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ORIGINAL REPORT

Phase III Prospective Randomized Comparison Trial of Depot Octreotide Plus Interferon Alfa-2b Versus Depot Octreotide Plus Bevacizumab in Patients With Advanced Carcinoid Tumors: SWOG S0518

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ABSTRACT

Purpose
Treatment options for neuroendocrine tumors (NETs) remain limited. This trial assessed the progression-free survival (PFS) of bevacizumab or interferon alfa-2b (IFN-α-2b) added to octreotide among patients with advanced NETs.

Patients and Methods
Southwest Oncology Group (SWOG) S0518, a phase III study conducted in a US cooperative group system, enrolled patients with advanced grades 1 and 2 NETs with progressive disease or other poor prognostic features. Patients were randomly assigned to treatment with octreotide LAR 20 mg every 21 days with either bevacizumab 15 mg/kg every 21 days or 5 million units of IFN-α-2b three times per week. The primary end point was centrally assessed PFS. This trial is registered with ClinicalTrials.gov as NCT00569127.

Results
A total of 427 patients was enrolled, of whom 214 were allocated to bevacizumab and 213 to IFN-α-2b. The median PFS by central review was 16.6 months (95% CI, 12.9 to 19.6 months) in the bevacizumab arm and was 15.4 months (95% CI, 9.6 to 18.6 months) in the IFN arm (hazard ratio [HR], 0.93; 95% CI, 0.73 to 1.18; $P = .55$). By site review, the median PFS times were 15.4 months (95% CI, 12.6 to 17.2 months) for bevacizumab and 10.6 months (95% CI, 8.5 to 14.4 months) for interferon (HR, 0.90; 95% CI, 0.72 to 1.12; $P = .33$). Time to treatment failure was longer with bevacizumab than with IFN (HR, 0.72; 95% CI, 0.58 to 0.89; $P = .003$). Confirmed radiologic response rates were 12% (95% CI, 8% to 18%) for bevacizumab and 4% (95% CI, 2% to 8%) for IFN. Common adverse events with bevacizumab and octreotide included hypertension (32%), proteinuria (9%), and fatigue (7%); with IFN and octreotide, they included fatigue (27%), neutropenia (12%), and nausea (6%).

Conclusion
No significant differences in PFS were observed between the bevacizumab and IFN arms, which suggests that these agents have similar antitumor activity among patients with advanced NETs.

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INTRODUCTION

Neuroendocrine tumors (NETs), though once thought rare, have experienced an increased incidence.[1] Their clinical course is often indolent but also can be highly aggressive and resistant to therapy. Despite the approval of targeted agents, everolimus and sunitinib, for pancreatic NETs,[2,3] there remains tremendous unmet need in NETs of other sites, previously called carcinoid tumors. Although lanreotide delays progression compared with placebo in indolent gastroenteropancreatic NETs with less than 10% Ki-67 labeling, and everolimus delays progression in progressive NETs that develop in the lung and gastrointestinal tract, additional treatment options are needed.[4,5]

Well-differentiated NETs are highly vascular tumors. Vascular endothelial growth factor (VEGF) expression has been demonstrated in

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both gastrointestinal and pulmonary NETs and is associated with poor outcome.[6-8] In a phase II study of octreotide plus bevacizumab versus octreotide plus pegylated interferon alpha, bevacizumab therapy was associated with a rapid decrease in tumor perfusion, a higher response rate, and a longer progression-free survival (PFS) compared with low-dose pegylated interferon.[9] Subsequently, several smaller phase II studies of bevacizumab in combination with capecitabine, everolimus, temsirolimus, or temozolomide demonstrated promising activity in NETs.[10-14]

Interferon alfa has been widely studied and used in NET. In one meta-analysis of published studies, 37 (12%) of 309 treated patients experienced an objective response.[15] The value of combined interferon and octreotide was tested in a randomized study in which patients with NETs who had undergone debulking by surgery and hepatic artery embolization were randomly assigned to octreotide or octreotide plus interferon. A significant improvement in time to progression was observed in the interferon arm (hazard ratio [HR], 0.28; 95% CI, 0.16 to 0.45).[16] Though controversy remains about the utility of interferon, octreotide plus interferon was considered an accepted systemic therapy option by the National Comprehensive Cancer Network at the time of this study design in 2005.[17]

Southwest Oncology Group (SWOG) S0518 was conducted to determine whether depot octreotide plus bevacizumab prolongs PFS compared with depot octreotide plus interferon alfa-2b in patients with advanced, poor-prognosis NET.

