Efficacy of Nivolumab in Comparison to Chemotherapy and Gefitinib for Advanced Non Small Cell Lung Cancer (NSCLC)

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Abstract:

Background: Lung cancer is one of the major causes of cancer related death worldwide, while non-small cell lung cancer (NSCLC) consists of 85% of all lung cancer cases. Despite adequate treatment, most of the NSCLC patients progress to advance stages. Single or doublet-chemotherapy are considered as standard care for advance NSCLC patients. Gefitinib is considered as standard therapy for epidermal growth factor receptor (EGFR) mutant advanced NSCLC. Recently, a human monoclonal antibody called Nivolumab has shown encouraging efficacy for advanced NSCLC patients. The aim of this systematic review is to show the efficacy of nivolumab in comparison to single or doublet chemotherapy and gefitinib.

Method: A systematic search was performed in PubMed, Google Scholar and Cochrane Library to identify primary research, published in English language between 2000 and 2018, involving Nivolumab, chemotherapy and gefitinib for advanced NSCLC patients. The primary outcome of interest was median overall survival (mOS). The secondary outcome of interest were progression free survival, objective response rate and grade-3 and treatment related adverse effects.

Results: After screening 600 full-text articles, 17 clinical studies involving 9284 patients of advanced NSCLC were included. All treatment regimen seemed to be feasible. The mOS for nivolumab was ranging between 9.2 months and 16.2 months; for chemotherapy between 6 months and 18.8 months; and for gefitinib between 7.6 months and 30.5 months.

Conclusion: Nivolumab is more effective and safe for EGFR non-mutant advanced NSCLC patients than either chemotherapy or gefitinib. However, gefitinib is more effective than nivolumab for EGFR-mutant NSCLC patients.

Key words= Docetaxel, paclitaxel, carboplatin, EGFR-TKI

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Introduction:

Lung cancer is the most common cancer in men, consisting 17% of all newly diagnosed male cancers (1). Globally, it is the major cause of cancer related death in male, while it is only the second most prevalent cause in female after breast cancer (2). Lung cancer has two types such as small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC); NSCLC comprises almost 85% of all lung cancer cases (3). The spreading of lung cancer from its site of origin is regarded as advanced disease (4). The stage-3 is considered as locally advanced disease (5), while stage-4 consists of distal metastases (6). Apparently, 75% NSCLC patients are diagnosed at late stage with surgically unresectable condition (7), while nearly 60%-70% patients develop postoperative relapse and metastases after surgery (8). Docetaxel and platinum-based doublet-chemotherapy have been considered as standard therapy for advanced NSCLC (9, 10). However, chemotherapy has failed to provide significant benefit with narrow safety profile (10). Innovative therapy such as chemo-radiotherapy have been tried with enormous efforts to solve this problem over the last ten years; however, the 5-year survival rate is still below 20% (11). An epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) called gefitinib, is currently approved for EGFR mutant NSCLC as it shows better mPFS (median progression free survival), objective response rate (ORR) and safety profile than platinum-based doublet chemotherapy (12, 13). Gefitinib is more economical than other EGFR-TKI drugs and chemotherapy for EGFR mutant NSCLC (14). A human monoclonal, immunoglobulin G4 antibody called nivolumab, works by blocking the inhibitors of T-cell (PD-L1 and PD-L2) and enhancing the anti-tumour immunity (15). In simple terms, it works by blocking the PD-1 receptor of the T-cell. Nivolumab has shown efficacy in different histological type of NSCLC (16, 17). Additionally, it shows efficacy and safety for EGFR mutant NSCLC in phase-3 clinical trial (9). Nivolumab is recently approved by FDA for NSCLC (18). Currently, there are limited studies available that directly compare nivolumab with chemotherapy, while there are no available studies on comparison between gefitinib and

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nivolumab. The aim of this systematic review is to show the efficacy of nivolumab in comparison to single or doublet-chemotherapy for advanced NSCLC. Moreover, it shows the efficacy of nivolumab in comparison to gefitinib for EGFR mutant NSCLC.

Method:

The systematic review was conducted in accordance with the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guidelines (19).

