ALTER0302: Anlotinib Increased PFS as Third-Line Treatment for Refractory Advanced NSCLC

Written by Anita Misra-Press, PhD

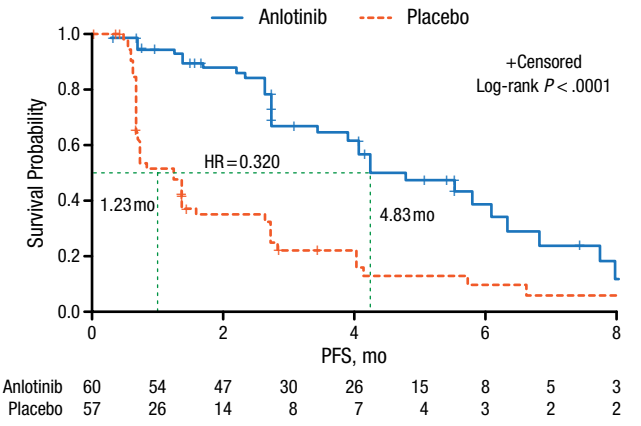
Lung cancer, approximately 85% of which is non–small cell lung cancer (NSCLC), is the leading cause of cancer-related mortality worldwide, with an overall 5-year survival rate of 14% for stage IIIA and 1% for stage IV [American Cancer Society. http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-survival-rates. Accessed April 22, 2015]. In the past 30 years, mortality from lung cancer in China has increased by 465%, and lung cancer has been the main cause of death in urban populations [She J et al. *Chest*. 2013; Wen C, Dehnel T. *Lancet Oncol*. 2011].

Baohui Han, MD, PhD, Shanghai Chest Hospital, Shanghai, China, and colleagues examined the efficacy and safety of anlotinib—a multitargeted tyrosine kinase inhibitor, with targets that include vascular endothelial growth factor receptors 2 and 3—as third-line therapy for refractory advanced NSCLC in the randomized double-blind placebo-controlled phase 2 trial ALTER0302 [Han B et al. *Ann Oncol*. 2015]. The primary end point for this study was progression-free survival (PFS), while the secondary end points included objective response rate (ORR), overall survival, and safety.

Prof Han and colleagues enrolled 117 patients (aged ≥ 18 years) from 13 hospitals in China with histologically confirmed metastatic advanced NSCLC who had progressed after first- and second-line chemotherapy; had adequate hematologic, renal, and liver function; and had an ECOG PS of 0 or 1. Patients with small cell lung cancer or those with a history of hemoptysis or symptomatic brain metastases were excluded. Patients were randomized 1:1 to either anlotinib (n = 60; 12 mg/d, orally, day 1–14 every 3 weeks) or placebo (n = 57; 0 mg/d, orally, day 1–14 every 3 weeks) until disease progression, unacceptable toxicity, withdrawal of patient consent, or death.

Baseline characteristics of patients stratified by age, sex, smoking history, ECOG PS, histology, stage, and number of metastases were comparable between patients receiving anlotinib and placebo. The majority of the patients had adenocarcinoma with an ECOG PS of 1, stage IV NSCLC, and > 3 metastatic lesions. Prof Han reported that PFS, the primary end point of this study, was significantly increased from 1.23 months in the placebo arm to 4.83 months in the anlotinib arm (log-rank $P < .0001$; Figure 1). This survival benefit was observed in all patient-stratified subgroups.

Figure 1. Comparison of PFS: Anlotinib vs Placebo Treatment Arms



PFS, progression-free survival.

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Although overall survival data have yet to accrue, secondary end points of this study, including ORR, extended the observed beneficial effects seen with anlotinib. Patients in the anlotinib arm exhibited a 10.00% ORR compared with 0% in the placebo arm ($P < .027$), and the disease control rate was reported in 83.33% of anlotinib-treated patients vs 31.58% in those treated with placebo ($P < .0001$). Although no serious adverse events (AEs) were noted in this study, AEs were increased from 70.2% in patients receiving placebo to 91.7% in those receiving anlotinib ($P = .004$). Grade 3 and 4 AEs were 15.8% in the placebo arm and 26.7% in the anlotinib arm ($P = .1797$) and included hypertension, hand-foot syndrome, and thyroglobulin. Based on the results of this clinical trial, Prof Han and colleagues concluded that anlotinib has significant PFS benefit as a third-line therapy in this selected Chinese population of patients with refractory advanced NSCLC with no associated serious AEs.

Prognostic Factors Identified in Stage IV NSCLC

Written by Mary Mosley

A retrospective analysis using the National Cancer Registry in The Netherlands has found that patients with metastasis to a single organ have a better prognosis compared with patients with metastasis in multiple organs, particularly when they also have a low TN status [Hendriks LE et al. *Ann Oncol*. 2015]. The analysis was conducted in patients with stage IV non–small cell lung cancer (NSCLC) to evaluate the prognostic effect

of the number of organs with metastasis, the specific organs with metastasis, as well as the local disease status, and it was presented by Lizza E. Hendriks, MD, Maastricht University Medical Center, Maastricht, The Netherlands.

