# Progression-Free Survival Estimation of Docetaxel-Based Second-Line Treatment for Advanced Non- Small Cell Lung Cancer: A Pooled Analysis from 18 Randomized Control Trials

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## *Abstract*

***Objectives:*** Lung cancer is the foremost cause of cancer-related death globally with NSCLC accounting for 85–90% of cases. The objective of the study was to estimate whether the progression-free survival (PFS) is an outcome of NSCLC extracted from 18 randomized control trials with docetaxel as experimental group and antineoplastic agent, kinase inhibitor and monoclonal antibodies as a control group.

***Methods:*** Meta package of R Studio was used to perform the meta-analysis. Graphical funnel plots were used to visually evaluate publication bias.

***Results:*** Patients who underwent docetaxel-based therapy had a considerably longer PFS than those who got antineoplastic agents, kinase inhibitors, or monoclonal antibodies-based treatment, according to data from 18 trials including a total of 9738 patients. Patients in the standard treatment arm had a slightly longer PFS than those in the experimental therapy arm in the overall meta-analysis.

***Conclusion:*** Docetaxel outperformed monoclonal antibodies, antineoplastic agents, and kinase inhibitors in the second-line therapy of advanced NSCLC since PFS was extensively utilized.

**Keywords:** Non- Small Cell Lung Cancer (NSCLC), Meta analysis, Progression-free Survival, Docetaxel.

## Introduction

Cancer is the result of a complex multistep system that includes the accumulation of several gene mutations, which comprises encoding microRNA.[1] Heredity Ionizing radiation, Chemical substances, alcohol, nitrates, estrogens, viruses, stress, age are the main risk factors.[2] Carcinoma, sarcoma, leukemia, lymphoma and myeloma are the types of cancer.[3] According to the World Health Organization (WHO), it is the first or second largest cause of mortality before the age of 70 in 112 of 183 nations, ranks third or fourth in another 23 countries, and is a major impediment to improving life expectancy in every country on the planet in 2019.[4] It has an impact on the high incidence of stroke and coronary heart disease mortality in many nations.[5] Human papillomavirus (HPV), hepatitis B virus (HBV), human immunodeficiency virus (HIV) and bacteria like *Helicobacter pylori* (stomach cancers) are infectious agents increasing the risk of cancer.[6] The number of cancer cases is expected to increase from 979,786 cases in 2010 to 1,148,757 cases in 2020.[7] Lung cancer is the most recurrently diagnosed and the main cause of mortality rate of cancer. The two most common types of lung cancer are non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC makes for 80 to 85% of lung cancer cases, with SCLC accounting for the rest. Patients with lung cancer may be eligible for a variety of therapies, including surgery, radiation, chemotherapy, and targeted therapy, depending on their stage. Targeted therapy is the most essential therapeutic option for NSCLC, however other common treatments include radiation therapy, surgery, chemotherapy, and immunotherapy. Targeted therapies include monoclonal antibodies and small-molecule inhibitors. Specific mutations have been detected thanks to advances in genetics and biomarker testing, allowing doctors to better target treatment for individual patients.[8,9] Cigarette smoking is executed as the significant hazard factor with an 82% mortality rate high in males compared to females.[10] It is asymptomatic at early-stage patients are diagnosed at an advanced stage and experience poor prognosis..[11] The objective of the study is to estimate whether the progression-free survival (PFS) is an outcome of NSCLC extracted from 18 randomized control trials.[12] Progression-free survival (PFS), the time from therapeutic initiation to disease progression, may be used as a measure of clinical benefit for drug approvals, depending on the condition and response observed.[13]

## Methods

### *Literature study*

The relevant studies were retrieved through google scholar, PubMed, Scopus, Science Direct and Cochrane Library which were published between 2010 to 2021. Advanced non-small cell lung cancer, chemotherapy, randomized control trial, docetaxel, and second-line treatment were the terms included in the search.

### *Selection criteria*

Randomized trials which evaluate docetaxel with a kinase inhibitor, antineoplastic agents, monoclonal antibodies for NSCLC were included. Patients diagnosed by NSCLC were involved in inclusion criteria. Docetaxel compared with other therapeutic agents except kinase inhibitors, monoclonal antibodies and antineoplastic agents were considered as exclusion criteria. Similarly, studies that compared docetaxel to other drugs were excluded, as well as early studies published as a series of articles by the same author with overlapping data that could lead to publication bias, and editorials, case reports, conference articles, experimental studies, and related studies that failed to provide significant findings. Authorship, publication bias, clinical trials, demographic attributes, histology characteristics, smoking status, treatment for each group, and adverse events were all extracted using a fixed standardized procedure. The conventional treatment in this trial was docetaxel, while the experimental arm was a kinase inhibitor, antineoplastic drug, or monoclonal antibody.

