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Lung Cancer

A Randomized, Double-Blinded, Phase II Trial of Carboplatin and Pemetrexed with or without Apatorsen (OGX-427) in Patients with Previously Untreated Stage IV Non-Squamous-Non-Small-Cell Lung Cancer: The SPRUCE Trial

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Heat-shock protein 27 • Non-small cell lung cancer • Oligonucleotide

Abstract

Background. This randomized, double-blinded, phase II trial evaluated the efficacy of carboplatin and pemetrexed plus either apatorsen, an antisense oligonucleotide targeting heat shock protein (Hsp) 27 mRNA, or placebo in patients with previously untreated metastatic nonsquamous non-small cell lung cancer (NSCLC).

Methods. Patients were randomized 1:1 to Arm A (carboplatin/pemetrexed plus apatorsen) or Arm B (carboplatin/pemetrexed plus placebo). Treatment was administered in 21-day cycles, with restaging every two cycles, until progression or intolerable toxicity. Serum Hsp27 levels were analyzed at baseline and during treatment. The primary endpoint was progression-free survival (PFS); secondary endpoints included overall survival (OS), objective response rate, and toxicity.

Results. The trial enrolled 155 patients (median age 66 years; 44% Eastern Cooperative Oncology Group performance status 0). Toxicities were similar in the 2 treatment arms; cytopenias, nausea, vomiting, and fatigue were the most frequent treatment-related adverse events. Median PFS and OS were 6.0 and 10.8 months, respectively, for Arm A, and 4.9 and 11.8 months for Arm B (differences not statistically significant). Overall response rates were 27% for Arm A and 32% for Arm B. Sixteen patients (12%) had high serum levels of Hsp27 at baseline. In this small group, patients who received apatorsen had median PFS of 10.8 months, and those who received placebo had median PFS 4.8 months.

Conclusion. The addition of apatorsen to carboplatin and pemetrexed was well tolerated but did not improve outcomes in patients with metastatic nonsquamous NSCLC cancer in the first-line setting. ***The Oncologist*** 2019;24:e1409–e1416

Implications for Practice: This randomized, double-blinded, phase II trial evaluated the efficacy of carboplatin and pemetrexed plus either apatorsen, an antisense oligonucleotide targeting heat shock protein 27 mRNA, or placebo in patients with previously untreated metastatic nonsquamous non-small cell lung cancer (NSCLC). The addition of apatorsen to carboplatin and pemetrexed was well tolerated but did not improve outcomes in patients with metastatic nonsquamous NSCLC cancer in the first-line setting.

Introduction

Lung cancer represents the leading cause of cancer-related mortality worldwide [1, 2]. Nearly half of patients present with metastatic disease [2], and the prognosis for patients with advanced NSCLC is poor with <5% of patients alive 5 years after diagnosis [3]. Combination chemotherapy can extend survival and improve the quality of life in patients

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with advanced NSCLC. Although treatment paradigms are changing, the combination of carboplatin and pemetrexed is still considered a standard first-line treatment for many patients with nonsquamous NSCLC [4].

Heat shock protein 27 (Hsp27) is a protein chaperone whose expression is induced by cytotoxic chemotherapy, as well as other cell stressors including hyperthermia, oxidative stress, and radiation, resulting in cytoprotection against these insults [5, 6]. Hsp27 is commonly overexpressed in cancer cells, serving to stabilize mutated or inappropriately activated oncoproteins that contribute to the initiation, growth, and metastasis of human cancers [6, 7]. Hsp27 is expressed in approximately 70% of NSCLC [8]. The protein has been shown to limit activity of chemotherapeutic agents *in vitro* in lung [9], pancreatic [9–11], bladder [12], and prostate cancer [13] cell lines. Hsp27 is a marker of poor prognosis in patients with NSCLC and is a predictor for lower 5-year overall survival [14].

Apatorsen is an antisense oligonucleotide that binds to Hsp27 mRNA and inhibits the production of Hsp27 protein [8, 15]. Apatorsen also enhances the efficacy of various chemotherapeutic agents in NSCLC cell lines [8]. The phase I dose-escalation study of this agent in patients with castration-resistant prostate cancer and other advanced cancers showed evidence of monotherapy activity as demonstrated by decline in tumor markers and circulating tumor cells, as well as stable measurable disease in 12 of 42 patients [16]. This randomized phase II trial was undertaken to evaluate the efficacy and safety of apatorsen when added to a standard carboplatin/pemetrexed regimen in the first-line treatment of patients with metastatic nonsquamous NSCLC.