A total of 11 094 patients with histologically confirmed NSCLC entered into the database between January 2006 and December 2012 were included in this analysis. Study exclusions included a malignancy within the previous 5 years, stage IV disease according to TNM6 based solely on pulmonary metastasis, no documented metastasis sites or TNM classification, and no survival data. Their mean age was 65 years; 60% were men; and 73% had adenocarcinoma (AdC). Staging of the N compartment was conducted using clinical data, including histology and imaging studies (eg, computed tomography and positron emission tomography [PET]).

Metastasis to a single organ was identified in 5676 (51.2%) of patients, and bone was the most frequent site of metastasis (41.3%) in the overall cohort. Bone, brain, pleura, and lymph node metastases were more common in patients with AdC compared with squamous cell carcinoma. The investigators found that patients with single-organ metastasis were more likely to be older and have squamous NSCLC and a low TN status.

The median overall survival (OS) was significantly higher in patients with disease classified as TNM7 with intrathoracic metastasis (M1a) compared with distant metastasis (M1b) and compared with patients with TNM6 stage IV NSCLC (Table 1).

In patients with metastasis to only 1 organ, compared with multiple organs, the OS was significantly higher (Table 2). The risk for a shorter OS increased as the number of organs with metastasis increased (HR, 1.3 for 2 vs 1 organ; HR, 1.9 for ≥3 vs 1 organ; $P<.001$ for both). The multivariable analysis showed that OS was significantly better in patients who were younger (<50 years) and those who were women, as well as those who had AdC, TNM7 M1a cancer, metastasis to 1 organ, and limited local disease.

Table 1. Median Overall Survival by TNM Status

	No.	Median OS, mo	95% CI	*P* Value
TNM7 M1a	1419	8.3	7.6 to 9.0	<.001[a]
TNM7 M1b	5091	4.7	4.4 to 4.9	
TNM6	4584	4.6	4.4 to 4.8	

M1a, intrathoracic metastasis; M1b, distant metastasis; OS, overall survival; TNM, tumor, node, metastasis.

[a]Versus both comparative groups.

Table 2. Median OS by Degree of Organ Metastasis in Total and ^{18}FDG-PET Cohorts

Cohort: Metastasis	No.	Median OS, mo	95% CI	*P* Value
Overall				
1 organ	5676	6.7	6.4 to 7.0	
2 organs	3280	4.3	4.1 to 4.6	<.001
≥3 organs	2138	2.8	2.6 to 3.0	<.001
^{18}FDG-PET staged	1517			
1 organ		8.6	7.9 to 9.4	
2 organs		5.7	5.0 to 6.4	<.001
≥3 organs		3.8	3.1 to 4.4	<.001

^{18}FDG-PET, 18-fluoro-deoxyglucose positron emission tomography; OS, overall survival.

The OS was longer in patients whose disease was staged using 18-fluoro-deoxyglucose PET imaging compared with the total cohort (Table 2). As the number of organs with metastasis increased, the risk of a shorter OS also increased for this subgroup (HR, 1.4 for 2 vs 1 organ; HR, 2.2 for ≥3 vs 1 organ; $P<.001$ for both).

Single-organ metastasis plus a low TN status, compared with single-organ metastasis with a high TN status, conferred a longer OS in the total cohort (8.5 vs 6.5 months; HR, 1.4; $P<.001$) and in the 18-fluoro-deoxyglucose PET cohort (11.6 vs 8.2 months; HR, 1.6; $P<.001$). Moreover, it also conferred a longer OS in the subgroup of patients who were receiving active anticancer treatment. In these patients, the median OS was 10.4, 7.3, and 5.7 months for metastasis to 1, 2, or ≥3 organs, respectively; the HR was 1.4 and 1.9 for metastasis to 2 vs 1 organ and ≥3 vs 1 organ ($P<.001$).

The TN status also predicted survival, with a median OS of 13.7 vs 9.9 months for patients with a low vs high TN status (HR, 1.5; $P<.001$). In patients with single-organ metastasis, the OS was better only with intrathoracic M1a and extrathoracic lymph node metastasis, which included only current M1b lymph nodes. The HR was 0.6, 0.8, and 0.8 for pulmonary, pleural, and extrathoracic lymph node metastasis, respectively.

In conclusion, the prognosis was better in stage IV NSCLC patients who had metastasis to only a single organ and a low TN status, who had metastasis limited to the intrathoracic region, and who were receiving active anticancer treatment. In the patients with distant metastasis, only those with an extrathoracic lymph node metastasis (ie, lymph nodes currently staged as M1b) had a better OS.