### *Quality management*

To reduce the risk of publishing bias, a comprehensive search approach was devised. Graphical funnel plots were used to visually evaluate a publication bias to evaluate the quality of randomized control trials (RCTs).

### *Statistical methods*

Pooled HR (Hazard Ratio) was calculated with 95% CI. The Forest plot and the inconsistency statistic (I2) determine the heterogeneity. The odds ratio was the summary measure used for the pooling of studies. Hedge's method evaluates the effect size calculated by standard mean difference (SMD) given as Hedge's g value. The meta-analysis was summarized graphically using a forest plot. Meta package of R Studio was used to perform the meta-analysis.

## Results

The details of study selection criteria followed for the meta-analysis of drug intervention prevalence are given in Figure 1. The number of published articles was 1009, of which 25 were rejected for duplication in one or the other form,549 were excluded as non-randomized control trials, 36 were excluded due to phase 1 randomized control trial, and 68 were excluded since meta-analysis and also 53 excluded because of NSCLC. Then after filtering 278 randomized control trials were selected for detailed evaluation, in which 156 were excluded which were treatment arms without docetaxel, and 104 were excluded which were without monoclonal antibodies, kinase inhibitors, and antineoplastic agents. Hence 18 Randomized control trials were selected for the study.

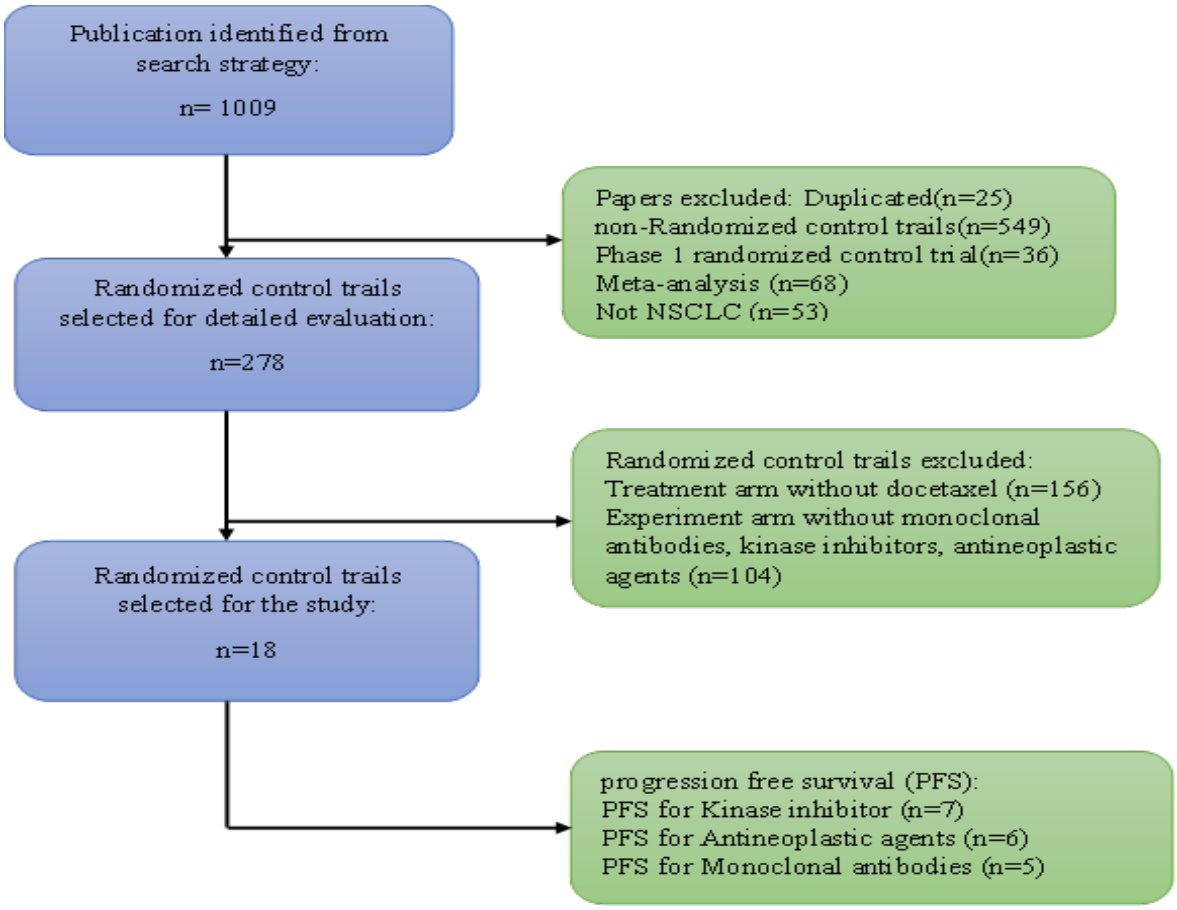


**Figure 1:** The flowchart summarizing the steps of study selection

The characteristics of selected randomized control trials of meta-analysis are shown in Table 1. A total of 6 RCTs phase 3 data for the antineoplastic agent class of intervention were analyzed, with the maximum number of patients recorded was 596, with a median age of 62, and PFS as the primary endpoint. Data from seven phase 2 and 3 RCTs were analyzed for the kinase inhibitor class of intervention, with 1314 highest number of patients having a primary endpoint of PFS, the median age of 60 The remaining 5 RCTs of phase 2 and 3 monoclonal antibody class intervention data were analyzed with PFS as the main endpoint, and the highest number of patients recorded was 1253 with a median age of 61.5

**Table 1:** Characteristics of the selected RCTs for meta-analysis.

| Sl. no | Study Reference | Phase of trail | No. of Patients | Median age | Drug class-intervention | Intervention and dosage | Treatment and dosage | Primary endpoint |