PATIENTS AND METHODS

Patients

Adult patients (age $\geq$ 18 years) with pathologically confirmed, advanced (unresectable or metastatic), grade 1 or grade 2 NET were eligible for participation. Patients must have had one of the following poor-prognosis features: (1) progressive disease; (2) refractory carcinoid syndrome; (3) grade 2 histology and more than six sites of metastasis[1,18]; (4) metastatic hindgut NET[1]; or (5) metastatic gastric NET.[1]

Additional key inclusion criteria included measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0; Zubrod performance status of 0, 1, or 2; and adequate bone marrow, liver, and kidney function. The urine protein creatinine ratio had to be 0.5 or less, or the 24-hour urine protein had to be less than 1,000 mg, for patient enrollment. Patients with a history of hypertension must have had controlled blood pressure ($<$ 150/90 mmHg) and been on a stable regimen of antihypertensive therapy. One prior regimen of cytotoxic chemotherapy or targeted therapy, excluding VEGF inhibitors, was allowed. Prior surgery, liver directed therapy, and radiotherapy were allowed if completed more than 28 days before the start of study therapy, the patient had recovered from the procedure, and there were residual sites of measurable disease. Prior depot octreotide was allowed provided at least 21 days had elapsed since the last dose until the start of study therapy.

Study Oversight

The study was conducted in accordance with Good Clinical Practice, ethical principles of the Declaration of Helsinki, and local regulations. The Cancer Trials Support Unit central institutional review board and local institutional review board at participating centers reviewed and approved the study and all the amendments. All patients provided written informed consent. The SWOG independent Data and Safety Monitoring Committee provided ongoing oversight of safety and study conduct. This trial was registered with ClinicalTrials.gov, number NCT00569127.

All authors contributed to the interpretation of data and the subsequent writing, reviewing, and/or amending of the manuscript; the first draft of the manuscript was prepared by the first author (J.C.Y.) and SWOG statisticians (K.A.G., S.M.). All authors vouched for the accuracy and completeness of the data and attested that the study conformed to the protocol and analysis plan.

Random Assignment

In this open-label, phase III study, patients were randomly assigned in a 1:1 manner into the two treatment groups by using a dynamic balancing algorithm by Pocock and Simon,[19] with stratification on the basis of primary site (small bowel, cecum, appendix [midgut] *v* other), progressive disease (radiologic report within 6 months of registration that documented progressive disease), grade (1 *v* 2), and prior octreotide (treatment within 2 months before registration *v* none within 2 months).

Treatment Plan

After random assignment, all patients received depot octreotide 20 mg intramuscularly on day 1 of each 21-day cycle. This dosing regimen of octreotide LAR delivered approximately the same dose of octreotide (0.95 mg/day) as the 30-mg monthly regimen used in the PROMID study.[20] In arm 1, patients received bevacizumab 15 mg/kg intravenously on day 1; in arm 2, they received 5 million units of interferon alfa-2b three times per week as a subcutaneous injection. A maximal delay of 4 weeks was allowed for safety. No dose reduction was allowed in the bevacizumab arm. In the interferon arm, the protocol permitted, at the discretion of the treating investigator, a 1-week treatment break from interferon alfa every 6 weeks. Sequential dose reduction for neutropenia or clinically significant grade 3 or 4 adverse events to 3, 2, or 1 million units three times per week was allowed per protocol in the interferon arm.

Study Assessments

The primary study end point of PFS from random assignment was assessed independently and centrally (but case-level results were not shared in real-time with sites) according to RECIST 1.0. In both arms, tumor measurements were made by multiphasic computed tomography (CT) scans or magnetic resonance imaging (MRI) at baseline and every 9 weeks. Central radiology review, blinded to treatment assignment, was performed by the American College of Radiology Imaging Network.

A retrospective central pathology review was conducted by an experienced NET pathologist (C.M.). Adequate tumor tissue was assessed in 341 patient cases (80%). Differentiation and grade, determined by mitotic rate, were determined and classified.

Adverse events (AEs) were assessed as per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. All patients who received at least one dose of the study drug and had at least one postbaseline safety evaluation were included in the safety analyses. Sites were required to report only AEs of grade 3 or higher.

Biomarkers

Baseline blood chromogranin A (CGA), neuron-specific enolase (NSE), and 24-hour urinary 5-hydroxyindoleacetic acid (5HIAA) were collected and assayed per standard medical practice in a commercial laboratory used by participating sites. Baseline CGA was considered elevated if it was greater than twice upper limit of normal.[2,5,21,22] 5HIAA and NSE were considered elevated if they were greater than the laboratory upper limit of normal. Additional exploratory biomarkers, including somatostatin receptor scintigraphy as well as blood- and tissue- based assessment of angiogenic biomarkers, are planned.

Outcomes

The primary outcome, PFS according to central radiology review, was defined as one of the following events: documented progression of lesions

on the basis of centrally reviewed scans, new lesion formation, symptomatic deterioration (as documented by the institution), or death. Patients were censored at the time of the last scan that was centrally reviewed and did not show progression.