1.1 Eligibility criteria:

The studies regarding nivolumab for advanced NSCLC, gefitinib for advanced NSCLC and chemotherapy for advanced NSCLC were included reporting outcomes on ORR, mPFS, mOS (median overall survival) and grade-3 and 4 treatment related adverse effects (TRAE). The included studies were phase-3 and phase-2 clinical trials studying the application of nivolumab, gefitinib, and single or doublet chemotherapy for advanced NSCLC patients. The participants of any age, sex and race were considered. The included studies have any of the following 3 types of interventions such as nivolumab, gefitinib, and single or doublet chemotherapy. The excluded articles were review articles, systematic review and meta-analysis, conference abstracts, case reports, animal studies and phase-1 studies.

1.2 Information source:

A systematic search was carried out in Google Scholar, PubMed and Cochrane Library to find the studies, published in English Language between 2000 and 2018. The articles were recognised by searching the electronic database and scanning the reference lists.

1.3 Search:

Different keywords and terms of Medical subject headings (MeSH) were linked together with 'and' and 'or'. The primary keyword was "advanced NSCLC", while the secondary keywords were nivolumab, chemotherapy and gefitinib. The terms were limited to MeSH, article title and abstract. The studies were screened by headlines and abstracts for acceptability based on inclusion and exclusion principles, and duplicates were deleted.

1.4 Study selection:

The included studies were assessed independently in an open standardized method. The retrieved record were typically screened by titles and abstracts, and total of 60 studies' full-text publication were reviewed (Figure-1).

1.5 Data collection process:

Data were collected independently from the selected studies. The collected data were assessed (appendix) and presented in two tables (table-1 and 2). No researchers were contacted for data collection or additional information collection.

1.6 Data Items:

Data concerning ORR, mOS, mPFS and TRAE in advanced NSCLC patients were collected from the selected studies. Precisely, data were extracted from each selected studies on 1) participant's characteristics (age, stage of the disease, therapeutic response assessment method, performance status); (2) therapeutic regimen (name of the therapy, dose, duration and frequency); (3) Comparison between therapeutic regimens such as nivolumab versus gefitinib or placebo or docetaxel or doublet chemotherapy; (4) outcome measures (including TRAE).

1.7 Risk of bias in individual studies and quality assessment:

The risk of bias was assessed individually in a blind manner (appendix). The methodological quality of each clinical trial was assessed by modified Jadad scale (20). The quality of the studies were evaluated by scale based on the subsequent assessment criteria: randomization, blinding, inclusion and exclusion criteria, dropouts and withdrawals, side effects and statistical analysis.

1.8 Summary measures:

The outcome of primary interest was overall survival. The secondary outcomes of interests were ORR and mPFS. Nivolumab's safety was assessed by grade-3 and 4 TRAE. The tumour response of these studies were assessed by Response Evaluation Criteria in Solid Tumours (RECIST). The grade-3 and 4 TRAE were assessed and classified according to Common Terminology Criteria for Adverse Events (CTCAE).

Results:

2.1 Study selection:

A total 17 studies involving 14 phase-3 studies (9, 10, 13, 21-31) and 3 phase-2 studies (17, 32, 33) were included in this systematic review by screening title, abstract, method and full-text, and after removing the duplicates

(figure-1). After initial search, 45595 studies were identified. The title and abstracts of 600 studies were screened. After reviewing the abstracts, 540 studies were excluded because these studies did not fulfil the inclusion criteria. The full-text of 60 studies were assessed in details. Finally, 17 studies met the inclusion criteria and were included in this systematic review.

2.2 Study Characteristics:

All the selected studies are either phase-3 or phase-2 clinical trials published. Therapeutic regimen included nivolumab therapy in 6 studies (9, 10, 17, 21, 22, 32), doublet chemotherapy in 3 studies (23-25), single chemotherapy in 5 studies (27-31) and gefitinib therapy in 3 studies (13, 26, 33). The patients received nivolumab, gefitinib and pemetrexed until the disease progression, docetaxel in between 4 and 8 cycles, paclitaxel plus carboplatin for 5 cycles, and paclitaxel/carboplatin for 6 cycles or less. The selected trials involved 9284 patients of advanced NSCLC agede" 18 years. The performance status of the patients were ECOGd"2 or WHO 0-2. The trials included patients of all different races such as White, Black or Asian. The researcher of included studies assessed the primary outcome by mOS, mPFS or ORR. The results of the included studies were presented in two tables (table-1 and 2).