Subjects, Materials, and Methods

Study Design and Objectives

This was a randomized, double-blinded, multicenter phase II study evaluating the combination of carboplatin and pemetrexed plus either apatorsen or placebo in patients with untreated metastatic NSCLC (NCT01829113). The primary objective of the study was to compare progression-free survival (PFS) between the two study arms. Secondary objectives included evaluation of objective response rate (ORR), overall survival (OS), and safety/toxicity profiles.

The study was conducted according to ethical principles of the Declaration of Helsinki and in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice. The protocol was approved by the Institutional Review Boards of participating sites, and patients were enrolled following written informed consent.

Patients

Patients were required to have histologically or cytologically confirmed metastatic nonsquamous NSCLC. Prior treatment for localized disease was allowed if completed more than 12 months from the time of study enrollment, but any prior systemic therapy for metastatic disease was prohibited. Additional eligibility criteria included the following: Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; adequate bone marrow function (absolute neutrophil count ≥1,500/μL; hemoglobin ≥9 g/dL; platelets ≥100,000/μL), hepatic function (aspartate transaminase, alanine transaminase, and alkaline phosphatase ≤3.0 × the upper limit of normal [ULN]; total bilirubin ≤1.5 × the institutional ULN), and renal function (serum creatinine ≤1.5 × ULN); and the ability to provide written informed consent. Patients were not required to have measurable disease per RECIST *version* 1.1 [17].

Patients were ineligible if any of the following was present: ALK translocations; EGFR activating mutations; central nervous system metastases; history of, or current, cardiac disease, including but not limited to congestive heart failure, symptomatic coronary artery disease, cardiac arrhythmias not well controlled with medication, and myocardial infarction within 6 months; concurrent or recent active malignancy (excluding nonmelanomatous skin cancer), defined as any malignancy with current need for cancer therapy or high possibility (>30%) of recurrence during the study; or any other medical comorbidities that would render the patient at high risk for treatment-related complications.

Randomization and Blinding

Patients who met all entry criteria were randomly assigned 1:1 to receive the combination of carboplatin and pemetrexed plus either apatorsen or placebo. The investigator, study sponsor, and all site staff were blinded to the individual patient's treatment assignment, with the exception of an unblinded pharmacist at each site (or qualified designee). Patients were not unblinded until all patients completed treatment and the trial database was locked.

Study Assessments

Before treatment initiation, patients underwent complete medical history, physical examination, assessment of ECOG performance status, computed tomography (CT) scans of the chest, abdomen, and pelvis with contrast (magnetic resonance imaging was an acceptable alternative for any patients with contraindications to CT), and laboratory studies including complete blood count, including differential and platelets, comprehensive metabolic profile, prothrombin time/partial thromboplastin time, and a serum or urine pregnancy test for women of child-bearing potential. Blood samples were also collected to measure serum Hsp27 levels at baseline and at additional prespecified time points during the course of study treatment. Serum samples were sent to a commercial laboratory (LabCorp) for analysis using an enzyme-linked immunosorbent assay. The normal reference range for this assay was 1.4 ng/mL to 9.3 mL. Samples with Hsp27 concentrations >9.3 ng/mL were considered high.

All patients who received at least one dose of protocol treatment were followed for safety. Adverse events and serious adverse events (SAEs), regardless of relationship to study medication, were collected from the day of the first dose to 30 days after the last dose of study medication. Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0 [18].

Response evaluations according to RECIST 1.1 [17] were performed after every two treatment cycles (approximately 6 weeks). Final response presented for these patients is the best response experienced during treatment.