|---|---|---|---|---|---|---|---|---|
| 1 | Barlesi F et al. (2018)[14] | 3 | 792 | 63.5 | 3 | Avelumab 10mg/kg/2 W | Docetaxel 75mg/$m^2$/3 W | PFS |
| 2 | Fehrenbacher L et al. (2016)[15] | 2 | 287 | 62 | 1 | Atezolizumab 1200mg/3 W | Docetaxel 75mg/$m^2$/3 W | PFS |
| 3 | Garassino M C et al. (2013)[16] | 2 | 219 | 66.5 | 2 | Erlotinib 150mg/D | Docetaxel 75mg/$m^2$/3 W | PFS |
| 4 | Garon E B et al. (2014) [17] | 3 | 1253 | 61.5 | 3 | Ramucirumab 10mg/kg/3 W + Docetaxel 75mg/$m^2$/3 W | Placebo + Docetaxel 75mg/$m^2$/3 W | PFS |
| 5 | Gerber D E et al. (2018) [18] | 3 | 597 | 62.5 | 3 | Bavituximab 3mg/kg/W + Docetaxel 75mg/$m^2$/3 W | Placebo + Docetaxel 75mg/$m^2$/3 W | PFS |
| 6 | Herbst R S et al. (2015) [19] | 2&3 | 689 | 63 | 3 | Pembrolizumab 10mg/kg/3 W | Docetaxel 75mg/$m^2$/3 W | PFS |
| 7 | Jänne P A et al. (2017) [20] | 2&3 | 510 | 61.4 | 2 | Selumetinib 75mg/0.5D + Docetaxel 75mg/$m^2$/3 W | Placebo + Docetaxel 75mg/$m^2$/3 W | PFS |
| 8 | Kawaguchi T et al. (2014)[210] | 3 | 301 | 68 | 2 | Erlotinib 150 mg/D | Docetaxel 75mg/$m^2$/3 W | PFS |
| 9 | Kubota k et al. (2015)[22] | 3 | 596 | 62 | 1 | S-1 80mg/$m^2$/ D + cisplatin 60mg/m2/ W | Docetaxel 60mg/$m^2$/3 W + Cisplatin 80mg/$m^2$/3 W | PFS |
| 10 | Lee D H et al. (2010)[23] | 3 | 161 | 57.5 | 2 | Gefitinib 250mg/D | Docetaxel 75mg/$m^2$/3 W | PFS |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 11 | Manegold C et al. (2013)[24] | 2 | 70 | 60.2 | 1 | Cilengitide 600mg/m$^2$/ 0.5D | Docetaxel 75mg/m$^2$/3 W | PFS |
| 12 | Ramlau R et al. (2012)[25] | 3 | 913 | 59.6 | 2 | (Ziv-)aflib ercept 6mg/kg/3 W + Docetaxel 75mg/m$^2$/3 W | Placebo + Docetaxel 75mg/m$^2$/3w | PFS |
| 13 | Reck M et al. (2014)[26] | 3 | 1314 | 60 | 2 | Docetaxel 75mg/m2/ 3W + Nintedanib 200mg/0.5 D | Docetaxel 75mg/m$^2$/3 W | PFS |
| 14 | Rittmeyer A t al. (2016)[27] | 3 | 850 | 64 | 1 | Atezolizu mab 1200mg/3 W | Docetaxel 75mg/m$^2$/3 W | PFS |
| 15 | Rodrigues-Pereira J et al. (2011)[28] | 3 | 211 | 59.5 | 1 | Pemetrexe d 500mg/m$^2$/ 3W + Carboplati n 5mg/ml/mi n | Docetaxel 75mg/m$^2$/3 W + Carboplatin 5mg/ml/min | PFS |
| 16 | Socinski M A et al. (2010) [29] | 2 | 146 | 66 | 1 | Pemetrexe d 500mg/m$^2$/ 3W + Carboplati n 6mg/ml/mi n | Docetaxel 75mg/m$^2$/3 W + Carboplatin 6mg/ml/min | PFS |
| 17 | Yoh K et al. (2016)[30] | 2 | 157 | 65 | 3 | Ramuciru mab 10mg/kg/3 W + Docetaxel 60mg/m2/ 3W | Placebo + Docetaxel 75mg/m$^2$/3 W | PFS |
| 18 | Pillai R N et al. (2019)[31] | 3 | 672 | 68 | 2 | Ganetespib 150mg/m$^2$/ 2W + Docetaxel 75mg/m$^2$/3 W | Docetaxel 75mg/m$^2$/3 W | PFS |