Secondary outcomes included site-reported PFS, overall survival (OS), time to treatment failure (TTF), objective response (confirmed and unconfirmed complete response and partial response), and toxicity. TTF criteria included central review–based progression of lesions, symptomatic deterioration, death, or discontinuation of treatment as events; censoring was defined as for the primary outcome. For site-reported PFS and OS, censoring time was defined as the date of last contact. All time-to-event end points were measured from the time of random assignment. Patients were observed until death or 3 years after registration, whichever occurred first.

Statistical Considerations

At the time of the trial design, little information was available about PFS of NETs on the basis of large prospective clinical trials that used RECIST. On the basis of available information, it was estimated that the median PFS in the octreotide-plus-interferon group of patients was 6 months, and that an improvement of 50% (HR of 0.67, which corresponded to a median PFS of 9 months) would be of clinical interest. Before the first interim analysis, the event rate was lower than originally hypothesized and was more consistent with approximately 15 months. Thus, the originally proposed HR of 0.67 would correspond to a median of 22.5 months, a difference of 7.5 months. It was determined that an HR of 0.71 (which corresponded to a median of 21 months) would be of sufficient clinical interest. If an additional year of accrual (from 3 to 4 years) was assumed, and a total of 2 years of follow-up was required after the end of accrual, 400 eligible patients would provide 84% power to detect a 0.71 HR on the basis of a two-sided .05-level test.

According to the intent-to-treat principle, all eligible patients were included in the analyses according to the randomized treatment assignment, regardless of actual treatments received. Probabilities of OS, PFS, and TTF were estimated by using the Kaplan-Meier method. Statistical differences in event rates between treatment arms were assessed via stratified Cox regression model. Disease response was described by waterfall plots, separately by treatment arm, and rates of objective response were compared via the χ^2 test in the subset of patients with measurable disease. Statistical differences in central radiology review of PFS and OS event rates between groups according to elevated versus normal levels of potential biomarkers (CGA, NSE, and 5HIAA) were assessed via the Cox regression model. The following factors were considered as potential PFS treatment effect modifiers: midgut versus nonmidgut disease, grade 1 versus 2 disease, Zubrod performance status of 0 versus 1 or 2, and normal versus elevated CGA, NSE, and 5HIAA levels. Tests for interaction between these variables and treatment assignment were performed within the Cox

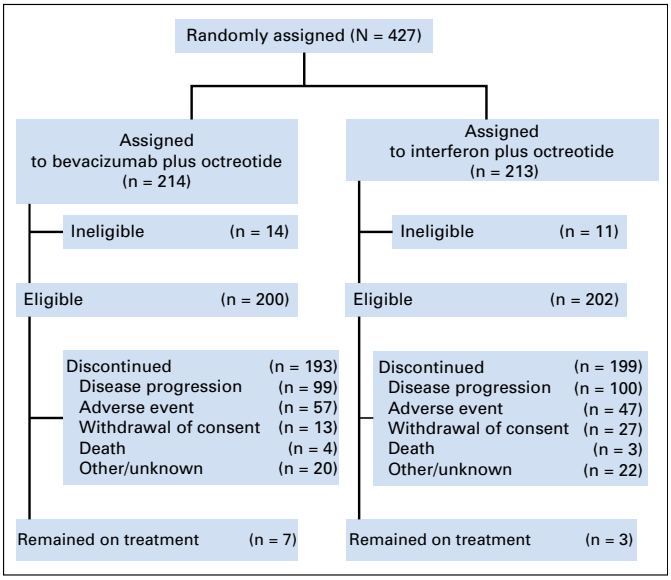

Fig 1. CONSORT diagram.

Table 1. Patient Characteristics

Characteristic	No. (%) of Patients: Bevacizumab + Octreotide LAR (n = 200*)	No. (%) of Patients: IFN-α-2b + Octreotide LAR (n = 202*)
Median (range) age, years	61 (27-85)	61 (23-85)
Sex		
Male	102 (51)	90 (45)
Female	98 (49)	112 (55)
Zubrod PS		
0	107 (54)	99 (49)
1	88 (44)	98 (49)
2	5 (3)	4 (2)
Site		
Small bowel, cecum, appendix	71 (35)	72 (36)
Other	129 (64)	130 (64)
PD since diagnosis	182 (91)	188 (93)
Refractory carcinoid syndrome	16/184 (9)	21/187 (11)
Histologic grade		
1	169 (84)	171 (85)
2	31 (15)	31 (15)
Site of involvement		
Liver	172 (86)	173 (86)
Distant lymph nodes	47 (24)	43 (21)
Bone	38 (19)	34 (17)
Other abdominal	43 (22)	44 (22)
Other	50 (25)	51 (25)
Biomarker		
CGA > 2× ULN	124/197 (63)	117/196 (60)
NSE > ULN	62/195 (32)	64/189 (34)
5HIAA > ULN	127/193 (66)	113/191 (59)
Prior therapy		
Octreotide within 2 months	114 (57)	115 (57)
Radiation therapy	67 (34)	62 (31)
Chemotherapy	56 (28)	50 (25)
Central pathology review		
Differentiation		
Well differentiated	140 (83)	144 (83)
Moderately differentiated	25 (15)	28 (16)
Poorly differentiated	3 (2)	1 (1)
Grade		
1	141 (84)	144 (83)
2	24 (14)	28 (16)
3	3 (2)	1 (1)
Mitotic rate, per 10 HPF†		
< 2 (grade 1)	81/111 (73)	95/122 (78)
2-20 (grade 2)	29/111 (26)	27/122 (22)
> 20 (grade 3)	1/111 (1)	0/122 (0)

NOTE. Total No. of patients are listed in table cells when they differ from the group totals.

