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Efficacy and safety of bevacizumab in combination with docetaxel for the first-line treatment of elderly patients with locally recurrent or metastatic breast cancer: Results from AVADO

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ABSTRACT

Background: Oncologic treatment in elderly patients is challenging, due to comorbidities, often impaired organ function, limited clinical trial evidence, inadequate guidelines and no consistent 'elderly' definition. We report exploratory sub-analyses of safety and efficacy in elderly patients, defined as ⩾65 years old, in AVastin And DOcetaxel (AVADO) receiving first-line bevacizumab plus docetaxel for metastatic breast cancer (mBC).

Patients and methods: Patients with HER2-negative, locally recurrent or mBC were randomised to 3-weekly docetaxel (100 mg/m^2) with placebo, bevacizumab 7.5 mg/kg or bevacizumab 15 mg/kg, for 9 cycles or until disease progression or unacceptable toxicity. Patients had no prior chemotherapy for mBC.

Results: Progression-free survival (PFS) was increased with bevacizumab in the elderly subpopulation (n = 127), the effect being greater with higher dose (hazard ratio = 0.63 [95% confidence interval (CI) 0.383–1.032] versus 0.76 [95% CI: 0.46–1.262], respectively). PFS was numerically similar in the elderly and overall populations, but the former failed to achieve statistical significance. Overall response rates for docetaxel plus placebo, bevacizumab 7.5 mg/kg and 15 mg/kg were 44.7%, 36.6% and 50.0%, respectively. Effects on survival were not statistically significant. Bevacizumab was well tolerated in elderly patients, the most common adverse effects were neutropenia and febrile neutropenia; there was no excess

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of grade ⩾ 3 cardiovascular events. There was no clear correlation between baseline hypertension and its development during study treatment.

Conclusions: In this exploratory sub-analysis in AVADO, bevacizumab plus docetaxel showed efficacy in elderly patients similar to the overall study population. There were no unexpected safety signals in patients aged 65 years or older.

1. Introduction

The incidence of breast cancer increases with age; approximately half of all breast cancers occur in patients older than 65 years.[1,2] Compared with younger patients, older patients with breast cancer are more likely to have tumours with lower proliferative rates and tumours that are oestrogen-receptor positive, making them amenable to treatment with endocrine therapy or an aromatase inhibitor.[3–5] However, there remain a significant proportion of older women with breast cancer who do not have such favourable tumour characteristics and who are candidates for chemotherapy in either the adjuvant or metastatic setting.[6] Notably, age-specific breast cancer incidence rates from the Surveillance Epidemiology and End Results database indicate that approximately 42% of cases in the United States occur in women aged 65 years and over; more than 20% of cases are in women 75 years and over. Breast cancer in older patients is set to increase substantially in coming decades in Western countries, in line with the ageing population.[7] Issues such as life expectancy, benefits and possible toxicity of treatments, and comorbidities are of prime importance in the management of elderly patients with breast cancer, only a minority of whom are considered to be in 'perfect health'.[8]

Unfortunately, there are limited data on the efficacy and safety of cancer therapy in older patients with advanced or metastatic breast cancer (mBC), due to a lack of clinical studies specifically targeting elderly patients, and the frequent exclusion of elderly patients from clinical trials.[7,9] An analysis of Southwest Oncology Group (SWOG) clinical trials between 1993 and 1996 revealed a substantial under-representation of patients aged 65 years and over in studies of cancer treatment[10] and in most randomised clinical trials there are few, if any, patients aged 70 years or over.[7]

Single-agent chemotherapy regimens are preferred to combination chemotherapy regimens in elderly patients,[8] since the greater efficacy of combination chemotherapy regimens compared with single agents comes at the expense of increased toxicity.[11] Use of targeted agents such as bevacizumab in combination with a taxane chemotherapeutic agent offers the potential to increase treatment response and generally has a tolerability profile that compares favourably with that of taxane-chemotherapy doublet regimens.[12]

In the phase III study AVastin and DOcetaxel (AVADO), the combination of bevacizumab with docetaxel significantly increased progression-free survival (PFS) and overall response rate, with limited impact on toxicity.[13] Here we report an exploratory retrospective sub-analysis evaluating data from the AVADO study for patients aged 65 years or older.[14]

2. Patients and methods

Details of the AVADO (ClinicalTrials.gov identifier: NCT-00333775) study methodology have been reported previously.[13] AVADO enrolled patients aged ⩾18 years with HER2-negative locally recurrent or mBC. Patients were randomly assigned to one of three treatments: docetaxel (100 mg/m^2 on day 1 of a 3-week cycle) in combination with bevacizumab 7.5 mg/kg, bevacizumab 15 mg/kg or placebo.

The primary end-point was PFS, and secondary end-points included overall response rate, duration of response, time to treatment failure, overall survival (OS) and safety. To assess the efficacy and safety of first-line docetaxel–bevacizumab in older patients, a subpopulation analysis was conducted using data from the primary intent-to-treat (ITT) analysis for patients aged ⩾ 65 years. The analysis had a cut-off date of 30th April 2009, corresponding to a median follow-up of 25 months.