*Drug class of intervention: 1- Antineoplastic agents, 2- Kinase inhibitors, 3- Monoclonal antibodies; Treatment and dosage: W- Week, D- day*

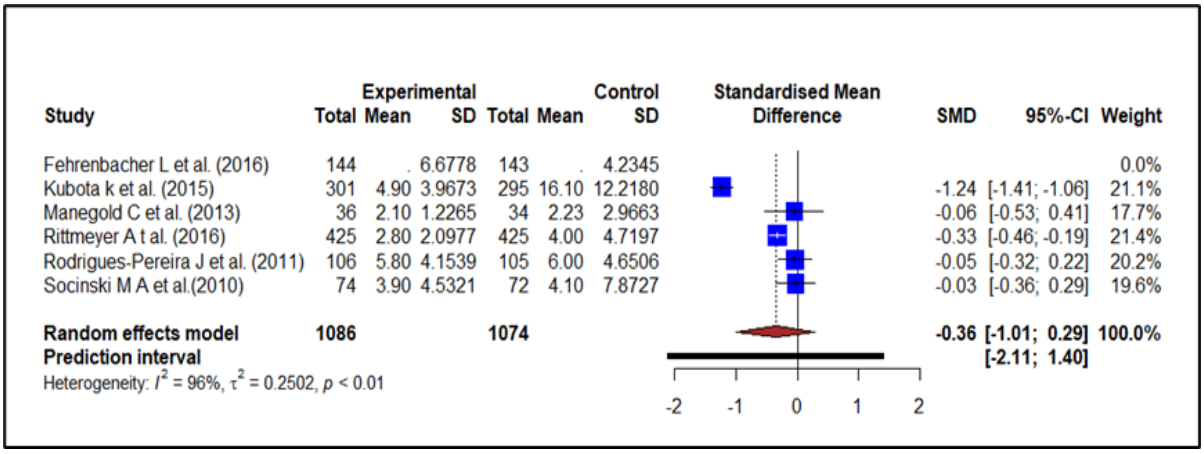


**Figure 2:** Forest plot representing the PFS of docetaxel- versus antineoplastic agents- treatment; the Hedge's corrected standardized mean difference (SMD) is -0.36 and Higgin's and Thompson's I2 statistic is 96%.

