

# An Open-Label Phase II Trial of Bevacizumab plus Docetaxel and Gemcitabine in Advanced, Previously Untreated Nonsquamous Non-Small Cell Lung Cancer

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## TRIAL INFORMATION

- **ClinicalTrials.gov Identifier:** NCT00970684
- **Sponsor(s):** Genentech, Inc.
- **Principal Investigator:** Nathan A. Pennell
- **IRB Approved:** Yes

## LESSONS LEARNED

- The combination of bevacizumab with docetaxel-gemcitabine resulted in unacceptable toxicity, particularly a high rate of pulmonary toxicity (30%).
- Despite promising efficacy, excessive toxicity of this regimen does not support its use in patients with advanced nonsquamous non-small cell lung cancer.

## ABSTRACT

**Background.** Prior to immunotherapy, standard treatment for advanced non-small cell lung cancer (NSCLC) was platinum doublet chemotherapy. In a previous phase II study, docetaxel-gemcitabine demonstrated comparable efficacy and tolerability to platinum doublets. In this phase II trial, we evaluated the efficacy and tolerability of adding bevacizumab to docetaxel-gemcitabine in patients with advanced nonsquamous NSCLC.

**Methods.** Patients with untreated advanced nonsquamous NSCLC were treated with up to six cycles of docetaxel-gemcitabine-bevacizumab, followed by bevacizumab until progression. The primary endpoint for this study was 1-year progression-free survival (PFS); secondary endpoints were safety, overall response rate (ORR) and overall survival (OS). The planned sample size was 46 patients.

**Results.** A total of 13 patients were enrolled and received a median of six cycles of chemotherapy and four cycles of bevacizumab. The treatment was poorly tolerated, with five patients requiring dose reduction and four discontinuing treatment for toxicity. Grade 3–5 nonhematologic toxicity was seen in 10 patients, and 4 (30%) were hospitalized with pulmonary toxicity possibly related to study drugs. At

this point, enrollment was halted for safety concerns. The 12-month PFS was 8%. In 11 evaluable patients, ORR was 72%, median PFS 6 months, and median OS was 11 months.

**Conclusion.** Docetaxel, gemcitabine, and bevacizumab at this dose and schedule resulted in excessive toxicity. Despite promising efficacy, in light of efficacious and safe alternative therapies, this regimen should not be used to treat advanced NSCLC. *The Oncologist* 2019;24:457–e126

## DISCUSSION

When this trial was conceived, the standard of care for advanced NSCLC was combination chemotherapy and most patients were treated with platinum doublets. Emerging evidence at the time suggested that certain patients may have inherently platinum-resistant disease due to high levels of expression of excision repair cross-complementation group 1 and DNA mismatch repair protein MSH2, which are heavily involved in the repair of platinum-DNA adducts [1, 2]. In a randomized multicenter trial of patients with advanced NSCLC who were assigned treatment based on their ERCC1 expression level (docetaxel-gemcitabine in ERCC1-high and

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**Table 1.** Adverse events

Event	Grade 1/2	Grade 3	Grade 4	Overall
Neutropenia	1 (8%)	7 (54%)	5 (38%)	13 (100%)
Leukopenia	1 (8%)	6 (46%)	4 (31%)	11 (85%)
Lymphopenia	3 (23%)	6 (46%)	0	9 (69%)
Anemia	9 (69%)	1 (8%)	0	10 (77%)
Thrombocytopenia	6 (46%)	1 (8%)	0	7 (54%)
Pneumonitis	0	1 (8%)	1 (8%)	2 (15%)
Pneumonia	0	2 (15%)	0	2 (15%)
Fatigue	7 (54%)	2 (15%)	0	9 (69%)
Bleeding	8 (62%)	0	0	8 (62%)
Nausea/Vomiting	8 (62%)	0	0	8 (62%)
Taste alterations	8 (62%)	0	0	8 (62%)
Anorexia	7 (54%)	0	0	7 (54%)
Arthralgias/myalgias	7 (54%)	0	0	7 (54%)
Mucositis	7 (54%)	0	0	7 (54%)
Skin reactions	7 (54%)	0	0	7 (54%)

docetaxel-cisplatin in ERCC1-low patients), the ORR in the docetaxel-gemcitabine arm was 44%, compared with 37% with platinum doublet chemotherapy [3]. The superior efficacy and safety of docetaxel-gemcitabine over cisplatin-docetaxel in patients with advanced NSCLC was also documented in a randomized European multicenter trial [4]. These studies provided a rationale for exploring the role of non-platinum-containing regimens in the treatment of advanced NSCLC.