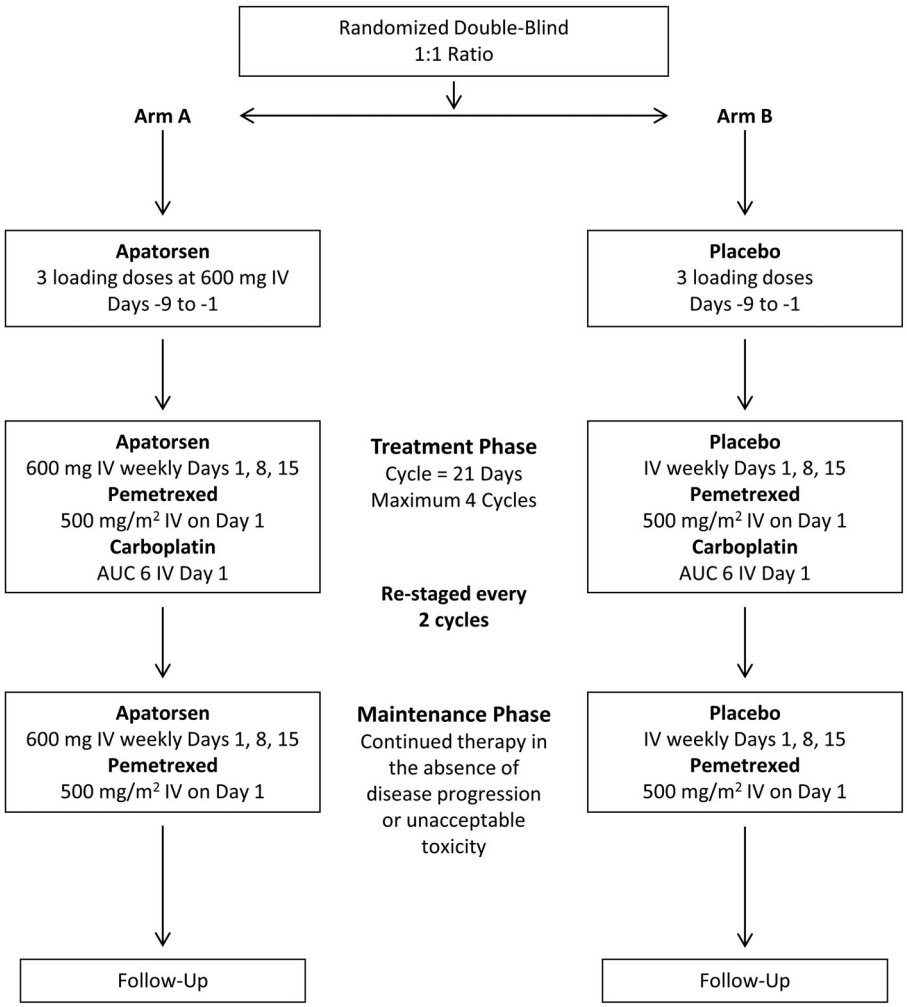


Figure 1. Treatment schema.
Abbreviations: AUC, area under the curve; IV, intravenously.

Treatment and Dose Modifications

The treatment schema is shown in Figure 1. Patients were randomized 1:1 to receive either apatorsen (3 loading doses of 600 mg intravenously (IV) over 9 days prior to cycle 1 of chemotherapy, followed by 600 mg IV apatorsen once weekly on days 1, 8, and 15 of a 21-day cycle concurrent with chemotherapy); or placebo IV at the same dosing schedule. All patients received pemetrexed 500 mg/m^2 IV and carboplatin area under the curve (AUC) 6 IV, both agents administered on day 1 of each 21-day cycle for up to four cycles. After completing four treatment cycles, responding or stable patients received maintenance treatment with pemetrexed (500 mg/m^2 IV on day 1 of each cycle) plus either apatorsen (600 mg on days 1, 8, and 15) or placebo (IV on the same dosing schedule). Maintenance treatment continued until disease progression or unacceptable toxicity.

All patients received premedication for study drug (apatorsen or placebo) with an antihistamine, an H2 antagonist, and a corticosteroid. Premedications for pemetrexed included folic acid, vitamin B12, and dexamethasone using standard guidelines. Antiemetics were administered according to institutional standards.

Doses of pemetrexed, carboplatin, and apatorsen/placebo could be reduced by up to two dose levels for prespecified hematologic and nonhematologic toxicity. For grade 2–3 infusion reactions associated with apatorsen/placebo, patients could be rechallenged at a slower rate, with a dose reduction for subsequent infusions.

