Randomized, phase II, placebo-controlled trial of nintedanib for the treatment of radiation pneumonitis

Zachary R. Moore[1], Andreas Rimner[1], Stephanie Lobaugh[1], Alexander Geyer[1], Daphna Y. Gelblum[1], Annemarie F. Shepherd [1], Narek Shaverdian[1], Abraham J. Wu[1], Jamie E. Chaft[1], Marjorie G. Zauderer[1], Charles M. Rudin[1], Nicholas Vander Els[1], Mohit Chawla[1], David R. Jones[1], Dennis M. Sopka[2], Raymond Mak[3], Zhongxing Liao[4], Zhigang Zhang[1], Daniel R. Gomez[1], Paul K. Paik[1]

[1]Memorial Sloan Kettering Cancer Center, New York, NY [2]Lehigh Valley Health Network, MSKCC Alliance, Allentown, PA [3]Brigham and Women's Hospital/Dana-Farber Cancer Institute Boston, MA [4]MD Anderson Cancer Center, Houston, TX

Background

Radiation pneumonitis (RP) is the most common dose-limiting toxicity for thoracic radiation therapy. RP can cause substantial morbidity, with approximately 50% of patients experiencing subsequent acute pulmonary exacerbations, and the majority eventually developing radiation fibrosis.[1] The pathogenesis of radiation pneumonitis is thought to be mediated through the release of multiple cytokines and growth factors, which results in an inflammatory response and eventually leads to the activation of fibroblasts and myofibroblasts to deposit fibrin and cause permanent structural and functional changes in the lung.[2,3] Nintedanib is used for the treatment of idiopathic pulmonary fibrosis, which shares many pathophysiological pathways with the subacute phase of RP.[4] Our goal was to investigate the efficacy and safety of nintedanib added to a standard prednisone taper compared to a prednisone taper alone in reducing pulmonary exacerbations in patients with grade 2 or higher (G2+) RP.

Methods

In this phase II, randomized, double-blinded, placebo-controlled trial, patients with newly diagnosed G2+ RP were randomized 1:1 to nintedanib 150mg twice daily for 12 weeks or placebo, in addition to a standard 8-week prednisone taper. The primary endpoint was freedom from pulmonary exacerbations within one year. Secondary endpoints included total number of exacerbations and pulmonary function tests (PFTs). Kaplan-Meier analysis was used to estimate the probability of freedom from pulmonary exacerbation. The study was closed early due to slow accrual.

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Figure 1. Baseline Characteristics

Characteristic	Overall *n* = 30	Nintedanib *n* = 18	Placebo *n* = 12
Age in years	72 (47-86)	72 (58-80)	70 (47-86)
Sex			
Female	22 (73%)	13 (72%)	9 (75%)
Male	8 (27%)	5 (28%)	3 (25%)
Race			
Asian	3 (10%)	1 (6%)	2 (17%)
Black or African American	1 (3%)	0	1 (8%)
Not reported	1 (3%)	0	1 (8%)
White	25 (83%)	17 (94%)	8 (67%)
Smoking Status			
Former	24 (83%)	15 (83%)	9 (82%)
Never	5 (17%)	3 (17%)	2 (18%)
KPS	80 (70-100)	80 (70-90)	80 (70-100)
Pneumonitis Grade			
Grade 2	24 (80%)	14 (78%)	10 (83%)
Grade 3	6 (20%)	4 (22%)	2 (17%)
Prior Steroids	23 (77%)	13 (72%)	10 (83%)