In preclinical models, addition of antiangiogenic agents to chemotherapy resulted in synergistic effects, likely due to vessel normalization and reduced vessel density and permeability [5, 6]. Addition of the vascular endothelial growth factor antibody bevacizumab to platinum chemotherapy has been associated with improved outcomes [7]; however, its safety and efficacy in combination with non-platinum doublets was poorly understood. In a previously conducted phase IB study of docetaxel-gemcitabine-bevacizumab in 38 patients with soft tissue sarcoma, this combination was safe and efficacious [8]. We therefore sought to study the safety and efficacy of bevacizumab-docetaxel-gemcitabine in patients with previously untreated, advanced nonsquamous NSCLC. Because patients with squamous histology had a greater incidence of major hemoptysis in early trials of bevacizumab with

chemotherapy, patients with squamous histology were excluded [9].

In this study, conducted over a decade ago, a sizeable proportion of patients either had dose reduction (38%) or discontinued treatment for toxicity (31%). In addition, three patients (23%) had to discontinue bevacizumab before progression (two for tumor cavitation and one for hemoptysis). Sixty-nine percent of patients developed grade 3–5 nonhematologic toxicity, and all patients developed hematologic toxicities (92% grade 3–4 neutropenia; Table 1). An alarmingly high rate of pulmonary toxicity was observed in four patients (30%), thought to be possibly related to study drugs. Although this combination was well tolerated in patients with sarcoma, it is likely that the higher rate of pulmonary toxicity is reflective of the underlying compromised pulmonary function in patients with NSCLC.

Compared with alternative regimens available at the time, this combination showed promising efficacy with an ORR of 72%. However, the trial was terminated because of unacceptable toxicity of the regimen. Since this trial was conducted, many alternative therapies including immunotherapy have emerged as safe and efficacious options. Therefore, further investigation into clinical applications of this regimen is not warranted.

#### TRIAL INFORMATION

<b>Disease</b>	Lung cancer – NSCLC
<b>Stage of Disease/Treatment</b>	Metastatic/advanced
<b>Prior Therapy</b>	None
<b>Type of Study – 1</b>	Phase II
<b>Type of Study – 2</b>	Single arm
<b>Primary Endpoint</b>	Progression-free survival
<b>Secondary Endpoint</b>	Toxicity
<b>Secondary Endpoint</b>	Overall response rate
<b>Secondary Endpoint</b>	Overall survival

**Additional Details of Endpoints or Study Design**

The historical control for the trial was the Eastern Cooperative Oncology Group (ECOG) 4599 study with a 12-month PFS of 14% and time to progression of 6.4 months. Based on this experience, a 12-month PFS of greater than 28% was deemed as being sufficiently important to warrant further study. Enrolling 46 patients on the study would have allowed us to detect this difference using a 5% level of significance with 80% power.

<b>Investigator's Analysis</b>	Poorly tolerated/not feasible
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**DRUG INFORMATION****Drug 1**

<b>Generic/Working Name</b>	Bevacizumab
<b>Trade Name</b>	Avastin
<b>Company Name</b>	Genentech
<b>Drug Type</b>	Antibody
<b>Drug Class</b>	Angiogenesis – VEGF
<b>Dose</b>	15 mg/kg
<b>Route</b>	IV
<b>Schedule of Administration</b>	

**Drug 2**

<b>Generic/Working Name</b>	Docetaxel
<b>Trade Name</b>	Taxotere
<b>Company Name</b>	
<b>Drug Type</b>	Other
<b>Drug Class</b>	Microtubule-targeting agent
<b>Dose</b>	75 mg/m <sup>2</sup>
<b>Route</b>	IV
<b>Schedule of Administration</b>	Day 1 of a 21-day cycle, up to a maximum of six cycles

**Drug 3**

<b>Generic/Working Name</b>	Gemcitabine
<b>Trade Name</b>	Gemzar
<b>Company Name</b>	
<b>Drug Type</b>	Other
<b>Drug Class</b>	Antimetabolite
<b>Dose</b>	900 mg/m <sup>2</sup>
<b>Route</b>	IV
<b>Schedule of Administration</b>	Days 1 and 8 of a 21-day cycle, up to a maximum of six cycles