3. Results

The cut-off age of 65 years was chosen, since too few patients aged over 70 years were enrolled in AVADO for meaningful data to be obtained ($n = 43$; bevacizumab 7.5 mg/kg $n = 15$, 15 mg/kg $n = 18$, and placebo $n = 10$).

In the overall ITT population, 127 patients (17.2%) were aged ⩾ 65 years and formed the elderly ITT subpopulation. Baseline demographic and disease characteristics were similar in the two patient populations (Table 1). Overall, elderly patients had lower rates of prior chemotherapy and higher rates of hormone therapy in the metastatic setting. In the elderly ITT subgroup, previous or concomitant antihypertensive treatment was recorded in one (2.7%), six (14.6%) and six (12.5%) patients in the placebo, bevacizumab 7.5 mg/kg and 15 mg/kg groups, respectively. Urinary protein at baseline was reported in 21%, 5% and 10% of placebo, bevacizumab 7.5 mg/kg and 15 mg/kg elderly patients, respectively.

3.1. *Efficacy*

Bevacizumab plus docetaxel improved PFS compared with placebo plus docetaxel in the elderly ITT subpopulation, the numerical benefit being similar to that in the overall ITT population. In the stratified analysis, in which patients receiving non-protocol treatment were censored, median PFS values in the placebo, bevacizumab 7.5 mg/kg and bevacizumab 15 mg/kg arms were 7.6, 9.0 and 10.3 months, respectively, in the elderly patients and 8.1, 9.0 and 10.0 months, respectively, in the overall ITT population (Fig. 1). Whereas improvement in PFS versus placebo was statistically significant with

Table 1 – Patient demographic and baseline disease characteristics in the overall ITT population and the elderly ITT subpopulation.

Characteristic	Randomised treatment arm					
	Placebo + docetaxel		Bevacizumab 7.5 mg/kg + docetaxel		Bevacizumab 15 mg/kg + docetaxel	
	Overall ITT population (*n* = 241)	⩾65 years (*n* = 38)	Overall ITT population (*n* = 248)	⩾65 years (*n* = 41)	Overall ITT population (*n* = 247)	⩾65 years (*n* = 48)
Median age (years)	55	67	54	69	55	68
Range	29–83	65–83	26–83	65–83	27–76	65–76
ECOG performance status, n (%)						
0	147 (62)	22 (58)[a]	149 (61)	27 (56)[a]	150 (61)	27 (56)
1	91 (38)	14 (37)[a]	94 (39)	21 (44)[a]	94 (39)	21 (44)
ER and PgR positive, *n* (%)	198 (78)	32 (84)	193 (78)	34 (83)	187 (76)	32 (67)[b]
Disease-free interval ⩾ 12 months, *n* (%)	195 (81)	NA	187 (75)	NA	202 (82)	NA
⩾3 metastatic sites	99 (41)	16 (42)	122 (49)	28 (68)	122 (49)	22 (46)[b]
Site of disease, *n* (%)						
Liver	120 (50)	21 (55)	98 (40)	16 (39)	112 (46)	12 (25)
Lung	91 (38)	14 (37)	102 (42)	23 (56)	117 (48)	27 (56)
Bone	142 (59)	24 (63)	146 (60)	24 (59)	135 (55)	23 (48)
Measurable disease, *n* (%)	207 (86)	32 (84)	201 (81)	34 (83)	206 (83)	37 (78)
Prior adjuvant chemotherapy, n (%)						
Any	156 (65)	17 (45)	162 (65)	20 (49)	167 (68)	26 (54)
Taxane	35 (15)	3 (8)	38 (15)	2 (5)	42 (17)	2 (4)
Anthracycline	133 (55)	13 (34)	131 (53)	14 (34)	136 (55)	19 (40)
Prior hormone therapy						
(Neo)adjuvant	135 (56)	19 (50)	137 (55)	24 (59)	120 (49)	22 (46)
Metastatic	76 (32)	15 (40)	74 (30)	21 (51)	69 (28)	17 (35)
Previous/concomitant antihypertensive treatment, *n* (%)	1 (<1)	1 (3)	2 (1)	6 (15)	2 (1)	6 (13)
Urinary protein at baseline, *n* (%)	NA		NA		NA	
Missing		4 (11)		3 (7)		2 (4)
Negative		22 (58)		33 (81)		38 (79)
Trace		4 (11)		3 (7)		3 (6)
+1		8 (21)		2 (5)		5 (10)

ITT: intent-to-treat; ECOG: Eastern Cooperative Oncology Group; ER: oestrogen receptor; PgR: progesterone receptor; NA: not available.
[a] Data missing for one patient receiving bevacizumab 7.5 mg/kg and for two patients receiving placebo.
[b] Missing/unknown in one patient.

bevacizumab 15 mg/kg in the overall ITT population (10.0% versus 8.1%; hazard ratio [HR] = 0.67 [95% confidence interval (CI): 0.54–0.83]; $p < 0.001$), this was not achieved for either of the active treatment arms in the smaller elderly ITT subpopulation. As in the overall ITT population, in those aged ⩾ 65 -years the extent of benefit versus placebo was greater with bevacizumab 15 mg/kg (HR = 0.63 [95% CI: 0.383–1.032]; $p = 0.07$) than with the 7.5 mg/kg dose (HR = 0.76 [95% CI: 0.46–1.262]; $p = 0.35$) (Fig. 1).