Abbreviations: 5HIAA, 5-hydroxyindoleacetic acid; CGA, chromogranin A; HPF, high-powered field; IFN-α-2b, interferon alfa-2b; LAR, long-acting repeatable; NSE, neuron-specific enolase; PD, progressive disease; PS, performance status; ULN, upper limit of normal.

*No. of patients assessed for central pathology review: n = 168 in bevacizumab arm; n = 173 in IFN-α-2b arm.

†Mitotic rate determined when adequate tumor material that contained at least 10 HPF were available.

regression model. The strength of associations between patient characteristics and treatment assignment were tested via the t or χ^2 test. All P values were two sided.

RESULTS

Between December 2007 and September 2012, 427 patients with advanced, well-differentiated, grade 1 or 2 NETs with progressive disease or other poor prognostic features were randomly assigned (1:1) to the treatment arms (Fig 1). Four hundred two patients were eligible and included in the efficacy analyses. The baseline characteristics of patients were balanced across arms (Table 1).

Most patients had good performance statuses. In the bevacizumab and interferon arms, 54% and 49% of the patients, respectively, had a performance status of zero. Midgut was the most common primary site; 35% and 36% of the patients in the bevacizumab and interferon arms, respectively, had small bowel, cecum, or appendix as primary sites. Radiologic disease progression was documented in 91% and 93% of patients in the bevacizumab and interferon arms, respectively. More than half of the patients in each arm were receiving octreotide at the time of study entry.

At the time of final analysis, 10 patients were still taking study treatment. In the bevacizumab and interferon arms, 193 and 199 patients, respectively, discontinued protocol treatment. Common reasons for treatment discontinuation included disease progression, AEs, and withdrawal of consent (Fig 1).

PFS

No significant differences were observed in the primary end point, PFS by blinded central radiology review (Fig 2A). The median PFS assessed by central review was 16.6 months (95% CI, 12.9 to 19.6 months) in the bevacizumab arm and was