**PATIENT CHARACTERISTICS**

<b>Number of Patients, Male</b>	11
<b>Number of Patients, Female</b>	2
<b>Stage</b>	IIIB (with malignant effusion) or IV by American Joint Committee on Cancer 6th edition
<b>Age</b>	Median (range): 63
<b>Number of Prior Systemic Therapies</b>	None
<b>Performance Status: ECOG</b>	0 – 5 1 – 8 2 – 3 – Unknown –

**Other**

We excluded patients with hemoptysis, tumor cavitation, underlying bleeding diathesis, uncontrolled hypertension, history of myocardial infarction or stroke within 6 months, metastasis to the gastrointestinal tract, history of diverticulitis, fistula, and intra-abdominal abscess or surgery within 3 months to reduce the risk of bleeding with bevacizumab

**Cancer Types or Histologic Subtypes**

Nonsquamous non-small cell lung cancer, 13

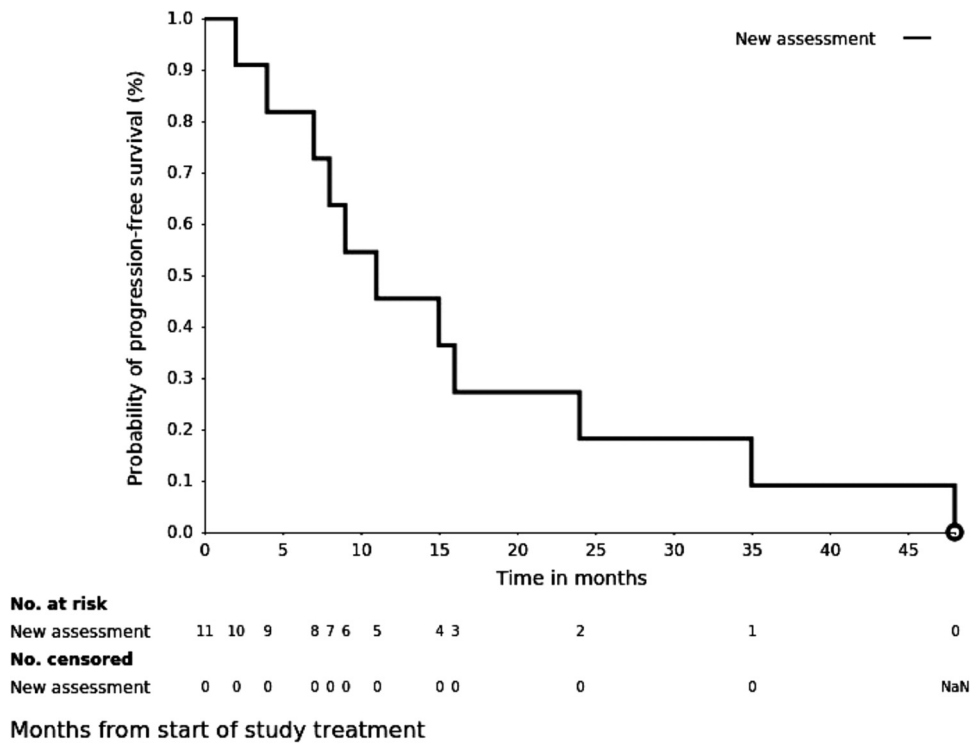
**PRIMARY ASSESSMENT METHOD**

Title	New assessment
Number of Patients Screened	16
Number of Patients Enrolled	13
Number of Patients Evaluable for Toxicity	13
Number of Patients Evaluated for Efficacy	11
Evaluation Method	RECIST 1.0
Response Assessment CR	<i>n</i> = 0 (0%)
Response Assessment PR	<i>n</i> = 8 (72.7%)
Response Assessment SD	<i>n</i> = 2 (18.1%)
Response Assessment PD	<i>n</i> = 1 (9.09%)
Response Assessment OTHER	<i>n</i> = 0 (0%)
(Median) Duration Assessments PFS	6 months
(Median) Duration Assessments TTP	7.5 months
(Median) Duration Assessments OS	11 months
(Median) Duration Assessments Response Duration	4–37 months