Results of the unstratified analysis showed a similar pattern. In the elderly ITT subpopulation, median PFS was 7.7 months with placebo, 9.0 months with bevacizumab 7.5 mg/kg (HR = 0.83 [95% CI: 0.518–1.315]; $p = 0.48$) and 10.3 months in the bevacizumab 15 mg/kg arm (HR = 0.68 [95% CI: 0.428–1.076]; $p = 0.095$). Corresponding results for the overall ITT population were 8.2 months, 9.0 months (HR = 0.86 [95% CI: 0.72–1.04]; $p = 0.12$), and 10.1 months (HR = 0.77 [95% CI: 0.64–0.93]; $p = 0.006$), respectively. PFS data were generally consistent with results for the overall study population in all patient subgroups analysed, including the elderly subpopulation (Fig. 2).

In elderly patients with measurable disease at baseline, the overall response rate was increased with bevacizumab 15 mg/kg plus docetaxel compared with placebo plus docetaxel (50.0% [95% CI: 35.2–64.8] versus 44.7% [95% CI: 28.6–61.7]); overall response rate with bevacizumab 7.5 mg/kg plus docetaxel (36.6% [95% CI: 22.1–53.1]) was lower than in the placebo arm. In the overall ITT group, response rates were higher than in the elderly ITT subpopulation, with the higher dose bevacizumab ITT arm being statistically superior to the ITT placebo group (64.1% versus 46.4%; $p < 0.001$). In elderly patients, progressive disease was the best response recorded in five patients in the placebo group (13.2%), two patients (4.9%) in the bevacizumab 7.5 mg/kg group and three patients (6.3%) in the bevacizumab 15 mg/kg group.

At the time of this analysis, no treatment effect was evident for OS in either population. One-year survival did not vary substantially among the treatment groups in the elderly ITT subpopulation; in the bevacizumab 15 mg/kg group, one-year survival was lower compared with placebo but this difference was not statistically significant (65% versus 71%;

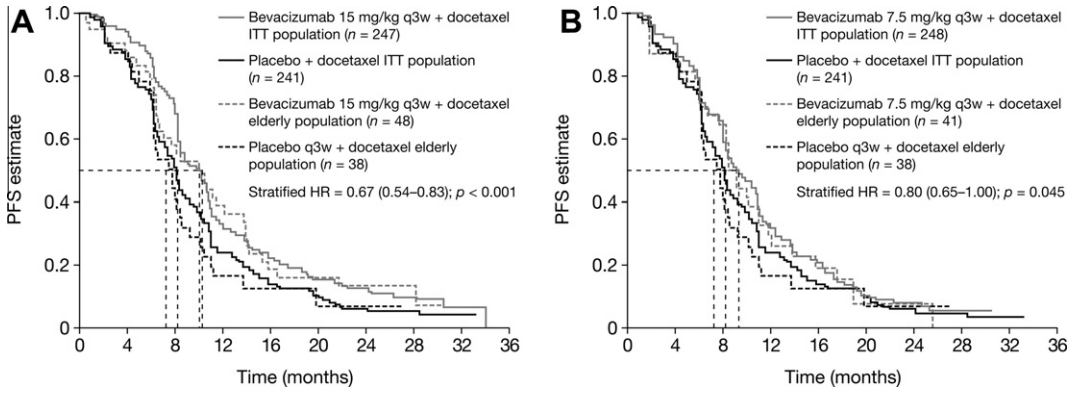

Fig. 1 – Kaplan–Meier curves of PFS in the overall ITT population and the elderly ITT subpopulation for (A) bevacizumab 15 mg/kg plus docetaxel versus placebo plus docetaxel; and (B) bevacizumab 7.5 mg/kg plus docetaxel versus placebo plus docetaxel. PFS: progression-free survival; ITT: intent-to-treat; q3w: every 3 weeks; HR: hazard ratio.