Statistical Analysis

This study was designed to compare the PFS of patients in the two treatment arms. The intent-to-treat population (all patients who met eligibility requirements and gave written informed consent) was used for all efficacy analyses.

The safety analysis population consisted of all patients who received at least one dose of study treatment. PFS was defined as the time (in months) between the date of randomization and the earlier of either the date of disease progression or the date of death due to any cause. OS was defined as the time (in months) from first study treatment until the date of death (or date last known alive). Analyses for PFS and OS were summarized using the methods of Kaplan and Meier [19]. Exploratory analyses of response and survival stratified by baseline serum Hsp27 levels were also performed.

Sample size was based on a predicted 5-month median PFS for patients with advanced NSCLC treated with pemetrexed and carboplatin [4]. Randomization of 155 patients provided

Table 1. Baseline patient characteristics

Characteristic	Pemetrexed/ carboplatin + apatorsen	Pemetrexed/carboplatin + placebo	All patients (*n* = 155)
Median age, (range), years	66 (32–82)	67 (38–82)	66 (32–82)
Sex, *n* (%)	(*n* = 77)	(*n* = 78)	(*n* = 155)
Female	39 (51)	40 (51)	79 (52)
Male	38 (49)	38 (49)	76 (49)
Baseline ECOG, *n* (%)	(*n* = 76)	(*n* = 78)	(*n* = 154)
0	35 (46)	32 (41)	67 (44)
1	41 (54)	46 (59)	87 (56)
Tobacco use *n* (%)	(*n* = 70)	(*n* = 73)	(*n* = 143)
Smoker or former smoker	54 (77)	50 (68)	104 (73)
Nonsmoker	16 (23)	23 (32)	39 (27)
Hsp27 expression, *n* (%)	(*n* = 68)	(*n* = 71)	(*n* = 139)
Hsp27 high	6 (9)	10 (14)	16 (12)
Hsp27 low	62 (91)	61 (86)	123 (88)
Median Hsp27 expression, ng/mL	4.7	4.6	4.6
Histology, *n* (%)	(*n* = 77)	(*n* = 78)	(*n* = 155)
Adenocarcinoma	77 (100)	76 (97)	153 (99)
Large cell carcinoma	0 (0)	2 (3)	2 (1)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