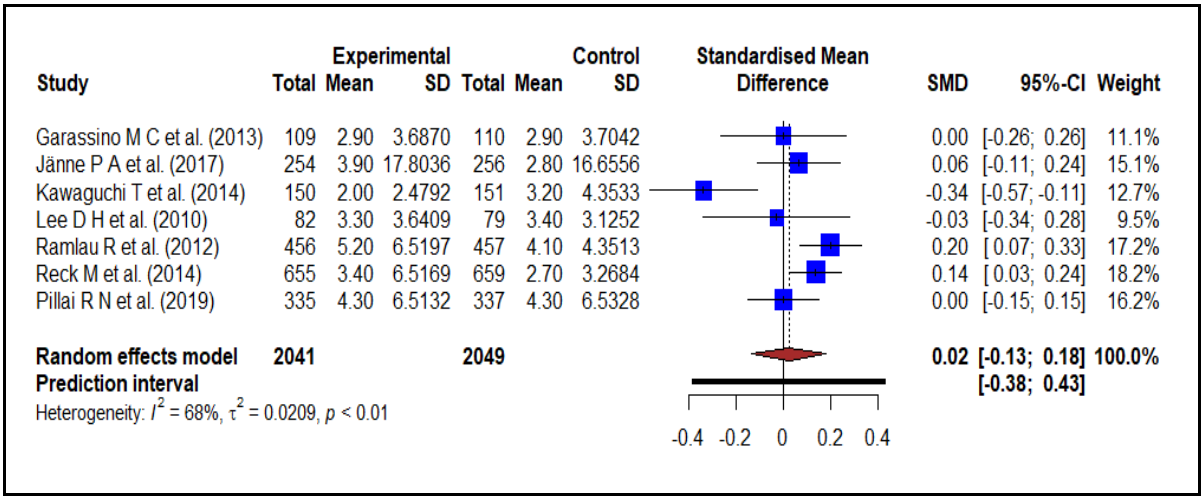


**Figure 3:** Forest plot representing the PFS of docetaxel- versus kinase inhibitors- treatment; the Hedge's corrected standardized mean difference (SMD) is 0.02 and Higgin's and Thompson's $I^2$ statistic is 68%.

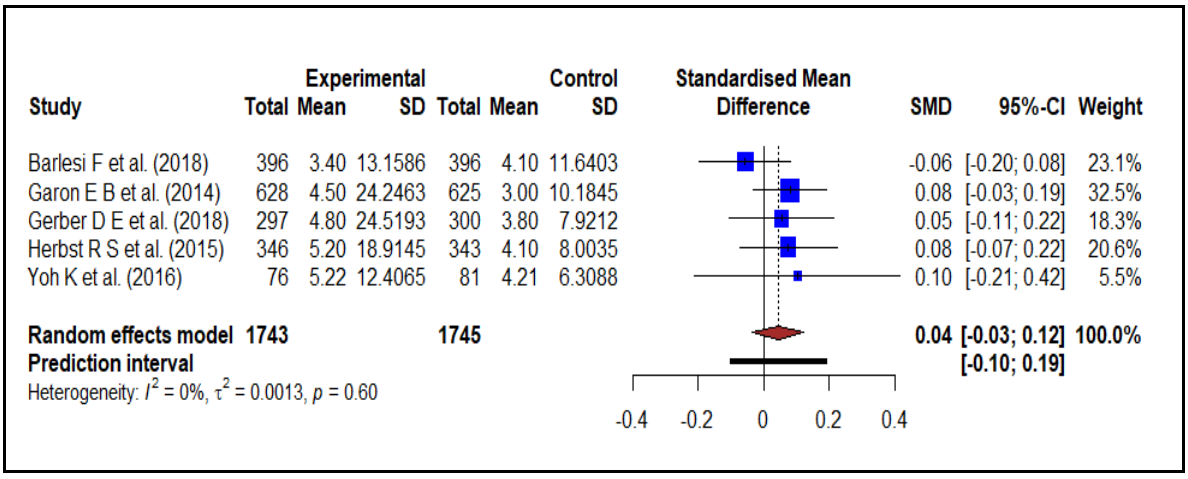


**Figure 4:** Forest plot representing the PFS of docetaxel- versus monoclonal antibodies- treatment; the Hedge's corrected standardized mean difference (SMD) is 0.04 and Higgin's and Thompson's $I^2$ statistic is 0%.