2.3 Results of individual studies:

Total 13 studies were included in table-1(10, 21-32). The patients received nivolumab showed mOS of 14.4 months, 9.2 months and 16.3 months, while the mPFS were 4.2 months and 3.5 months. In nivolumab group, there were no difference in mOS between the patients with prior chemotherapy and without prior chemotherapy, and different age groups. The ORR for Nivolumab were 27%, 20%, 35% and 25.7%; the grade-

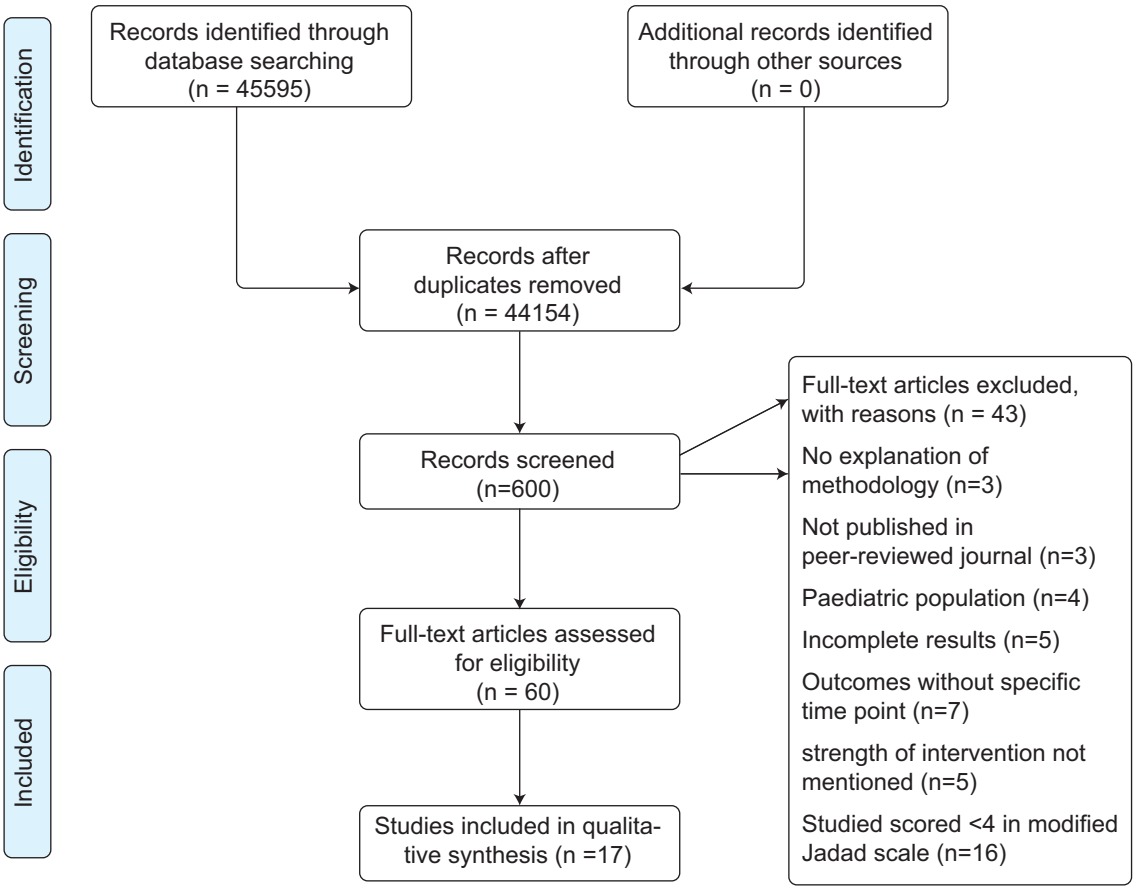

Figure-1: *Flow chart of study selection.*

Table-I

Comparison between nivolumab and single or doublet chemotherapy for advanced NSCLC patients.