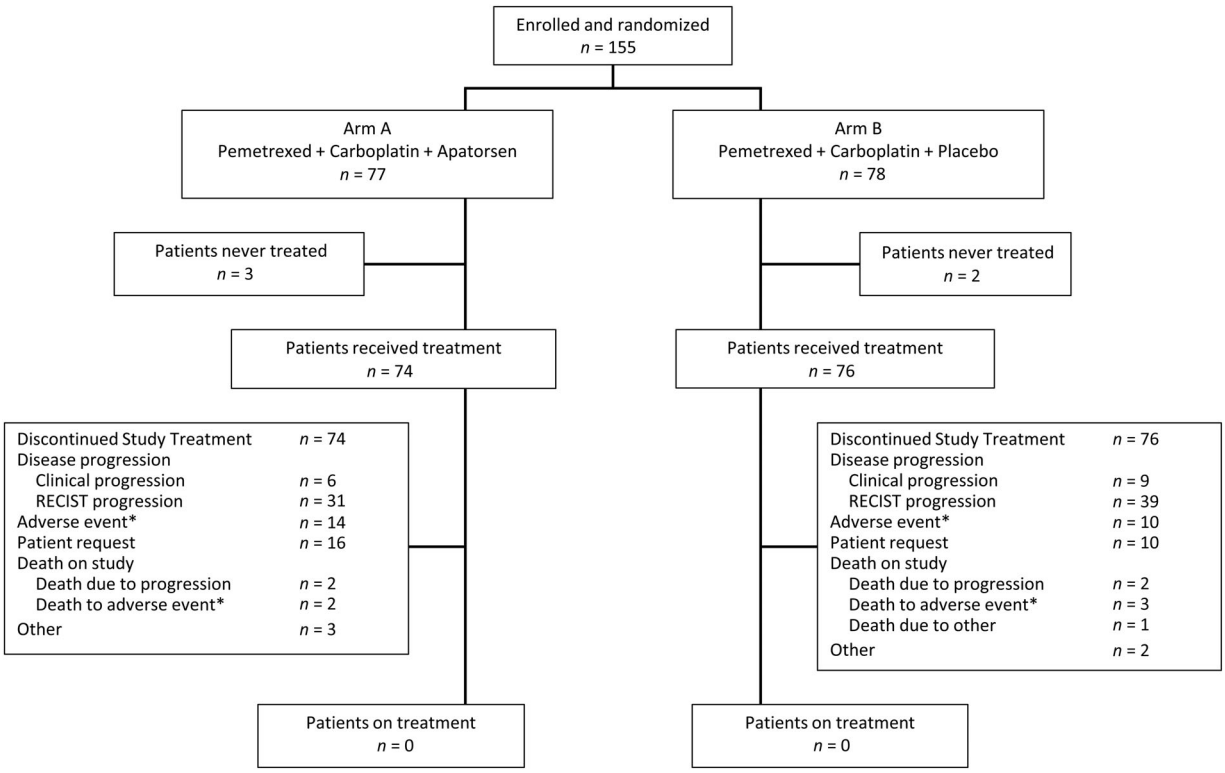


Figure 2. CONSORT diagram. Asterisk (*) indicates inclusion of both related and unrelated adverse events.

85% power to detect a treatment difference of 0.60 in hazard ratio for progression at a one-sided significance level of 0.05. This was equivalent to detecting a difference in median PFS of 5 months (expected in the placebo arm) and 8.3 months (target in the apatorsen arm).

Results

Between August 2013 and February 2015, a total of 155 patients (77 patients on the apatorsen arm and 78 patients on the placebo arm) were enrolled on the study. Baseline characteristics were similar between the two treatment groups (Table 1).

Table 2. Treatment-related adverse events (patients ≥ 5%, n=150)

	Pemetrexed/carboplatin + apatorsen (*n* = 74) *n* (%)			Pemetrexed/carboplatin + placebo (*n* = 76) *n* (%)		
Toxicity	**Grade 1–2**	**Grade 3–4**	**Total**	**Grade 1–2**	**Grade 3–4**	**Total**
Hematologic						
Anemia	23 (31)	14 (19)	37 (50)	22 (29)	16 (21)	38 (50)
Thrombocytopenia	10 (14)	19 (26)	29 (39)	13 (17)	16 (21)	29 (38)
Neutropenia	4 (5)	21 (28)	25 (34)	16 (21)	24 (32)	40 (53)
Leukopenia	7 (9)	9 (12)	16 (22)	9 (12)	19 (25)	28 (37)
Nonhematologic						
Fatigue	31 (42)	4 (5)	35 (47)	30 (40)	10 (13)	40 (53)
Nausea	31 (42)	1 (1)	32 (43)	37 (49)	1 (1)	38 (50)
Constipation	15 (20)	1 (1)	16 (22)	16 (21)	1 (1)	17 (22)
Decreased appetite	17 (23)	0 (0)	17 (23)	16 (21)	0 (0)	16 (21)
Vomiting	22 (30)	2 (3)	24 (32)	17 (22)	1 (1)	18 (24)
Diarrhea	15 (20)	2 (3)	17 (23)	10 (13)	0 (0)	10 (13)
Dyspnea	9 (12)	4 (5)	13 (18)	4 (5)	2 (3)	6 (8)
Dehydration	5 (7)	3 (4)	8 (11)	9 (12)	1 (1)	10 (13)
Peripheral edema	11 (15)	0 (0)	11 (15)	6 (8)	1 (1)	7 (9)
Dizziness	8 (11)	0 (0)	8 (11)	7 (9)	1 (1)	8 (11)
Platelet count decreased	3 (4)	4 (5)	7 (10)	3 (4)	7 (9)	10 (13)
Asthenia	7 (10)	1 (1)	8 (11)	6 (8)	1 (1)	7 (9)
Dysgeusia	6 (8)	0 (0)	6 (8)	8 (11)	0 (0)	8 (11)
Mucosal Inflammation	7 (10)	0 (0)	7 (10)	7 (9)	0 (0)	7 (9)
Increased alanine aminotransferase	5 (7)	0 (0)	5 (7)	5 (7)	2 (3)	7 (9)
Increased aspartate aminotransferase	5 (7)	0 (0)	5 (7)	6 (8)	0 (0)	6 (8)
Neutrophil count decreased	0 (0)	4 (5)	4 (5)	3 (4)	4 (5)	7 (9)
Blood creatinine increased	6 (8)	0 (0)	6 (8)	2 (3)	1 (1)	3 (4)
Hypokalemia	1 (1)	3 (4)	4 (5)	3 (4)	2 (3)	5 (7)
Paresthesia	6 (8)	0 (0)	6 (8)	3 (4)	0 (0)	3 (4)
Pyrexia	6 (8)	0 (0)	6 (8)	2 (3)	1 (1)	3 (4)
Weight decreased	6 (8)	0 (0)	6 (8)	3 (4)	0 (0)	3 (4)
Headache	3 (4)	0 (0)	3 (4)	5 (7)	0 (0)	5 (7)
Infusion-related reaction	7 (10)	1 (1)	8 (11)	0 (0)	0 (0)	0 (0)
Rash	3 (4)	0 (0)	3 (4)	4 (5)	1 (1)	5 (7)
Stomatitis	3 (4)	0 (0)	3 (4)	5 (7)	0 (0)	5 (7)