Figures 2,3,4 show a forest plot comparing the PFS of docetaxel to antineoplastic agents, kinase inhibitors, and monoclonal antibodies-based treatment. The 6 studies reported the PFS of antineoplastic agents compared with docetaxel with 2160 patients involved. The meta-analysis of all involved studies revealed significant statistical heterogeneity ($I^2$=96%, $\tau^2$=0.2502, p<0.01), and Hedge's corrected standardized mean difference (SMD) is -0.36(95% CI: -1.01-0.29). There was a moderate effect because it was a negative value smaller than -0.20, which implies the result was in favor of the antineoplastic agents-based treatment.

A total of 4090 patient data from 7 studies reported the PFS of kinase inhibitor compared with docetaxel-based treatment. A bias-corrected standardised mean difference; Hedge's g value was 0.02 (95% CI: -0.13-0.18), implying the result was in favor of the docetaxel-based standard treatment. A significant statistical heterogeneity ($I^2$=68%, $\tau^2$=0.0209, p<0.01) was found in the pooled analysis of all included studies.

The PFS of monoclonal antibodies was compared to docetaxel in 5 studies involving 3488 individuals. There was no substantial statistical heterogeneity in a pooled analysis of all included trials ($I^2$=0, $\tau^2$=0.0013, p=0.60), and Hedge's g value was 0.04 (95% CI: 0.03-0.12), indicating that the result was in favor of docetaxel-based treatment; but, the SMD value was less than 0.20, indicating that docetaxel had a minor effect.

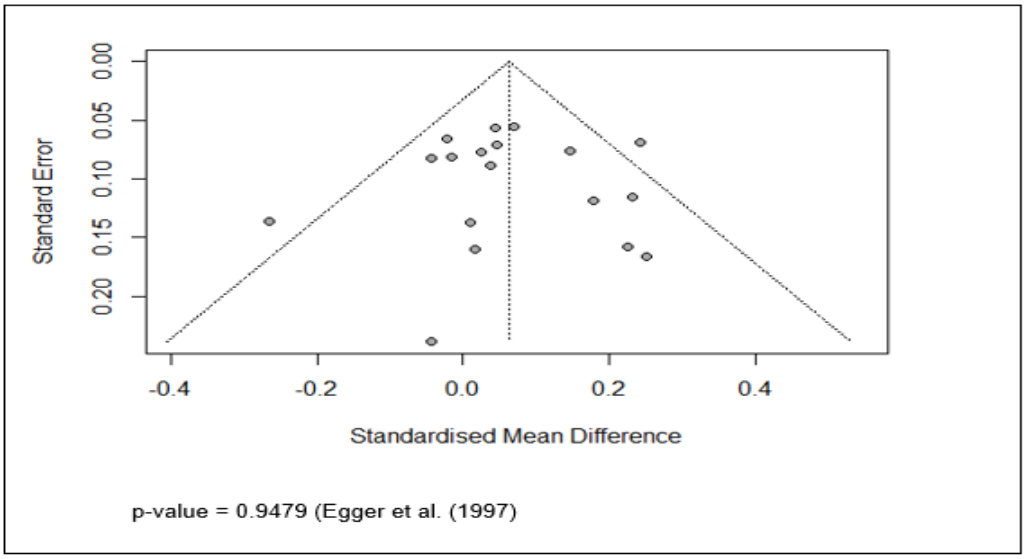


**Figure 5:** Funnel plot showing publication bias

Publication Bias: The p values for the meta-analyses of PFS of 18 RCTs are >0.05, indicating that formal statistical testing revealed no indication of significant publication bias (PFS: Egger's test, P = 0.9479).