Authors	Sample size	Participants' characteristics	Study design	Comparison	Therapeutic regimen	Primary endpoint PFS	ORR	mPFS (months)	mOS (months)	TRAE (Grade-3&4)
Carbone, Reck (10)	541	i) Stage-4 NSCLC. ii) ECOG status 0-1. iii) Median age=64 (29 to 89 year). iv) No prior anti-cancer therapy.	International, randomised, open-label, phase-3	N vs ICC	N=3mg/kg, QW2		27% vs 10%	4.2 vs 5.9	14.4 vs 13.2	18% vs 51%
Brahmer, Reckamp (21)	272	i) Stage-3b or 4 squamous NSCLC II) Age≥18 year (median age 63). iii) ECOG status 0-1.	International, prospective, randomised, phase-3 trial	N vs D	N=3mg/kg QW2 vs D=75mg/kg QW3	OS	20% vs 9%	3.5 vs 2.8	9.2 vs 6	7% vs 55%
Horn, Spigel (22)	854	i) Stage-3b or 4 squamous and non-squamous NSCLC.	Randomised, open-label, phase-3	N vs D	N=3mg/kg QW2 vs D=75mg/kg QW3	-	37% & 34% for N. vs NR for D.	-	-	10% vs 55%
Hida, Nishio (32)	35	i) Stage-3b or 4 squamous NSCLC. ii) Age≥20 year (Median age 65). iii) Prior platinum chemotherapy.	Multicentre, open-label, phase-2	N	N=3mg/kg QW2 up to 6 cycles.	ORR	25.7%	4.2	16.3	5.7%
Belani and Fossella (23)	1218	i) Stage-3 or 4 NSCLC. ii) Age≥18 year iii) No prior chemotherapy.	Multinational, randomised, phase-3	D+C vs D+Cb vs V+C	D+C (D=75mg/m^2+ C= 75mg/m^2), Cb=AUS 6, V+C (V=25mg/m^2+ C= 100mg/m^2)	OS	-	-	11.8 vs 9.35 vs 10	V+C> D+Cb> D+C
Quoix, Zalcman (24)	451	i) Unresectable stage-3 or 4 NSCLC. ii)ECOG status≤2 iii) Age= 70-89 years. iv) Life expectance≥ 12 weeks. v) No prior chemotherapy	Multicentre, open-label, randomised, phase-3	Cb+P vs V/G	Cb(AUS 6) + P(90mg/m^2) vs V(25mg/m^2) or G(1150mg/m^2)	OS	27.1 vs 10.2	6 vs 2.8	10.3 vs 6.2	Cb+P> V/G
Bonomi, Kim (25)	599	i) Stage-3b or 4 NSCLC. ii) Chemotherapy naïve.	Multinational, randomised, phase-3 trial	P+C vs E+C	P=135mg/m^2 and 250mg/m^2, C=75mg/m^2, E=100mg/m^2	OS	-	-	9.9 vs 7.6	-
Kim, Hirsh (26)	1433	i) Advanced or metastatic NSCLC. ii) Age≥ 18 years. iii) WHO performance status 0-2. iv) No prior EGFR-TKI	Multicentre, randomised, open-label, phase-3 trial	Ge vs D	Ge=250 mg/daily orally Vs D=75mg/m^2 QW3	OS	9.1% vs 7.6%	2.2 vs 2.7	7.6 vs 8	9% vs 41%
Schuette, Nagel (27)	215	i) Advanced or metastatic NSCLC. ii) Age= 18-75 years. iii) Received >1 previous chemotherapy. iv) ECOG status 0-2.	Multicentre, randomised, phase-3 study	D-QW3 vs D-QW1	D=75mg/m^2 for QW3 cycle group; D=35mg/m^2 for QW1 group.	OS	12.6% vs 10.5	-	6.3 vs 9.2	9.7% vs 12.4%

(table continued)

Table-I (cont'd)