The median age of patients was 66 years (range, 32–82 years), with 44% having an ECOG performance status of 0. The cigarette smoking history was known in 143 patients; 104 patients (73%) were current or previous smokers. Baseline serum Hsp27 levels were measured in 139 patients and were high (>9.3 ng/mL) in 16 (12%).

Treatment Received

One hundred fifty of the 155 patients received at least one dose of study treatment (74 patients on the apatorsen arm and 76 patients on the placebo arm). Patients remained on study treatment for a median of 18.4 weeks (14.8 weeks for patients on the apatorsen arm, 18.7 weeks for patients on the placebo arm). At the time of data cutoff, all patients had discontinued therapy. The CONSORT diagram (Fig. 2) shows the disposition for all patients enrolled in the study. Disease progression was the most common reason for discontinuing treatment (50% in the apatorsen arm; 63% in the placebo arm).

Safety

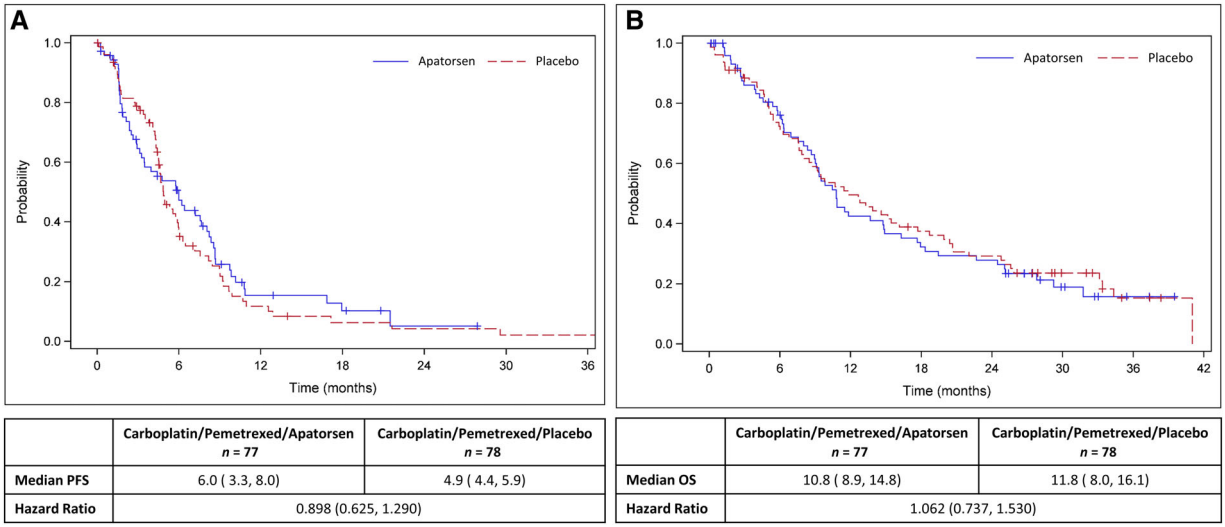
A summary of all treatment-related toxicities occurring in ≥5% of patients is shown in Table 2. The most common treatment-related toxicities (all grades) on both arms included fatigue, cytopenias, constipation, decreased appetite, and gastrointestinal symptoms (nausea, vomiting, and diarrhea). The incidence of these toxicities did not differ significantly between the two treatment arms. Severe (grade 3–4) nonhematologic toxicities were uncommon in both treatment arms.