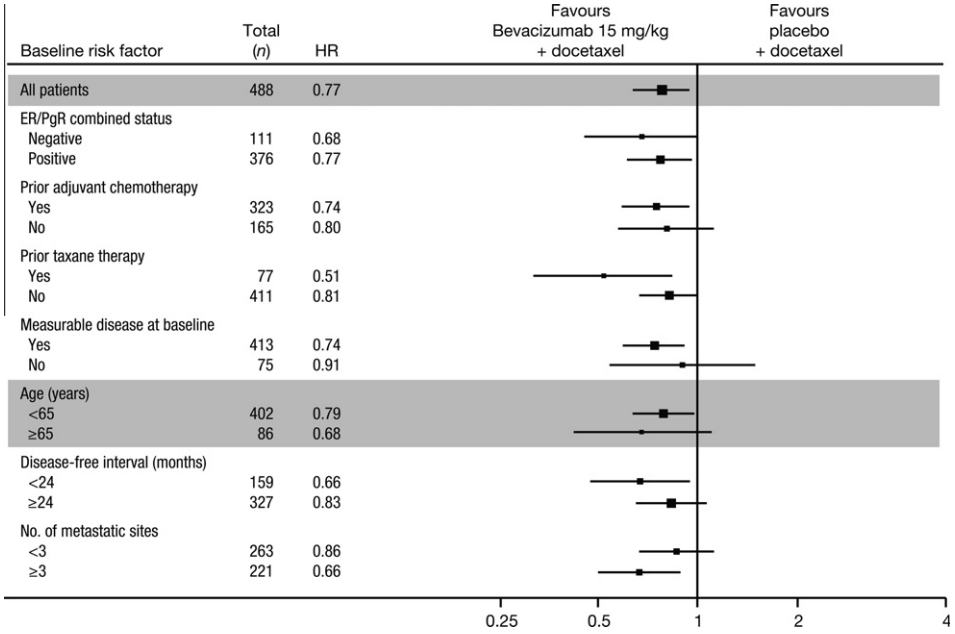

Fig. 2 – HR for PFS in clinically relevant patient subgroups (unstratified analysis). HR: hazard ratio; PFS: progression-free survival; ER: oestrogen; PgR: progesterone.

$p = 0.49$). However, in the overall ITT population there was evidence of a statistically significant treatment effect of bevacizumab 15 mg/kg compared with placebo (84% versus 76%; $p < 0.02$; Fig. 3), in terms of 1-year survival rates. One-year survival in the bevacizumab 7.5 mg/kg group was 81% and 73% for the overall ITT and elderly ITT subpopulations, respectively, with no statistically significant difference versus placebo.

3.2. *Safety*

In both the overall ITT and elderly ITT subpopulation, the safety profile of bevacizumab plus docetaxel was consistent with the known adverse effects of each agent, and there were no substantial differences in safety between the groups. Median dose intensities for placebo/bevacizumab were similar between the elderly and overall ITT populations: 100% and 98% for placebo, 99.5% and 97% for bevacizumab 7.5 mg/kg, and 99.2% and 96% for bevacizumab 15 mg/kg, respectively. Median docetaxel dose intensity was also similar between the two populations: 97.2% and 95% in the placebo arm, 91.1% and 91% in the bevacizumab 7.5 mg/kg arm, and 95.5% and 89% in the bevacizumab 15 mg/kg arm, respectively. In addition, the median number of treatment cycles was similar for each agent in the elderly and overall ITT populations: placebo 9 cycles (elderly) and 10 cycles (ITT) with docetaxel 6 cycles (elderly) and 7 cycles (ITT); bevacizumab 7.5 mg/kg 9 cycles (elderly) and 11 cycles (ITT) with docetaxel 7 cycles (elderly) and 7 cycles (ITT); bevacizumab 15 mg/kg 10 cycles (elderly) and 11 cycles (ITT) with docetaxel 6 cycles (elderly) and 8 cycles (ITT).

The majority of adverse events in both populations were known toxicities of docetaxel. In the elderly subgroup, the incidence of adverse events of grade $\geqslant 3$ was 76%, 88% and

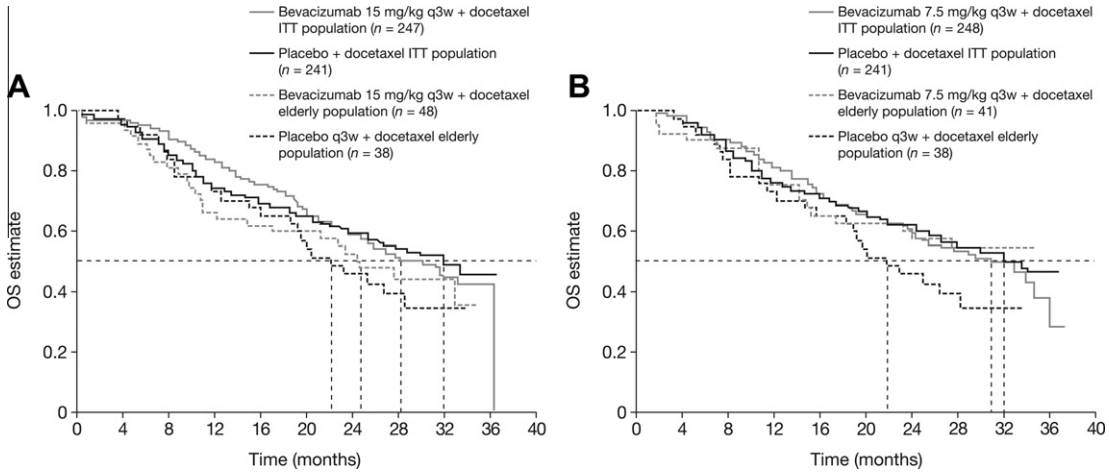

Fig. 3 – Kaplan–Meier curves of OS in the overall ITT population and the elderly ITT subpopulation for (A) bevacizumab 15 mg/kg plus docetaxel versus placebo plus docetaxel; and (B) bevacizumab 7.5 mg/kg plus docetaxel versus placebo plus docetaxel. OS: overall survival; ITT: intent-to-treat; q3w: every 3 weeks; HR: hazard ratio.