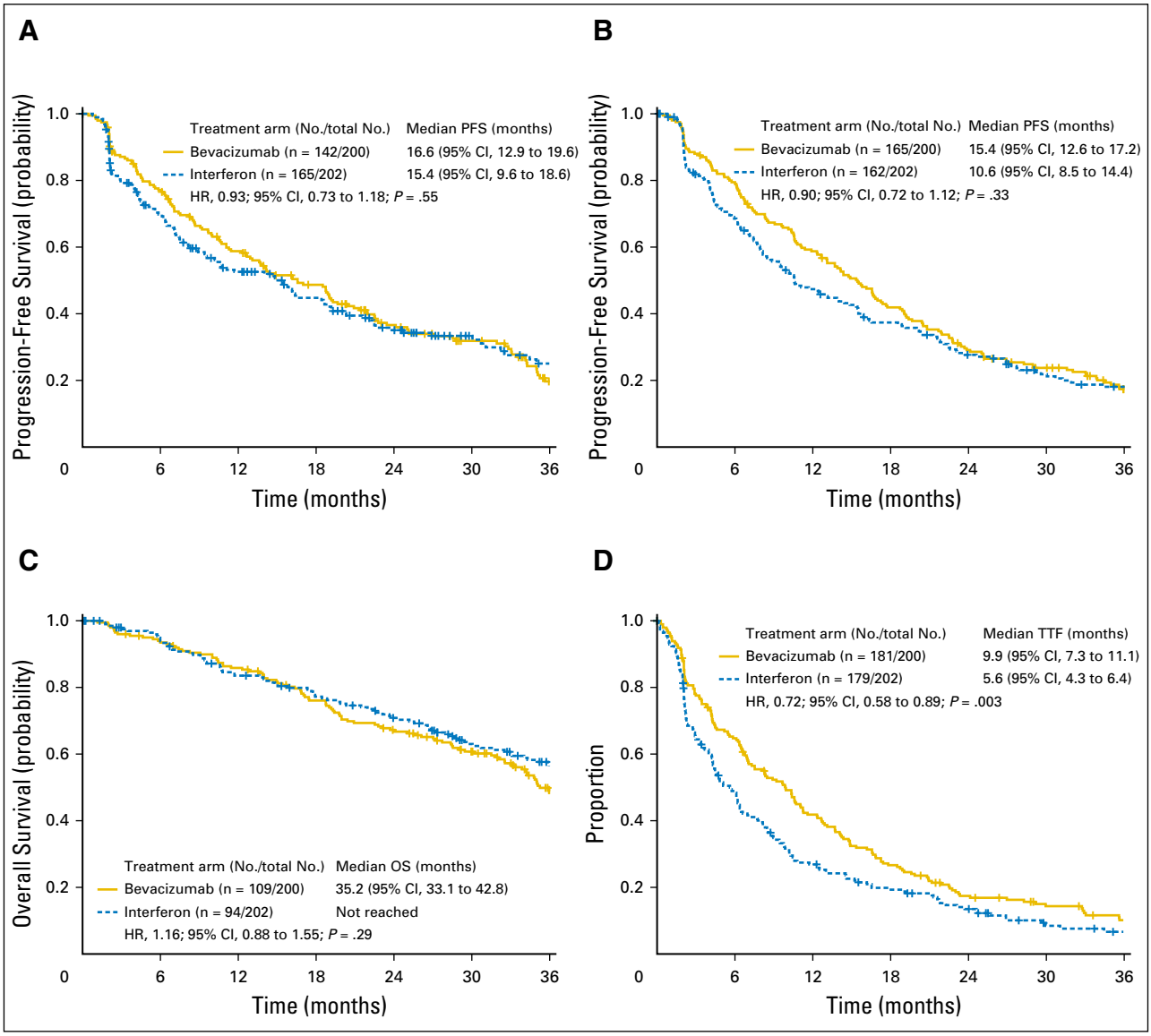

Fig 2. Survival plots by treatment arm: (A) central-review progression-free survival (PFS); (B) site-review (investigator-reviewed) PFS; (C) overall survival; (D) time to treatment failure.