**KAPLAN-MEIER PLOT**

Time of scheduled assessment and/or time of event, months <sup>a</sup>	No. progressed (or deaths)	No. censored	Percentage at start of evaluation period	Kaplan-Meier %	No. at next evaluation/No. at risk
0	0	0	100.00	100.00	11
2	1	0	100.00	90.91	10
4	1	0	90.91	81.82	9
7	1	0	81.82	72.73	8
8	1	0	72.73	63.64	7
9	1	0	63.64	54.55	6
11	1	0	54.55	45.45	5
15	1	0	45.45	36.36	4
16	1	0	36.36	27.27	3
24	1	0	27.27	18.18	2
35	1	0	18.18	9.09	1
48	1	0	9.09	0.00	0

<sup>a</sup>Months from start of study treatment. Progression-free survival.



<b>ADVERSE EVENTS</b>				
<b>Event</b>	<b>Grade 1/2</b>	<b>Grade 3</b>	<b>Grade 4</b>	<b>Overall</b>
Neutropenia	1 (8%)	7 (54%)	5 (38%)	13 (100%)
Leukopenia	1 (8%)	6 (46%)	4 (31%)	11 (85%)
Lymphopenia	3 (23%)	6 (46%)	0	9 (69%)
Anemia	9 (69%)	1 (8%)	0	10 (77%)
Thrombocytopenia	6 (46%)	1 (8%)	0	7 (54%)
Pneumonitis	0	1 (8%)	1 (8%)	2 (15%)
Pneumonia	0	2 (15%)	0	2 (15%)
Fatigue	7 (54%)	2 (15%)	0	9 (69%)
Bleeding	8 (62%)	0	0	8 (62%)
Nausea/vomiting	8 (62%)	0	0	8 (62%)
Taste alterations	8 (62%)	0	0	8 (62%)
Anorexia	7 (54%)	0	0	7 (54%)
Arthralgias/myalgias	7 (54%)	0	0	7 (54%)
Mucositis	7 (54%)	0	0	7 (54%)
Skin reactions	7 (54%)	0	0	7 (54%)

<b>SERIOUS ADVERSE EVENTS</b>		
<b>Event</b>	<b>Grade</b>	<b>Attribution</b>
Atrial fibrillation	3	Unrelated
Thrombosis	2	Possible
Pleural effusion	5	Unrelated
Fever	1	Unrelated
Pneumonia	3	Probable
Aspiration pneumonia	3	Unrelated

Depressed level of consciousness	5	Unrelated
Aspiration pneumonia	3	Probable
Anemia and thrombocytopenia	3	Unrelated
Pneumonitis	4	Possible
Thromboembolism	3	Possible
Pneumonitis	3	Possible
Pneumonia and atrial fibrillation	3	Possible
Viral respiratory infection	2	Unrelated

## ASSESSMENT, ANALYSIS, AND DISCUSSION

<b>Completion</b>	Study terminated before completion
<b>Terminated Reason</b>	Toxicity
<b>Investigator's Assessment</b>	Poorly tolerated/not feasible

Lung cancer continues to be the leading cause of cancer-related mortality despite the many advances in the field over the last decade. In the U.S., the estimated incidence of new cases in 2018 is 234,000, with an estimated 154,000 deaths annually [10]. Prior to the immunotherapy and targeted therapy era, 5-year survival rates for patients with advanced non-small cell lung cancer (NSCLC) had reached a plateau with the various chemotherapeutic regimens that were being tested at the time. Adding bevacizumab to a chemotherapy backbone for the treatment of patients with metastatic nonsquamous NSCLC was not only shown to be tolerable but also resulted in a significantly longer progression-free survival (PFS) and overall survival (OS) in comparison with platinum doublet chemotherapy [6].