Authors	Sample size	Participants' characteristics	Study design	Comparison	Therapeutic regimen	Primary endpoint PFS	ORR	mPFS (months)	mOS (months)	TRAE (Grade-3&4)
Kudoh, Takeda (28)	**182**	**i) Stage-3b or 4 NSCLC. ii) Age=70-86 year (median age 76 year) iii) ECOG≤ 2. iv) Life expectance≤ 3 months.**	**Randomised, phase-3 study**	**D vs V**	**D=60mg/m^2 vs V=25mg/m^2**	**OS**	**22.7% vs 9.9%**	**5.5 vs 3.1**	**14.3 vs 9.9**	**Neutropenia (82.9% vs 69.2%); leukopenia (58% vs 51.7%)**
Fidias, Dakhil (29)	566	i) Stage-3b +pleural effusion or stage-4 NSCLC. ii) Age≥18 years. iii) Life expectance≥ 12 weeks. iv) ECOG status≤ 2. v) No chemotherapy.	Randomised, phase-3 study	D-immediately after GC Vs D after disease progression	D=75mg/m^2, G= 1000mg/m^2,	OS	11.7% vs 11.2%	5.7 vs 2.7	12.3 vs 9.7	Neutropenia (27.6% vs 28.6%)
Fukuoka, Wu (30)	1217	i) Stage-3b or 4 adenocarcinoma (NSCLC). ii) Never smoker or light smoker (stopped smoking≥15 years previously and smoke≤10 pack-years) iii) No prior chemotherapy. iv) Age< 65 years	Randomized, open-label, phase-3 study	G vs Cb/P	G=250mg daily, P=200mg/m^2, Cb= AUC 5/6	OS	-	-	18.8 vs 17.4	-
Hanna, Shepherd (31)	571	i) Stage-3 or 4 NSCLC. ii) Only 1 prior chemotherapy. iii) ECOG status≤ 2. iv) Age=22-87 years (median age; Pe=59, D=57).	Multinational, randomised, phase-3 trial	Pe vs D	P=500mg/m^2, D=75mg/m^2	OS	9.1% vs 8.8%	2.9 vs 2.9	9.5 vs 11.2	Neutropenia (5.3% vs 40.2%)

Table-II

Comparison between nivolumab and gefitinib therapy for EGFR mutant and non-mutant NSCLC.

Authors	Rizvi, Mazières (17)	Goss, Ferry (33)	Borghaei, Paz-Ares (9)	Maemondo, Inoue (13)
Sample Size (n)	117	201	582	230
Participants' characteristics	i) stage-3b or4 squamous NSCLC. ii) Age≥18 years, median age=65 year. iii) ECOG status 0 or 1. iv) Progression after platinum chemotherapy.	i) stage-3b or 4 NSCLC. ii) Chemotherapy naïve. iii) Age≥18 years. iv) WHO performance status 2 or 3. iv) No prior EGFR inhibitor therapy.	i) stage-3b or 4 NSCLC ii) EGFR mutant. iii) Age ≥18 years. iv) ECOG status 0 or 1.	i) Advanced NSCLC with EGFR mutation. ii) Age ≤75 year; Ge (43 to 75 year); Cb+ P (35 to 75 year). iii) No prior chemotherapy.
Study design	International, phase-2, single-arm trial	Randomised, double-blind, multicentre, parallel-group, phase-2	Randomised, open-label, international, phase-3 study	Multicentre, randomised, phase-3 trial
comparison		Ge+ BSC vs Placebo +BSC	N vs D	Ge vs Cb+ P
Therapeutic Regimen	N=3 mg/kg, IV, QW2	Ge= 250mg/day	N=3 mg/kg, IV, QW2 vs D= 75mg/m^2 QW3	Ge=250mg/day vs P (200mg/$m^{2)}$+ Cb (AUC 6)
Tumour response assessment	RECIST version 1.1	RECIST	RECIST version 1.1	RECIST version 1.0
Assessment of TRAE	CTCAE 4.0	CTCAE 3.0	CTCAE 4.0	CTCAE 3.0
Primary endpoint	Objective response	Progression free survival	Overall survival	Progression free survival
ORR	26%	6% vs 1%	39% vs 23%	73.7% vs 30.7%
mPFS	1.9 m	43 days vs 41 days	2.3m vs 4.2m	10.8 m vs 5.4 m
mOS (months)	8.2	3.7 vs 2.8	12.2 vs 9.4	30.5 vs 23.6
TRAEs (grade 3&4)	17%	36% vs 42.6%	10% vs 54%	41.2% vs 71.7%

Table-III

Methodological Quality assessment of RCTs by modified Jadad scoring system.