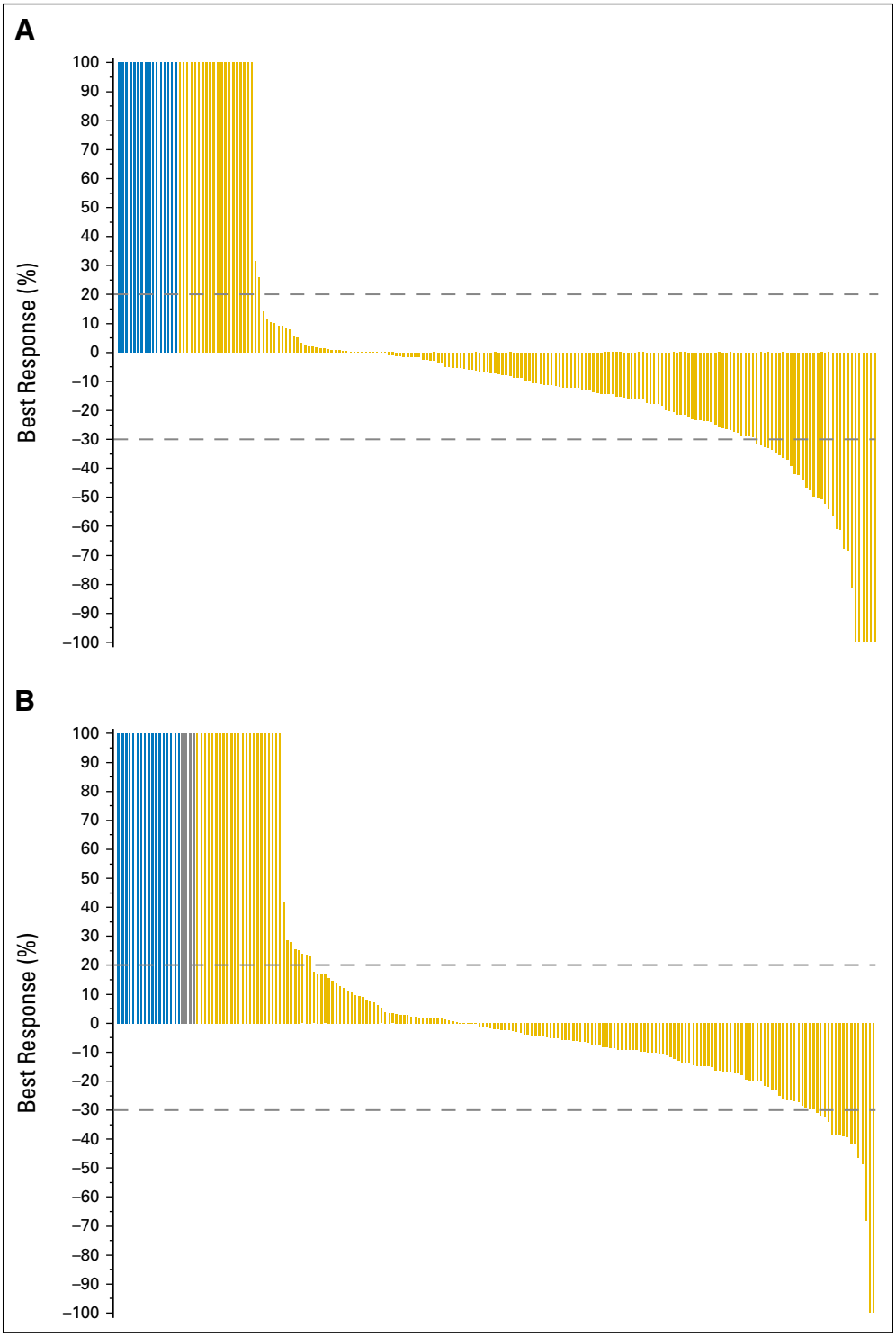

Fig 3. Waterfall plots: (A) bevacizumab; (B) interferon. The bars on each plot represent the largest decrease under baseline of the sum of longest diameters of all target measurable lesions or, if no decrease was observed, the smallest increase in the sum of longest diameters of target measurable lesions. Patients in whom the smallest increase in measurable lesions was greater than 100% over baseline had data truncated at 100%. Data for patients in whom the best response was progression because of new lesions, death (as a result of disease), or clear worsening of nonmeasurable disease are represented by a bar that shows a 100% increase. Data for patients in whom the best response could not be determined because of symptomatic deterioration or early death (before any follow-up assessments and clearly not as a result of disease) are represented by a gray bar showing 100% increase. Data for patients in whom the best response could not be determined because of inadequate assessment are represented on the far-left side of the plot with a blue bar that shows a 100% increase.

15.4 months (95% CI, 9.6 to 18.6 months) in the interferon arm (HR, 0.93; 95% CI, 0.73 to 1.18; $P = .55$). By investigator review, the median PFS was 15.4 months (95% CI, 12.6 to 17.2 months) in the bevacizumab arm and was 10.6 months (95% CI, 8.5 to 14.4 months) in the interferon arm (Fig 2B). Though 4.8 months longer, the difference in investigator-determined PFS was not statistically significant (HR, 0.90; 95% CI, 0.72 to 1.12; $P = .33$).

Other Efficacy Measurements

There were no significant differences in OS (HR, 1.16; 95% CI, 0.88 to 1.55; $P = .29$). The median OS was 35.2 months (95% CI, 33.1 to 42.8 months) in the bevacizumab arm and was not reached on the basis of 36 months of follow-up in the interferon arm (Fig 2C). The 12-, 24-, and 36- month survival rates for the bevacizumab versus interferon arms were 86% versus 84%, 67% versus 71%, and 49% versus 56%, respectively.

Table 2. Safety Analysis: CTCAE Events of Grade 3 or Higher

Event	No. (%) of Patients	
	Bevacizumab + Octreotide LAR (n = 197)	IFN-α-2b + Octreotide LAR (n = 194)
Hypertension	62 (31.5)	4 (2.1)
Fatigue	13 (6.6)	50 (25.8)
Neutropenia	0 (0.0)	23 (11.9)
Proteinuria	17 (8.6)	1 (0.5)
Leukopenia	2 (1.0)	14 (7.2)
Nausea	5 (2.5)	9 (4.6)
Headache	9 (4.6)	3 (1.5)
Diarrhea	7 (3.6)	9 (4.6)
Anorexia	1 (0.5)	8 (4.1)
Abdominal pain	7 (3.6)	5 (2.6)
Elevated AST	1 (0.5)	6 (3.1)
Depression	1 (0.5)	7 (3.6)
Elevated alkaline phosphatase	2 (1.0)	6 (3.1)
Dehydration	3 (1.5)	5 (2.6)
Hyperglycemia	2 (1.0)	5 (2.6)
Lymphopenia	3 (1.5)	5 (2.6)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; IFN-α-2b, interferon alfa-2b; LAR, long-acting repeatable.

TTF was significantly longer in the bevacizumab arm (median, 9.9 months; 95% CI, 7.3 to 11.1 months) than in the interferon arm (median, 5.6 months; 95% CI, 4.3 to 6.4 months); the HR was 0.72 (95% CI, 0.58 to 0.89; $P = .003$) in favor of bevacizumab (Fig 2D).

Although response rates were modest in both arms, objective response was more common in the bevacizumab than interferon arm ($P = .008$). In the bevacizumab arm, two patients (1%) had a complete response, and 22 patients (12%) had a partial response; in the interferon arm, there were no complete responses, and eight patients (4%) had a partial response. Waterfall plots of the best percentage change in target lesion measurement sums demonstrated that 65% of patients in the bevacizumab arm and 53% of patients in the interferon arm experienced some degree of tumor shrinkage (Fig 3).

Safety

All patients who received at least one dose of study drug were included in safety analyses. Without adjustment for duration of treatment, dose reductions or temporary treatment interruptions occurred in 116 (59%) of 197 patients who received bevacizumab and in 145 (75%) of 193 who received interferon.