Table 2 – Grade 3–5 adverse events of special interest in the overall safety population and the elderly subpopulation.

Adverse event, *n* (%)	Randomised treatment arm					
	Placebo + docetaxel		Bevacizumab 7.5 mg/kg + docetaxel		Bevacizumab 15 mg/kg + docetaxel	
	Safety population (*n* = 231)	⩾65 years (*n* = 38)	Safety population (*n* = 252)	⩾65 years (*n* = 41)	Safety population (*n* = 247)	⩾65 years (*n* = 48)
All	72 (31.2)	21 (56.8)	93 (36.9)	21 (51.2)	94 (38.1)	31 (64.6)
Neutropenia	40 (17.3)	7 (18.9)	50 (19.8)	11 (26.8)	49 (19.8)	16 (33.3)
Febrile neutropenia	26 (11.3)	10 (27.0)	38 (15.1)	7 (17.1)	40 (16.2)	9 (18.8)
Venous thromboembolic event	7 (3.0)	3 (8.1)	4 (1.6)	1 (2.4)	3 (1.2)	3 (6.3)
Hypertension	3 (1.3)	1 (2.7)	2 (0.8)	0	11 (4.5)	3 (6.3)
Bleeding event	2 (0.9)	1 (2.7)	3 (1.2)	1 (2.4)	2 (0.8)	2 (4.2)
Fistula/abscess	1 (0.4)	NR	2 (0.8)	NR	1 (0.4)	NR
Gastrointestinal perforation	2 (0.9)	NR	1 (0.4)	NR	0	NR
Wound-healing complication	2 (0.9)	0	1 (0.4)	0	1 (0.4)	0
CHF	0	0	3 (1.2)	1 (2.4)	0	0
Proteinuria	0	0	2 (0.8)	1 (2.4)	5 (2.0)	2 (4.2)
Arterial thromboembolic event	0	1 (2.7)	0	0	2 (0.8)	1 (2.1)

CHF: congestive heart failure; NR: not reported.

88% in the placebo, bevacizumab 7.5 mg/kg and bevacizumab 15 mg/kg treatment arms, respectively; slightly higher than observed in the overall safety population (67%, 78% and 75%, respectively). Around one-quarter of patients discontinued treatment due to adverse effects thought to be related to treatment in the elderly subpopulation (placebo 26%; bevacizumab 7.5 mg 22%; bevacizumab 15 mg/kg 25%), compared with rates of 14%, 12%, 9%, respectively, in the overall safety population.

Among the elderly patients, grade 5 adverse events were recorded in one patient (3%) in the placebo arm (febrile neutropenia), three patients (7%) in the bevacizumab 7.5 mg/kg arm (multi-organ failure, septic shock and respiratory failure), and two patients (4%) in the bevacizumab 15 mg/kg arm (febrile neutropenia and diarrhoea). In the overall safety analysis, rates of death related to adverse events were 2% (placebo) or 3% (bevacizumab arms).

In both the elderly and overall safety populations, adverse effects of special interest (overall and grade ⩾ 3) were generally more common with bevacizumab treatment. The highest incidences were in all grade bleeding (primarily epistaxis; placebo, 21.6%; bevacizumab 7.5 mg/kg, 61.0%; bevacizumab 15 mg/kg, 35.4%) and neutropenia (placebo, 18.9%; bevacizumab 7.5 mg/kg, 29.2%; bevacizumab 15 mg/kg, 43.8%) in the elderly population and in all grade bleeding (primarily epistaxis; placebo, 19.5%; bevacizumab 7.5 mg/kg, 48.4%; bevacizumab 15 mg/kg, 49.4%) and hypertension (placebo, 10.0%; bevacizumab 7.5 mg/kg, 14.3%; bevacizumab 15 mg/kg, 21.9%) in the overall safety population. In the elderly population, the bevacizumab-related increase in grade ⩾ 3