In total, 12 treatment-related SAEs occurred on the apatorsen arm, and 8 treatment-related SAEs occurred on the placebo arm. Fourteen patients (18%) on the apatorsen

Table 3. Comparison of median PFS and OS by treatment arm in the entire group and stratified by Hsp27 levels

Patient group	Median PFS (95% CI), mo				Median OS (95% CI), mo			
	Pemetrexed/ carboplatin + apatorsen	Pemetrexed/ carboplatin + placebo	Hazard ratio	*p* value	Pemetrexed/ carboplatin + apatorsen	Pemetrexed/ carboplatin + placebo	Hazard ratio	*p* value
All patients (*n* = 155)	6.0 (3.3–8.0)	4.9 (4.4–5.9)	0.90 (0.63–1.29)	.5588	10.8 (8.9–14.8)	11.8 (8.0–16.1)	1.06 (0.84–1.35)	.75
High Hsp27 (*n* = 16)	10.8 (1.8–NR)	4.8 (0.4–8.4)	0.46 (0.12–1.76)	.9124	10.8 (1.8–NR)	7.7 (0.4–16.1)	0.93 (0.24–3.52)	.91
Low Hsp27 (*n* = 123)	5.7 (2.9–7.7)	5.0 (4.3–6.3)	0.98 (0.65–1.46)	.9124	10.8 (9.0–16.3)	13.3 (9.2–20.4)	1.15 (0.77–1.71)	.51

Abbreviations: CI, confidence interval; Hsp, heat shock protein; NR, not reached; OS, overall survival; PFS, progression-free survival.



	Carboplatin/Pemetrexed/Apatorsen *n* = 77	Carboplatin/Pemetrexed/Placebo *n* = 78
Median PFS	6.0 (3.3, 8.0)	4.9 (4.4, 5.9)
Hazard Ratio	0.898 (0.625, 1.290)	

	Carboplatin/Pemetrexed/Apatorsen *n* = 77	Carboplatin/Pemetrexed/Placebo *n* = 78
Median OS	10.8 (8.9, 14.8)	11.8 (8.0, 16.1)
Hazard Ratio	1.062 (0.737, 1.530)	

Figure 3. Progression-free survival and overall survival on the two study arms. **(A):** Progression-free survival. **(B):** Overall survival. Abbreviations: OS, overall survival; PFS, progression-free survival.

arm and 10 patients (13%) on the placebo arm discontinued study treatment because of adverse events. At least one dose reduction was required in 17 patients (22%) on the apatorsen arm and in 15 patients (19%) on the placebo arm. There was one treatment-related death on the apatorsen arm (renal and urinary disorder) and none on the placebo arm. In addition, there were more grade 1 infusion reactions on the apatorsen treatment arm.

Efficacy

After a median follow-up time of 9.8 months (range, 0.1–41 months), the median PFS for patients on the apatorsen arm was 6.0 months (95% confidence interval [CI], 3.3–8.0 months), versus 4.9 months (95% CI, 4.4–5.9 months) for patients on the placebo arm. This difference was not statistically significant (p = .56; hazard ratio, 0.90; 95% CI, 0.63–1.29; Table 3, Fig. 3A). The median OS for patients on the apatorsen arm was 10.8 months (95% CI, 8.9–14.8 months) and 11.8 months (95% CI, 8.0–16.1 months) for patients on the placebo arm (p = .75; hazard ratio, 1.06; 95% CI, 0.74–1.53; Table 3, Fig. 3B).

Responses to treatment are detailed in Table 4. The ORRs were 27% (95% CI, 17.7–38.6) for patients on the apatorsen arm and 32% (95% CI, 21.9–46.6) for patients on the placebo arm. The only patient with a complete response was treated with apatorsen.

Correlative Studies

Baseline serum Hsp27 levels were measured in 139 patients. Median OS was shorter in the 16 patients on both treatment arms with high Hsp27 (>9.3 ng/mL) than in the 123 patients on both arms with lower Hsp27 levels (median 10.8 versus 7.7 months; p = .91).