AEs were consistent with the known safety profiles of bevacizumab and interferon. Rates of on-treatment deaths (those that occurred during the receipt of study medication or within 30 days of discontinuation of therapy) were similar between the treatment arms (n = 7 [4%] in the bevacizumab arm and n = 8 [4%] in the interferon arm).

Treatment-related AEs that occurred in at least 10% of patients are listed in Table 2. The most common were hypertension (32%) and proteinuria (8.6%) in the bevacizumab arm and fatigue (26.8%) and neutropenia (11.9%) in the interferon arm. The most frequent grade 3 or 4 AEs included hypertension, proteinuria, fatigue, and headache in the bevacizumab arm and fatigue, neutropenia, nausea, and diarrhea in the interferon arm. Treatment discontinuations attributed to AEs were reported in 57 patients (30%) who received bevacizumab and 47 patients (24%) who received interferon.

Biomarkers

Baseline CGA, NSE, and 5HIAA levels were elevated in 61%, 33%, and 63% of patients, respectively. Elevated CGA was associated with shorter OS ($P < .001$; Fig 4A). Elevated NSE was associated with shorter PFS by central radiology review ($P = .01$) and OS ($P < .001$). Elevated 5HIAA was associated with shorter OS ($P = .04$).

Subgroup Analyses

Of the factors considered for subgroup analysis, only biomarker 5HIAA was associated with a differential effect of bevacizumab on central review PFS. Patients with elevated 5HIAA were less likely than those with normal 5HIAA to benefit from bevacizumab ($P = .006$).

DISCUSSION

Despite recent advances, there remains a significant need for more therapeutic options for NETs. Although no significant differences in PFS were observed between the bevacizumab and the interferon arms of the SWOG S0518 study, the observed PFS for both the bevacizumab (median, 16.6 months) and the interferon (median, 15.4 months) arms were long compared with the placebo arms of recent phase III studies. For example, the median PFS observed in the PROMID, RADIANT-2 (RAD001 in Advanced Neuroendocrine Tumours), and RADIANT-4 studies were 6 months, 11.3 months, and 3.9 months, respectively.[5,20,22] Only in the CLARINET (Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors) study, which enrolled patients with predominantly stable disease, was a longer median PFS of 18 months observed.[4]

Bevacizumab did not prove to be superior to interferon in terms of PFS. The observed median duration and Kaplan Meier curves were similar. Ultimately, assessment of whether bevacizumab is active in NETs would depend on the extent that interferon truly delays progression. Given the significant risk reduction (HR, 0.28; 95% CI, 0.16 to 0.45) previously described when octreotide plus interferon was compared with octreotide alone, bevacizumab seems to have activity, though it is not proven superior to interferon. This is supported by the observation that substantial numbers of patients experienced some degree of tumor shrinkage in both arms of the study (65% of patients in bevacizumab arm and 53% of patients in the interferon arm), and a higher RECIST response rate of 12% versus 4% ($P = .008$) was observed in the bevacizumab arm. A placebo control arm was not included in this study, so definitive conclusions are not possible about the activity of bevacizumab in NETs.

Although PFS durations were similar, a significant difference in TTF was observed in favor of bevacizumab. This likely is due to differences in safety profiles between the two agents. Although the most common adverse events associated with bevacizumab were