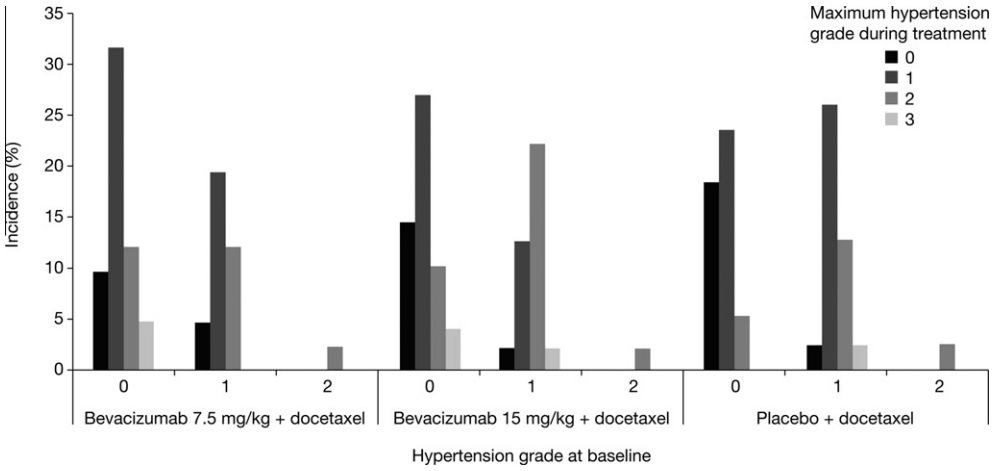

Fig. 4 – Relationship between presence and severity of hypertension at baseline and development of hypertension during study treatment in the elderly subpopulation.

adverse events with bevacizumab versus placebo was largely attributable to hypertension in the higher dose bevacizumab treatment arm (6.3% versus 2.7%); the incidence of grade ⩾ 3 hypertension was also slightly increased in the higher dose bevacizumab treatment arm in the elderly population (6.3%) versus the overall safety population (4.5%) but not in the lower dose bevacizumab treatment arm (0.0% versus 0.8%; Table 2). The main docetaxel-related increase in grade ⩾ 3 adverse events was neutropenia in the elderly subpopulation (33.3% bevacizumab 15 mg/kg, 26.8% bevacizumab 7.5 mg/kg, 18.9% placebo; Table 2). Grade ⩾ 3 cardiovascular events were no more frequent in the elderly than in the overall safety population (Table 2). Congestive heart failure (grade 3) occurred in three patients in the bevacizumab 7.5 mg/kg arm, one aged ⩾ 65 years. The rates of grade ⩾ 3 proteinuria (4.2% versus 2.0%), bleeding events (4.2% versus 0.8%) and venous thromboembolic events (6.3% versus 1.2%) in the bevacizumab 15 mg/kg arm were slightly increased in the elderly population versus the overall safety population.

In elderly patients, the incidence of most adverse effects was similar between the two bevacizumab arms. However, neutropenia, hypertension and venous thromboembolism were higher in the docetaxel plus bevacizumab 15 mg/kg arm than in the 7.5 mg/kg arm (grade 3–5: neutropenia 33.3% versus 26.8%, hypertension 6.3% versus 0% and venous thromboembolism 6.3% versus 2.4%, respectively). Findings were similar in the overall safety population, with epistaxis, hypertension and proteinuria being more common in the docetaxel plus bevacizumab 15 mg/kg arm than the 7.5 mg/kg arm.

Changes in hypertension status in the elderly subpopulation were analysed to evaluate the relationship between the severity and presence of hypertension at baseline and the development of hypertension during study treatment in the elderly subpopulation (Fig. 4). Among elderly patients, 40% and 3% presented at baseline with grade 1 or 2 hypertension, respectively. The incidence of the emergence of grade 2–3 hypertension during treatment was higher in this subset at 25% versus 15% in the subset of elderly patients who did not have hypertension at baseline in the bevacizumab 15 mg/kg arm.

4. Discussion

The treatment of mBC in elderly patients is unsatisfactory. Clinical trials often adopt arbitrary upper age limits, and trials designed for the elderly often start at 65 years with little representation in those over 75 years.[7] Although many older patients can benefit from intensive cancer treatment, evidence suggests that they are undertreated,[15] a major underlying factor being concern over toxicity. Common comorbidities that may impact on treatment success include hypertension, heart disease, stroke and diabetes.[2] Combination regimens tend not to be used in the elderly, due to the lack of a consistent clinical benefit and the potential for serious toxicity,[16–19] and sequential administration of cytotoxic agents is usually preferred in older patients.[20]

In the overall (ITT) population of the AVADO study of first-line treatment in patients with HER2-negative, locally recurrent or mBC, the addition of bevacizumab to docetaxel significantly improved PFS, with little overall impact on treatment toxicity.[13] The PFS benefit (stratified analysis) with bevacizumab was greater at a dose of 15 mg/kg (HR = 0.67; $p < 0.001$) than in the lower dose (7.5 mg/kg) treatment arm (HR = 0.80; $p = 0.045$). In the present retrospective analysis of AVADO patients aged ⩾ 65 years, the efficacy of bevacizumab–docetaxel was consistent with that in the overall primary study analysis. Although the magnitude of the PFS benefit with bevacizumab in the elderly ITT subpopulation and the overall ITT population was similar, the differences from placebo failed to reach statistical significance in the elderly subgroup, presumably due to the small patient numbers; the treatment effect in the higher dose bevacizumab treatment arm approached significance (HR = 0.63; $p = 0.07$). The median dose intensities for both docetaxel and bevacizumab (both doses) were similar in the overall and elderly populations. Dose intensities achieved in both populations were generally above 90%. Although approximately one-quarter of patients in the elderly population compared with 9–14% in the overall safety population discontinued treatment due to adverse events thought to be treatment related, the percentage of patients discontinuing in the elderly population