Study	Was the study described as randomised? (Yes=+1, No=0)	Was the method of randomisation appropriate? (Yes=+1, No=-1, not described=0)	Was the study described as blinding? (Yes=+1, No=0)	Was the method of blinding appropriate? (Yes=+1, No=-1, not described=0)	Was there a description of withdrawals and dropouts? (Yes=+1, No=0)	Was there a clear description of the inclusion/ exclusion criteria? (Yes=+1, No=0)	Was the method used to assess adverse effects described? (Yes=+1, No=0)	Was the method of statistical analysis described? (Yes=+1, No=0)	Modified Jadad Score
Carbone, Reck (10)	1	1	0	0	1	1	1	1	6
Brahmer, Reckamp (21)	1	1	0	0	1	1	1	1	6
Horn, Spigel (22)	1	0	0	0	1	1	1	1	5
Hida, Nishio (32)	0	0	0	0	1	1	1	1	4
Belani and Fossella (23)	1	1	0	0	1	1	1	1	6
Quoix, Zalcman (24)	1	1	0	0	1	1	1	1	6
Bonomi, Kim (25)	1	1	0	0	1	1	1	1	6
Kim, Hirsh (26)	1	1	0	0	1	1	1	1	6
Schuette, Nagel (27)	1	1	0	0	1	1	1	1	6
Kudoh, Takeda (28)	1	1	0	0	1	1	1	1	6
Fidias, Dakhil (29)	1	1	0	0	1	1	1	1	6
Fukuoka, Wu (30)	1	1	0	0	1	1	1	1	6
Hanna, Shepherd (31)	1	1	0	0	1	1	1	1	6
Rizvi, Mazières (17)	0	0	0	0	1	1	1	1	4
Goss, Ferry (33)	1	1	1	1	1	1	1	1	8
Borghaei, Paz-Ares (9)	1	1	0	0	1	1	1	1	6
Maemondo, Inoue (13)	1	1	0	0	1	1	1	1	6

3 and 4 TRAE of nivolumab were 18%, 7%, 10% and 5.7%.

Among the docetaxel group, the older patients (70 to 86 years) with poor performance status (28) showed highest mOS (14.4 months), mPFS (5.5 months), ORR (22.7%) and TRAE (82.9% of neutropenia). The patients received docetaxel with a history of at least one prior chemotherapy(27, 31) showed mOS of 11.2 months and 9.2 months, mPFS of 2.9 months, ORR of 8.8% and 10.5%, and TRAE of 40.2% and 12.4%. The patients received docetaxel with no history of previous chemotherapy (26) showed mOS of 8 months, mPFS of 2.7 months, ORR of 76% and TRAE of 41%.

Docetaxel plus cisplatin showed highest mOS (11.8 months) than other doublet-chemotherapy (docetaxel plus carboplatin=9.35 months, vinorelbine plus cisplatin= 10 months, carboplatin plus paclitaxel= 10.3 months, paclitaxel plus cisplatin=9.9 months, etoposide plus cisplatin= 7.6 months). Gemcitabine (18.8 months) and carboplatin/paclitaxel (17.4 months) in a study by Fukuoka, Wu (30) showed highest mOS among the single chemotherapeutic agents. However, the study

included non-smoker or light smoker patients, agedÂ 65 years. Besides this, vinorelbine showed higher mOS (9.9 months) and mPFS (3.1months) than other single chemotherapeutic agent such as gemcitabine (mOS=6.2 months, mPFS=2.8 months), gefitinib (mOS= 7.6 months, mPFS=2.2 months) and pemetrexed (mOS=9.5 months, mPFS=2.9 months). The patients received vinorelbine (70 to 86 years) were older than the patients received other single chemotherapeutic agents.

Total four studies (9, 13, 17, 33) were included in table-2. First two studies (17, 33) compare the efficacy and safety of nivolumab with gefitinib for EGFR non-mutant NSCLC patients. The patients received nivolumab had an OS of 8.2 months, while the patients received gefitinib showed an OS of 3.7 months. The performance status of nivolumab group was better (ECOGd"1 versus WHO 2/3) than the gefitinib group. It might affect the study outcome. Moreover, the mPFS, ORR and grade-3 and 4 TRAE of nivolumab group were 1.9 months, 26% and 17% respectively, and for gefitinib group were 43 days, 6% and 36% respectively.