## Discussion

Lung cancer is the foremost cause of cancer-related death globally with NSCLC accounting for 85–90% of cases. The meta-analysis was conducted for 18 RCT's[14-31] with Docetaxel as experimental group and antineoplastic agent, kinase inhibitor and monoclonal antibodies as a control group of 9738 patients with stage III-IV NSCLC. The objective of this study was to see if the PFS of patients had improved or not. Platinum-based two-drug combinatorial chemotherapy has been the standard of care for advanced NSCLC patients.[22-243] The main aim of the study was to compare the two treatment regimens in terms of progression-free survival in patients with advanced NSCLC. .[24] A total of 2160 cases with six RCTs were used to compare the docetaxel with antineoplastic agents. Fehrenbacher L et al. (2016), Rittmeyer A t al. (2016), Kubota k et al. (2015), Manegold C et al. (2013), Rodrigues-Pereira J et al. (2011), Socinski M A et al. (2010) compares the improvement of PFS between docetaxel and atezolizumab, S-1 plus cisplatin, cilengitide, pemetrexed/carboplatin. The period from randomization to either progressing illness or death was referred to as PFS.[22] The different randomisation methods are used to receive either 60mg/$m^2$ docetaxel plus cisplatin, 75mg/$m^2$ docetaxel, docetaxel 75mg/$m^2$/3W + carboplatin 5mg/ml/min or oral S-1 80 mg/$m^2$/day plus cisplatin 60 mg/$m^2$, cilengitide 600 mg/$m^2$, Pemetrexed 500mg/$m^2$/3W + carboplatin 5mg/ml/min, atezolizumab 1200mg to see the improvement of PFS between these groups.[15,22,24,27,29] The PFS was similar between each control and treatment group. The median PFS was 2·7 months with