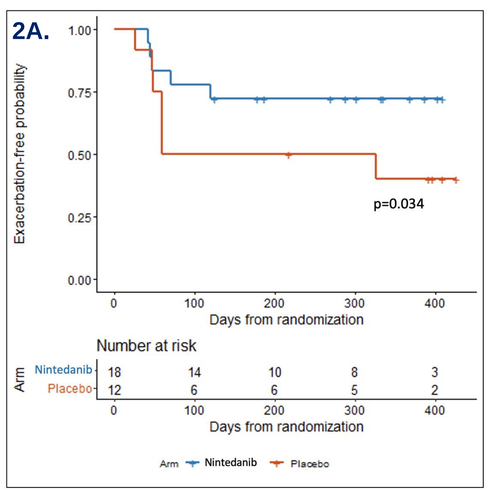
Figure 3. Adverse Events

	Nintedanib *n* =18	Placebo *n*=12
Grade 2+ AEs	16	5
Systemic		
Fatigue	1	1
Anorexia	1	-
Respiratory		
Cough	-	1
Dyspnea	3	-
Hypoxia	1	-
Lung Infection	2	-
Pleural effusion	1	-
Gastrointestinal		
Diarrhea	3	-
Nausea	-	1
Cardiovascular/Hematologic		
Pericardial effusion	1	-
Hypertension	1	-
Platelet count decreased	1	-
Lymphocyte count decreased	-	1
Thromboembolic event	1	-
Skin		
Rash	-	1

Fig 3. Grade 2+ adverse events possibly or probably attributed to study intervention

Figure 2. Freedom from Pulmonary Exacerbations

2A.



2B.

Arm	N	Events	Median FFE Months (95% CI)	FFE at 1 year % (95% CI)
Nintedanib	18	5	NR	72% (54%-96%)
Placebo	12	7	6.4 (2-NR)	40% (20%-82%)

Fig 2A. Kaplan-Meier plot of time to first acute pulmonary exacerbation beginning 2 weeks after the start of treatment with nintedanib + prednisone or placebo + prednisone. Prespecified one-sided Z-test for significance at one year p=0.034.

Fig 2B. Kaplan-Meier estimate of median freedom from exacerbation (FFE) and estimated freedom from pulmonary exacerbation at 1 year. NR=not reached

Results

Thirty-four patients were enrolled, three patients withdrew consent, and one was not treated. Of the evaluable 30 patients, 18 were randomized to the experimental Arm A (nintedanib + prednisone taper) and 12 to control Arm B (placebo + prednisone taper). Baseline patient characteristics are shown in Figure 1.

The Kaplan-Meier plot of freedom from pulmonary exacerbations is shown in Figure 2A. Freedom from pulmonary exacerbations at one year was 72% (CI 54%-96%) in Arm A and 40% (CI 20%-82%) in Arm B (Figure 2B). This difference was statistically significant based on the prespecified one-sided Z-test at one year p=0.037.

In Arm A there were 16 G2+ adverse events possibly or probably related to treatment compared to five in the placebo arm (Figure 3). There were two deaths during the study period in arm A due to cardiac failure and progressive respiratory failure, respectively, which were not thought to be attributed to the study drug. No baseline patient characteristics were associated with freedom from exacerbations, and there were no statistically significant changes in PFTs between treatment arms.

Conclusions

After the initial onset of G2+ RP, treatment with nintedanib plus prednisone taper improved freedom from pulmonary exacerbations at one year compared to placebo plus prednisone taper. These findings show promise for the use of nintedanib in the treatment of radiation pneumonitis.

Sources Cited

1. P Williams, J., J Johnston, C., & N Finkelstein, J. (2010). Treatment for radiation-induced pulmonary late effects: spoiled for choice or looking in the wrong direction?. Current drug targets, 11(11), 1386-1394.
2. Kong, Feng-Ming, et al. "Non-small cell lung cancer therapy-related pulmonary toxicity: an update on radiation pneumonitis and fibrosis." Seminars in oncology. Vol. 32. WB Saunders, 2005.
3. Käsmann, L., Dietrich, A., Staab-Weijnitz, C. A., Manapov, F., Behr, J., Rimner, A., ... & Belka, C. (2020). Radiation-induced lung toxicity–cellular and molecular mechanisms of pathogenesis, management, and literature review. Radiation Oncology, 15(1), 1-16.
4. Lamb, Y. N. (2021). Nintedanib: A review in fibrotic interstitial lung diseases. Drugs, 81(5), 575-586.