In patients with high pretreatment Hsp27 levels, treatment with apatorsen produced a median PFS of 10.8 months (95% CI, 1.8–not reached), whereas those treated with placebo had a median PFS of 4.8 months (95% CI, 0.4–8.4; Table 3). Patients with pretreatment Hsp27 levels <9.3 ng/mL had similar median PFS on apatorsen and placebo (5.7 and 5.0 months, respectively). The small number of patients with high Hsp27 precludes meaningful comparison of these treatment cohort results.

Discussion

The identification of critical molecular alterations that can be targeted with monoclonal antibodies or tyrosine kinase inhibitors has resulted in major treatment advances for specific subsets of patients. These drugs target intracellular proteins or cell surface components and are not applicable to all potential therapeutic targets. Antisense oligonucleotides (ASOs) are chemically modified stretches of single-strand DNA

Table 4. Response to treatment (n = 155)

Response	Pemetrexed/carboplatin + apatorsen (n = 77), n (%)	Pemetrexed/carboplatin + placebo (n = 78), n (%)	All patients (n = 155), n (%)
Objective response rate	21 (27)	25 (32)	46 (30)
Complete response	1 (1)	0 (0)	1 (1)
Partial response	20 (26)	25 (32)	45 (29)
Stable disease	31 (40)	38 (49)	69 (45)
≥6 months	9 (12)	6 (8)	15 (10)
<6 months	22 (29)	32 (41)	54 (35)
Progressive disease	10 (13)	6 (8)	16 (10)
Not evaluable	15 (20)	9 (12)	24 (16)

complementary to the mRNA regions of a target gene. These agents can inhibit translation by forming RNA-DNA duplexes, thereby acting at the gene expression level to prevent translation of functionally relevant genes.

Apatorsen is an ASO designed to bind to Hsp27 mRNA and inhibit the production of Hsp27 protein. Hsp27 is involved in multiple aberrant pathways implicated in cancer progression and treatment resistance. Therefore, successfully targeting this protein may disrupt multiple critical cancer cell functions. Given these potential mechanistic advantages and the preclinical evidence suggesting clinical activity in NSCLC, the current study was designed to evaluate the safety and efficacy of apatorsen when added to standard chemotherapy in this patient population.

In this randomized phase II study, there was no suggestion that the addition of apatorsen improved the efficacy of standard first-line chemotherapy for patients with advanced NSCLC. Median PFS, OS, and ORR in both treatment groups were similar and were consistent with the expected results of standard chemotherapy in this population. The addition of apatorsen to the carboplatin-pemetrexed regimen was well tolerated, with no significant increased toxicity in the apatorsen treatment cohort.

As part of this study, we measured pretreatment serum Hsp27 levels; our results are consistent with previous observations correlating increased Hsp27 levels with shorter survival [6, 14]. We also attempted to correlate pretreatment serum Hsp27 levels to response to each of these treatment regimens. Patients with high pretreatment serum Hsp27 levels who were treated with apatorsen had median PFS of 10.8 months, whereas those receiving placebo had a median PFS of 4.9 months. Although this is suggestive, only 12% of patients had high Hsp27 levels, so the small size of this group precluded meaningful comparison.

The family of heat shock proteins has been a focus of cancer investigation for the last 15 years. Overexpression of several heat shock proteins (including Hsp27, Hsp60, and Hsp90) has been correlated with poor prognosis [6], and attempts to successfully target these proteins are ongoing. In spite of encouraging preclinical data using inhibitors of each of these three targets, no definitive clinical studies to date have demonstrated the benefit of any Hsp inhibitor. Apatorsen, the Hsp27 inhibitor used in this study, has been added to several standard regimens and investigated in several cancer types. Randomized phase II studies in bladder and prostate cancer suggested a modest benefit [20–22], whereas no benefit was seen in combination with gemcitabine/nab-paclitaxel in pancreatic cancer [23]. Additional trials with several Hsp inhibitors are ongoing.

Conclusion

The addition of apatorsen to standard first-line chemotherapy did not improve treatment outcome for patients with advanced nonsquamous NSCLC. Further trials with apatorsen in unselected NSCLC are not recommended.

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Disclosures

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