancer. *Oncologist* 2001;6 (Suppl 1):4–7.
13. Gridelli C, Perrone F, Gallo C, et al. Chemotherapy for elderly patients with advanced non-small-cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. *J Natl Cancer Inst* 2003;95:362–372.
14. Sederholm C, Hillerdal G, Lamberg K, et al. Phase III trial of gemcitabine plus carboplatin versus single-agent gemcitabine in the treatment of locally advanced or metastatic non-small-cell lung cancer: the Swedish Lung Cancer Study Group. *J Clin Oncol* 2005;23:8380–8388.
15. Lilenbaum RC, Herndon JE, List MA, et al. Single-agent versus combination chemotherapy in advanced non-small cell lung cancer: the cancer and leukemia group B (study 9730). *J Clin Oncol* 2005;23:190–196.
16. Langer CJ, Manola J, Bernardo P, et al. Cisplatin-based therapy for elderly patients with advanced non-small cell lung cancer: implications of Eastern Cooperative Oncology Group 5592, a randomized trial. *J Natl Cancer Inst* 2002;94:173–181.
17. Belani CP, Fossella F. Elderly subgroup analysis of a randomised phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for first-line treatment of advanced nonsmall cell lung carcinoma (TAX 326). *Cancer* 2005;104:2766–2774.
18. Hensing TA, Peterman AH, Schell MJ, et al. The impact of age on toxicity, response rate, quality of life, and survival in patients with advanced, Stage IIIB or IV nonsmall cell lung carcinoma treated with carboplatin and paclitaxel. *Cancer* 2003;98:779–788.
19. Quoix EA, Oster J, Westeel V, et al. Weekly paclitaxel combined with monthly carboplatin versus single-agent therapy in patients age 70 to 89: IFCT-0501 randomized phase III study in advanced non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 2010;28:2a.
20. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;355:2542–2550.
21. Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for non-squamous non-small-cell lung cancer: AVAiL. *J Clin Oncol* 2009;27:1227–1234.
22. Reck M, von Pawel J, Zatloukal P, et al. Overall survival with cisplatin/gemcitabine and bevacizumab or placebo as first-line therapy for non-squamous non-small cell lung cancer: results from a randomised phase III trial (AVAiL). *Ann Oncol* 2010;21:1804–1809.
23. Crinò L, Dansin E, Garrido P, et al. Safety and efficacy of first-line bevacizumab-based therapy in advanced non-squamous non-small-cell lung cancer (SAiL, MO19390): a phase 4 study. *Lancet Oncol* 2010;11:733–740.
24. Pepe C, Hasan B, Winton TL, et al. Adjuvant vinorelbine and cisplatin in elderly patients: National Cancer Institute of Canada and Intergroup Study JBR. 10. *J Clin Oncol* 2007;25:1553–1561.
25. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology Version 2.2011: Senior Adult Oncology. Available at: <http://www.nccn.org>. Accessed May 23, 2011.
26. Leigh N, Zatloukal P, Mezger J, et al. Efficacy and safety of bevacizumab-based therapy in elderly patients with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC) in the phase III BO17704 study (AVAiL). *J Thorac Oncol* 2010;5:1970–1976.
27. Wingo PA, Cardinez CJ, Landis SH, et al. Long-term trends in cancer mortality in the United States, 1930–1998. *Cancer* 2003;97 (12 Suppl):3133–3175.
28. Earle CC, Venditti LN, Neumann PJ, et al. Who gets chemotherapy for metastatic lung cancer? *Chest* 2000;117:1239–1246.
29. Kumar A, Soares HP, Balducci L, et al. Treatment tolerance and efficacy in geriatric oncology: a systematic review of phase III randomized trials conducted by five National Cancer Institute-sponsored cooperative groups. *J Clin Oncol* 2007;25:1272–1276.
30. Hutchins LF, Unger JM, Crowley JJ, et al. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med* 1999;341:2061–2067.
31. Lewis JH, Kilgore ML, Goldman DP, et al. Participation of patients 65 years of age or older in cancer clinical trials. *J Clin Oncol* 2003;21:1383–1389.
32. Balducci L. Geriatric oncology: challenges for the new century. *Eur J Cancer* 2000;36:1741–1745.
33. Ramalingam SS, Dahlberg SE, Langer CJ, et al. Outcomes for elderly, advanced-stage non small cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: analysis of Eastern Cooperative Oncology Group Trial 4599. *J Clin Oncol* 2008;26:60–65.