was similar for bevacizumab/placebo (range 22–26%), suggesting no relationship with bevacizumab exposure. Furthermore, the higher rate of treatment discontinuation among the elderly was not unexpected given the physiologic changes associated with ageing that often lead to an increased likelihood of adverse drug reactions.[21] The median number of treatment cycles was not markedly different in the elderly and overall populations with most patients receiving 6–8 cycles of docetaxel and 9–11 cycles of bevacizumab. These data reflect the feasibility of the administration of such treatment in elderly patients.

The present findings are consistent with other randomised phase III studies of bevacizumab in patients with previously untreated mBC. E2100 evaluated paclitaxel (90 mg/m^2 every week for 3 weeks) plus bevacizumab 10 mg/kg (weeks 1 and 3) versus paclitaxel alone in first-line mBC ($n = 685$).[22] In patients aged $\geqslant$ 65 years, median PFS was substantially increased compared with paclitaxel alone (10.4 versus 6.1 months; HR = 0.67).[23] RIBBON-1 compared bevacizumab 3-weekly 15 mg/kg in combination with standard chemotherapy (anthracycline based, taxane or capecitabine) with chemotherapy plus placebo.[24] Among patients aged $\geqslant$ 65 years receiving taxane or anthracycline chemotherapy, median PFS was extended from 8.5 to 10.1 months with the addition of bevacizumab (HR = 0.83), while the PFS benefit was more pronounced for the combination of bevacizumab with capecitabine (9.1 versus 6.2 months; HR = 0.69).[25] The open-label, international ATHENA study evaluated the safety of bevacizumab combined with taxane-based chemotherapy as first-line treatment in 2251 patients with HER2-negative locally relapsed or mBC. An exploratory analysis showed a greater incidence of grade $\geqslant$ 3 hypertension and proteinuria in patients aged $\geqslant$ 65 years compared with younger subjects.[26] No significant correlation was observed ($r = 0.054$; $p = 0.291$) regarding the severity of baseline hypertension and the severity of hypertension during bevacizumab-containing treatment.[27] In phase III randomised studies conducted to date investigating bevacizumab as first-line therapy in mBC, the reported improvements in PFS have not translated into a significant benefit in terms of OS.[13,22–27] Consistent with this, the OS analysis in the current study failed to consistently demonstrate a statistically significant OS benefit with bevacizumab in the elderly subgroup versus placebo; however, it should be noted that the trial was not designed or adequately powered to detect a survival difference. The main reasons for the lack of PFS translation into OS in studies of first-line treatment are cross-over, several subsequent lines of therapy and length of post-progression survival. OS is a reasonable study end-point when median post-progression survival is short, but not when median post-progression survival is longer than 12 months.[28]

Discussing treatment options for mBC patients, it is helpful to place our findings into context with doublet chemotherapy. In the AVADO study, response rates achieved were up to 64%, median PFS was up to 10 months and median OS was up to 31 months. The main side-effects of the docetaxel/bevacizumab combination were neutropenia and febrile neutropenia related to docetaxel and hypertension related to bevacizumab. In phase III studies of chemotherapy, the combinations of doxorubicin or epirubicin and either docetaxel or paclitaxel, and doxorubicin or epirubicin plus cyclophosphamide are all proven effective regimens for mBC with response rates of up to 65%, median PFS up to 11 months and median OS up to 30 months (Table 3).[13,19,29–37] The toxicity of chemotherapy regimens takes on heightened importance in the elderly due to reduced functioning and presence of comorbidities. Anthracycline/taxane combinations are among the most effective regimens available in this setting, but unfortunately produce dose-limiting toxicities, the most clinically significant being neutropenia, febrile neutropenia, neurotoxicity and cardiotoxicity.[19,31,34] Doxorubicin plus paclitaxel was associated with grade 4 neutropenia in 89% of patients,[29] and febrile neutropenia (defined as grade 2 fever plus grade 4 neutropenia requiring anti-infectives) in almost one-third of recipients, substantially higher than reported in a comparative arm of doxorubicin plus cyclophosphamide.[29] In addition, an evaluation of cardiac safety in a phase III trial noted the cardiotoxicity of epirubicin plus paclitaxel was proportional to the dose of epirubicin;[38] over 8 cycles of treatment, left ventricular ejection fraction was reduced from 60% to 50% (combination regimen) and 65–60% (sequential regimen).

In the present sub-analysis, the median PFS and response rates in elderly patients, at least in the higher dose bevacizumab arm, appear to be equivalent to those with commonly used doublet chemotherapy regimens in previous studies. The rates of moderate to severe neutropenia, febrile neutropenia and cardiovascular toxicities such as CHF and

Table 3 – Summary of efficacy and safety data for combination regimens in mBC.