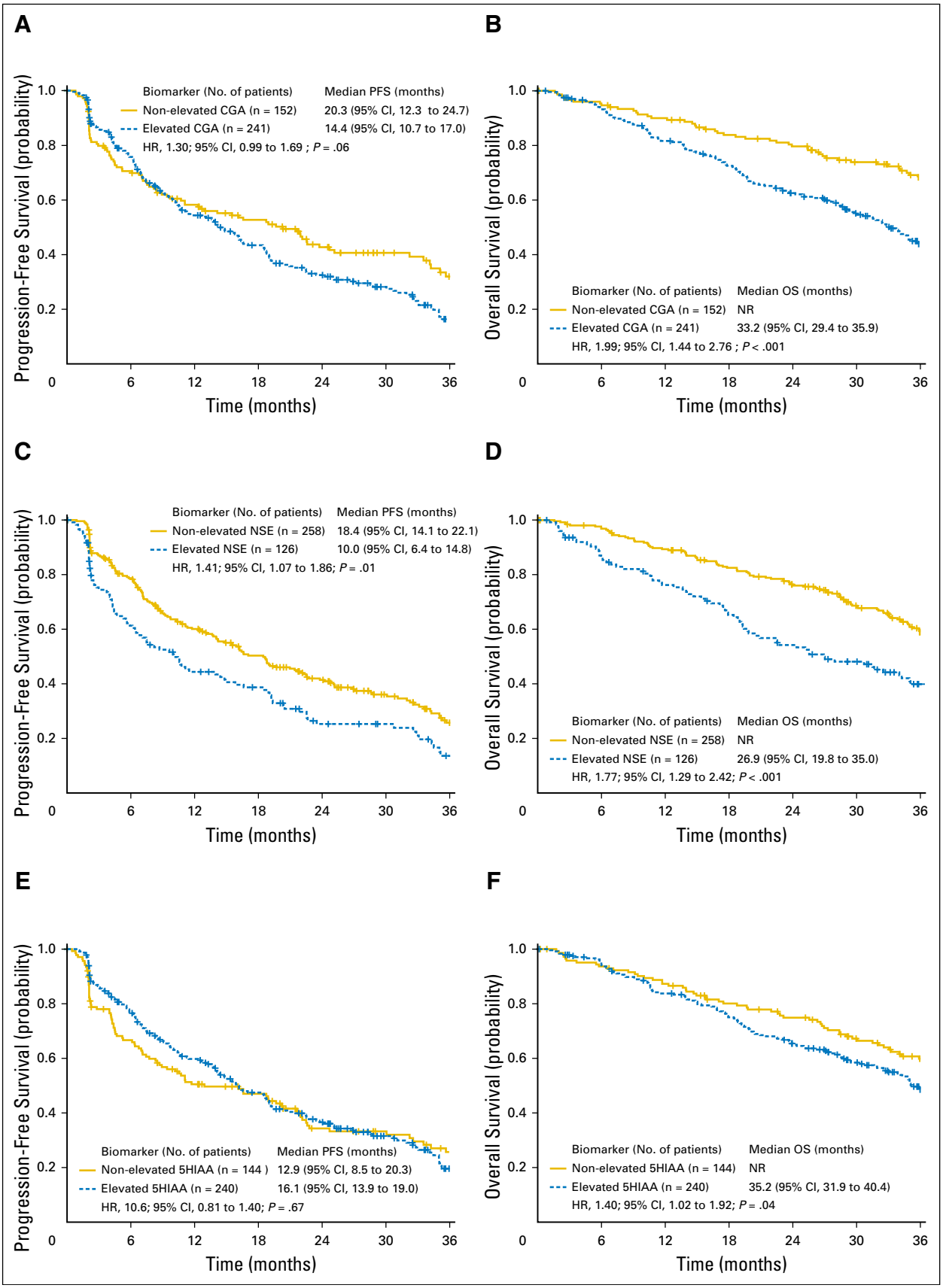

Fig 4. Survival plots by biomarker levels: (A) central-review progression-free survival (PFS) by chromogranin A (CGA); (B) overall survival by CGA; (C) central-review PFS by neuron-specific enolase (NSE); (D) overall survival (OS) by NSE; (E) central-review PFS by 5-hydroxyindoleacetic acid (5HIAA); and (F) overall survival by 5HIAA. HR, hazard ratio; NR, not reported.

measurement findings, such as hypertension and proteinuria, greater than a quarter of patients in the interferon arm experienced severe grade 3 or 4 fatigue, which may account for the greater number patients who withdrew consent in the interferon arm.

In this analysis, we also assessed the role of CGA, NSE, and 5HIAA as biomarkers in NETs. Although the prognostic roles of CGA and NSE have been reported in pancreatic NETs,[23] their value for NETs of nonpancreatic origin has not be been validated in prospective clinical trials. Although NSE, elevated in 33% of patients, is not a sensitive diagnostic biomarker, this study showed convincing evidence that both CGA ($P < .001$) and NSE ($P < .001$) are important prognostic factors for OS. NSE was also a significant prognostic factor for PFS ($P = .01$). Earlier studies also reported that 5HIAA was prognostic, but this study did not find 5HIAA to be prognostic for PFS; it did find moderate evidence that 5HIAA is prognostic for OS. This different result may be due, in part, to the choice of cutoff point or to the inclusion patients who had a variety of primary sites in which nonsecretory tumors may have a worse prognosis.

In summary, octreotide plus bevacizumab and octreotide plus interferon are associated with similar PFS in patients with advanced NETs. Although no improvement in PFS was observed, bevacizumab was associated with a higher response rate, a longer TTF, and a lower rate of fatigue than interferon.

Many advances have been made in the rapidly evolving field of NET since the conception of this study. These include the approval of everolimus[2] and sunitinib[3] for pancreatic NETs, the approval of lanreotide for gastroenteropancreatic NETs,[4] as well as the more recent approval of everolimus for lung and gastrointestinal NETs.[5] Whether VEGF inhibition will have a future role in NETs that do not begin in the pancreas remains an important question and is the subject of an ongoing randomized, phase II studies to compare pazopanib to placebo; this study has completed accrual (NCT01841736). Recent results also suggest that it is safe and feasible to add bevacizumab to everolimus to improve response rates and PFS, albeit at a cost of increased adverse events.[12,24] A larger question to address for future development is whether sequential application of active agents or a combination approach will have the best longer-term outcome.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: James C. Yao, Helen Chen, Charles D. Blanke
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