Emerging evidence at the time that this trial was designed suggested that a subset of patients with NSCLC had inherent resistance to platinum-based chemotherapy. A variety of mechanisms for platinum resistance such as high expression levels of proteins that are heavily involved in the repair of platinum-DNA adducts (such as ERCC1 and MSH2) had been implicated. Therefore, viable non-platinum-based chemotherapeutic regimens were being explored for such patients. Both docetaxel and gemcitabine are active in the treatment of metastatic NSCLC. The safety and efficacy of the combination of these drugs was further studied in clinical trials. The first randomized clinical trial that stratified patients by ERCC1 expression levels to either cisplatin-docetaxel (low expression) or docetaxel-gemcitabine (ERCC1 high) reported a higher (44%) response rate in the docetaxel-gemcitabine arm in comparison with 37% in the standard arm receiving platinum doublet chemotherapy [3]. Another randomized phase II trial of 108 patients with advanced NSCLC treated with docetaxel-gemcitabine or cisplatin-gemcitabine also reported superior response rates and lower toxicity with the former regimen [4]. Neither of these studies showed an improvement in PFS or OS with docetaxel-gemcitabine, but the number of patients enrolled in these studies were small.

The combination of docetaxel-gemcitabine with bevacizumab was particularly attractive because it would allow us

to target both cell proliferation and vascularization within the tumor. Because endothelial cells, which serve as the target for bevacizumab, are considered to be genetically stable, it was postulated that the combination was no more likely to result in acquired drug resistance than chemotherapy alone [11]. Although the safety and efficacy of this combination in patients with advanced nonsquamous NSCLC had not been studied previously, this regimen appeared to be well tolerated in early-phase trials in patients with sarcoma. We excluded patients who were at a higher risk of complications from bevacizumab such as those with squamous histology, hemoptysis, tumor cavitation, underlying bleeding diathesis, uncontrolled hypertension, history of myocardial infarction or stroke within 6 months, metastases to the gastrointestinal tract, history of diverticulitis, and intra-abdominal surgeries or abscess within 3 months. In addition to minimize the risk of hematologic toxicity noted with docetaxel-gemcitabine combination in previous studies, all patients received growth factor support.

This was a single-institution phase II study of docetaxel-gemcitabine-bevacizumab that was conducted from October 2009 to April 2011 in patients with previously untreated advanced nonsquamous NSCLC. Eligible patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, life expectancy of greater than 3 months, adequate organ function, and measurable disease. Key exclusion criteria included those listed above in addition to untreated brain metastases.

Unfortunately, the study regimen in the dose and schedule that was administered in the trial resulted in unacceptable toxicity. Although previous studies of docetaxel-gemcitabine did not report excessive pulmonary above what would be expected with each agent alone, the combination of docetaxel-gemcitabine and bevacizumab in our study resulted in grade 3–4 pulmonary toxicity in four (30%) of the patients. Of these, two patients developed pneumonitis thought to be related to the study drugs and two developed a pneumonia secondary to the immunosuppression associated with chemotherapy. In addition, two patients had to discontinue bevacizumab prior to progression due to tumor cavitation. Despite the growth factor

support, 92% of the enrolled patients developed grade 3–4 neutropenia. Because of safety concerns, this trial was terminated early. Although 72.7% of the evaluable patients had objective response to therapy, the 1-year PFS was 8% (in comparison with 14% 1-year PFS noted in the ECOG 4599 study of carboplatin, paclitaxel, and bevacizumab in patients with advanced NSCLC).

When this clinical trial was conducted, the armamentarium of therapeutic options for advanced NSCLC was quite limited. Particularly for patients with inherently resistant disease to platinum-based chemotherapy, which was considered the standard of care at the time, there were no well-defined treatment strategies. Although the regimen studied in this trial appeared to be well tolerated in patients with sarcoma, it is plausible that the higher rates of pulmonary toxicity observed in the trial were a reflection of underlying pulmonary compromise in patients with advanced non-small cell lung cancer. The cases of pneumonitis were sporadic, and no other precipitating or

predisposing risk factors were identified for any of the patients.

Since this trial was conducted a decade ago, many alternative therapies included molecular targeted agents and immunotherapy have revolutionized the management of advanced nonsquamous NSCLC. Not only are these newer agents more efficacious, they are less toxic than the toxicity profile noted in this trial. It is therefore unlikely that studying this regimen further would alter current clinical practice.

#### DISCLOSURES

**Nooshin Hashemi Sadraei:** Amgen (E); **Marc Shapiro:** AIM Specialty Health (C/A); **Nathan A. Pennell:** AstraZeneca, Eli Lilly & Co., Regeneron (C/A), Genentech, AstraZeneca, Cellgene, Merck, Bristol-Meyers Squibb, Incyte, Heat Biologics, Altor, Pfizer (RF). Pradnya Dinkar Patil indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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