Regimen	ORR (%)	Median PFS (months)	Median OS (months)	Main adverse events (grade $\geqslant$ 3)
Docetaxel + bevacizumab[13]	55–64	9–10	30–31	Neutropenia, febrile neutropenia, hypertension
Doxorubicin or epirubicin + taxane (paclitaxel or docetaxel)[19,29–37]	40–65	6–11	13–30	Neutropenia, febrile neutropenia, infection, neurotoxicity, cardiotoxicity
Anthracycline + cyclophosphamide[29,32,33,35]	42–55	6–7	14–21	Neutropenia, febrile neutropenia, cardiotoxicity, nausea/vomiting, stomatitis
Paclitaxel + gemcitabine[36]	41	6	19	Neutropenia, febrile neutropenia, fatigue, alopecia

ORR: overall response rate; PFS: progression-free survival; OS: overall survival.

venous thromboembolism in this sub-analysis are lower than typically encountered with anthracycline/taxane combinations.[31,22,34] Importantly, no unexpected toxicities were encountered in the elderly group. However, it is important to note that caution should be exercised when making cross-trial comparisons due to differences in trial design, inclusion criteria, dosing schedules and duration of treatment.

This sub-analysis of elderly patients included in AVADO has several limitations. The most notable is the small number of evaluable patients aged $\geqslant$ 65 years, reflected in the wide confidence intervals associated with efficacy variables in the elderly group. The subset of patients aged > 65 years in the current study was underrepresented in relation to the overall ITT population (17% versus expected > 40%[39]) and represented a relatively young cohort (median age 67–69 years in the three treatment arms) suggesting that the results cannot be extrapolated unequivocally to the elderly population as a whole. The retrospective nature of the data is a further caveat, as the age group under consideration was not a prespecified subgroup in the main AVADO study. Nevertheless, the elderly treatment groups were reasonably well matched in terms of baseline variables. A selection bias almost certainly applies to the patients in this analysis, reflecting recruitment into a randomised controlled trial. As with the overall ITT AVADO population, the elderly patients appeared relatively fit (approximately 55% having performance status of 0), and the results may not be applicable to more debilitated individuals or those of older age.

5. Conclusions

The rationale for combining cytotoxic therapies and bevacizumab in the treatment of mBC is that this approach would be more effective than standard regimens, while offering acceptable tolerability. The results of this sub-analysis of elderly subjects in AVADO suggest that the combination of docetaxel and bevacizumab offers effective antitumour activity with acceptable tolerability in this vulnerable population.

Author contributions

Xavier Pivot: Provision of patients, data analysis, manuscript writing, final approval of manuscript. Andreas Schneeweiss: Main investigator of the AVADO trial at the National Center for Tumor Diseases, University of Heidelberg, Germany, provision of patients, data analysis, manuscript cross-reading, final approval. Shailendra Verma: Accrual of patients, data review, manuscript analysis, review and final approval. Christoph Thomssen: Provision of patients, data analysis, manuscript writing, final approval of manuscript. José Luis Passos-Coelho: AVADO Principal Investigator at Instituto Português de Oncologia in Lisboa, Portugal, manuscript writing, final approval of manuscript. Giovanni Benedetti: AVADO co-investigator at Medical Oncology Hospital of Macerata, Italy, manuscript writing, final approval of manuscript. Eva Ciruelos: AVADO Principal Investigator at Hospital Universitario 12 de Octubre, Madrid, Spain, manuscript writing, final approval of manuscript. Roger von Moos: Provision of patients, data analysis, manuscript writing, final approval of manuscript. Hong-Tai Chang: Provision of patients, data analysis, manuscript writing, final approval of manuscript. Anja-Alexandra Duenne: Manuscript outline, data analysis, manuscript writing and revision, final approval. David W. Miles: Concept and design of AVADO study, provision of patients, data analysis, manuscript writing, final approval of manuscript.

Conflict of interest statement

Xavier Pivot: received honorarium from Roche SA. There is, however, no conflict of interest in regard to the content of this contribution. Andreas Schneeweiss: received honorarium from Roche and Sanofi-Aventis. There is, however, no conflict of interest in regard to the content of this contribution. Shailendra Verma: received honoraria for Advisory Boards from Roche and Sanofi-Aventis. No conflict of interest in regard to the content of this contribution. Christoph Thomssen: no conflict of interest in regard to the content of this contribution. José Luis Passos-Coelho: received honorarium from Roche as a consultant. However, there is no conflict of interest regarding this manuscript. Giovanni Benedetti: no conflict of interest in regard to the content of this contribution. Eva Ciruelos: no financial conflicts. Roger von Moos: Advisor for Roche, Novartis and Amgen, speaker honoraria from Roche and Amgen. Hong-Tai Chang: no conflicts to declare. Anja-Alexandra Duenne: Roche employee. David W. Miles: received consultancy fees and honoraria for Advisory Boards from Roche.

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