atezolizumab and 3·0 months with docetaxel with Hazard Ratio (HR) of 0·94 (95% CI 0·72–1·23).[15] The median PFS was 2·8 months with atezolizumab and 4·0 months with docetaxel with HR of 0·63[95%CI0·43–0·91].[27] The median PFS was 4.9 months in the SP group and 5.2 months in the DP group with HR 1.113; 95% CI, 0.945 to 1.311.[22] There were no statistically significant differences in PFS between the treatment groups with HR of 0.91 (0.67–1.23).[24] Therefore, there was no improvement in PFS between the groups. In patients with metastatic NSCLC, antibodies that target the immune checkpoint molecules PD-L1 or PD-1 enhance PFS in comparison to standard-of-care chemo treatment.[14] A total of 3488 patients with five trials (Barlesi F et al. (2018), Garon E B et al. (2014), Gerber D E et al. (2018), Herbst R S et al. (2015), Yoh K et al. (2016)) have been used to compare docetaxel-based treatment with monoclonal antibody-based therapy. The meta-analysis of avelumab vs docetaxel in advanced NSCLC patients and progression of disease following platinum-based treatment was described by Barlesi F et al. Block randomized method is used to acquire either docetaxel 75 mg/m$^2$ or avelumab 10 mg/kg and PFS as a secondary endpoint. The median PFS in the avelumab group was 2·8 months (95% CI 2·7–3·5) and 4·2 months (3·3–5·2) in the docetaxel group with HR 1·16 [95% CI 0·97–1·40]. As a result, with avelumab, PFS was substantially longer and objective responses were more likely than with docetaxel. Garon E B et al. (2014) compared the effectiveness and safety of docetaxel with ramucirumab vs placebo as second-line therapy for stage IV NSCLC patients. A randomized method was used to obtain either ramucirumab 10 mg/kg or docetaxel 75 mg/m$^2$ to the patients. The median PFS for the ramucirumab group was 45 months, compared to 30 months for the control group with HR 0·76, (0·68–0·86). The PFS is improved in Ramucirumab compared to docetaxel in patients with stage IV NSCLC. The efficacy of bavituximab in combination with docetaxel in patients with advanced NSCLC who have already been treated was investigated by Gerber D E et al. (2018). The stratified randomized technique was used either to accept docetaxel plus placebo or docetaxel plus bavituximab 3 mg/kg to the patients. With HR 1.00; 95% CI, 0.82-1.22, there was no alteration in PFS. The addition of bavituximab to docetaxel did not improve PFS. Herbst R S et al. (2015) compare pembrolizumab's effectiveness and safety to those of docetaxel. A randomized method was used to acquire either pembrolizumab 10 mg/kg or docetaxel 60 mg/m to the selected participants. The Median PFS was 3·9 months with pembrolizumab 4·0 months with docetaxel, with HR 0·88, 0·74–1·05. Therefore, PFS was significantly longer with pembrolizumab than with docetaxel. Yoh K et al. (2016) explain how a phase II, double-blind, randomized, placebo-controlled trial in Japanese patients with NSCLC examined the safety and effectiveness of second-line ramucirumab-docetaxel. The median PFS was 5.22 months for ramucirumab-docetaxel and 4.21 months for placebo-docetaxel with HR of 0.83 (95% CI 0.59–1.16). Hence, PFS was longer with ramucirumab-docetaxel than with placebo- docetaxel. 7 clinical studies with 4090 participants were conducted to compare the docetaxel-based therapy with kinase inhibitor for the patients with advanced NSCLC. Lee D H et al. (2010), Garassino M C et al. (2013), Ramlau R et al. (2012), Kawaguchi T et al. (2014), Reck M et al. (2014), Jänne P A et al. (2017), Pillai R N et al. (2019) compared the efficacy and safety of Gefitinib, erlotinib, aflibercept (Ziv-aflibercept), docetaxel plus nintedanib, mitogen-activated protein kinase (MEK) inhibitor, selumetinib + docetaxel and combination of ganetespib -docetaxel with the treatment group of docetaxel in patients with advance NSCLC to check the improvement of PFS between the groups. A randomised clinical method was used to receive either docetaxel (75 mg/m$^2$), IV placebo plus docetaxel (75 mg/m$^2$), Placebo + Docetaxel 75mg/m$^2$/3W or Gefitinib (250 mg/d), erlotinib orally 150mg/day, (Ziv-)aflibercept 6 mg/kg intravenous plus docetaxel 75 mg/m$^2$ erlotinib 150 mg/D, nintedanib 200 mg orally, selumetinib 75mg/0.5D + Docetaxel 75mg/m$^2$/3W, ganetespib 150 mg/m until unacceptable side effects or disease progression based on previous bevacizumab treatment, histology, ECOG performance status, and presence of brain metastases.[15,19,20,22,24,25,30] The PFS was estimated as a primary and secondary endpoint in these studies. The Median PFS was 3.9 months with selumetinib + docetaxel and 2.8 months with placebo + docetaxel with HR, 0.93 [95% CI, 0.77-1.12].[19] The median PFS in the ganetespib and docetaxel arm was 4.2 months, and 4.3 months in the docetaxel arm, with an HR of 1.16; 95% CI, 0.96 to 1.403.[31] Gefitinib had a better PFS than docetaxel, with a hazard ratio of 0.729; 90% CI, 0.533-0.998. The PFS was longer with gefitinib than docetaxel. As a result, gefitinib was a crucial and effective second-line treatment option for Korean NSCLC patients.[23] Gefitinib had a longer PFS than docetaxel. The median PFS was 2·9 months with docetaxel versus 2·4 months with erlotinib with HR 0·71, 95% CI 0·53–0·95.[16] Median PFS was significantly longer in the (Ziv-)aflibercept arm of 5.2 months than in the placebo arm of 4.1 months with HR was 0.82 (95% CI, 0.72 to 0.94.[24] Erlotinib had a median PFS of 2.0 months against 3.2 months when compared to docetaxel with an HR of 1.22; 95% CI, 0.97 to 1.55. In an EGFR-unselected patient sample, erlotinib failed to improve PFS when compared to docetaxel.[21] The median PFS in the docetaxel plus nintedanib group was 3·4 months compared to 2·7 months in the docetaxel plus placebo group, [HR] 0·79 [95% CI 0·68–0·92].[26] There are certain limits to our analysis that should be considered while evaluating the results. First, the different treatment regimens add to the meta-analysis' clinical heterogeneity, which makes meta-analysis interpretation more difficult. In three studies, docetaxel was used in conjunction with other medicines, either cisplatin or carboplatin, in the control arm. The quality of the results was influenced by the quality of each study's results. Finally, because the research included in this study was all conducted in the West, the findings must be confirmed in Asia. Docetaxel was revealed to be more effective in the second-line

therapy of advanced NSCLC than antineoplastic drugs, kinase inhibitors, and monoclonal antibodies, according to the findings.

## Conclusion

The phase 2 and 3 study of antineoplastic agents demonstrates a clinically significant survival benefit over docetaxel in patients with non-small-cell lung cancer. When compared to docetaxel, monoclonal antibodies and kinase inhibitors had no effect on progression-free survival in NSCLC patients. From the results of 18 trials involving a total of 9738 patients, who received docetaxel-based therapy had a significantly longer PFS than those who received kinase inhibitors or monoclonal antibodies. In the overall meta-analysis, patients in the standard treatment arm had a slightly longer PFS than those in the experimental therapy arm. Biological behaviour subgroups such as those entirely refractory, those with partial and incomplete responses, and those with short and extended disease-free intervals will be examined in future meta-analysis investigations.

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