The third and fourth study (9, 13) compared efficacy and safety of nivolumab with gefitinib for EGFR mutant NSCLC patients. The mOS, mPFS, ORR and grade-3 and 4 TRAE for nivolumab were 12.2 months, 2.3 months, 39% and 10% respectively; and for gefitinib were 30.5 months, 10.8 months, 73.7% and 41.2% respectively. The age of the patients of nivolumab group (9) was 18 years or more while the gefitinib study (13) was in between 43 to 75 years. Gefitinib group included relatively older patients, which may affect the outcomes.

Table-2: Comparison between nivolumab and gefitinib therapy for EGFR mutant and non-mutant NSCLC.

Abbreviation: N=nivolumab, Ge= Gefitinib, D=Docetaxel, Cb= Carboplatin, P= Paclitaxel, BSC= best supportive care, ORR= objective response rate, mPFS= median progression free survival, mOS= median overall survival, TRAE= treatment related adverse effects, RECIST= Response Evaluation Criteria in Solid Tumours, CTCAE= Common Terminology Criteria for Adverse Events, AUC= Area under the concentration-time curve, ECOG= Eastern Cooperative Oncology Group, QW2= every 2 weeks, QW3=every 3 weeks, m= month, vs= versus.

2.4 Risks of bias within studies:

In modified Jadad scale, the range of score for each study was 0 to 8. The trials were divided into two levels such as low quality (score 0 to 3) and high quality (score 4 to 8). Total 2 studies (17, 32) scored 4, one study (22) scored 5, 13 studies (9, 10, 13, 21, 23-31) scored 6 and one study (33) scored 8.

Discussion:

The studies on nivolumab and single or doublet chemotherapy for advanced NSCLC significantly favours nivolumab over chemotherapy.

3.1 Nivolumab versus docetaxel:

Nivolumab noticeably benefited patients over docetaxel regarding mOS, mPFS and ORR. The study by Brahmer, Reckamp (21) showed that the ORR(20% vs 9%), mPFS (3.5 months versus 2.8 months) and mOS (9.2 months versus 6 months) were higher with nivolumab than docetaxel. The other study (22) showed that the ORR was 37% and 34% for squamous and non-squamous NSCLC patients respectively, while the ORR for docetaxel group was not reachable. Docetaxel works by preventing microtubule formation and inhibition of mitotic cell division (34), while nivolumab works by blocking PD-1 receptor and promoting anti-tumour immunity (15). This might be a possible reason for nivolumab superiority over docetaxel. Both of the studies suggested that the TRAE with docetaxel were nearly 5 times higher (55% and 55% versus 7% and 10%, respectively) than nivolumab. TRAE with docetaxel monotherapy were decreased RBC and WBC count, asthenia, diarrhoea (27), and nivolumab were rash, diarrhoea and nausea (21, 22). It seems that the TRAE of nivolumab was not serious in comparison to docetaxel. Another systematic review by Sheng, Zhu (35) suggested that nivolumab reduced the mortality by 33% over docetaxel and extended mPFS of 17%. Overall, nivolumab therapy can be associated with high efficacy and safety than docetaxel for advanced NSCLC patients.

3.2 Nivolumab versus other single chemotherapeutic agents:

Nivolumab shows better therapeutic efficacy than single chemotherapy. The mOS (14.4 and 9.2 months of nivolumab was relatively higher than single chemotherapy (gemcitabine=6.2 months, gefitinib=7.6 months, vinorelbine=9.9 months and pemetrexed=9.5 months). One nivolumab study (32) showed an impressive mOS of 16.2 months; however the sample

size (n=35) was smaller than chemotherapy studies such as, Quoix, Zalcman (24) took 451 patients. Additionally, the mPFS of nivolumab in large clinical trials (10, 21) was also higher (4.2 and 3.5 months) than single chemotherapy (gemcitabine= 2.8 months, gefitinib= 2.2 months, vinorelbine= 3.1 months and pemetrexed= 2.9 months). Most of the chemotherapy works by eradicating neoplastic cells (36) while nivolumab works by enhancing T-cell function and anti-tumour immunity (15); this could be reason of nivolumab's superiority over chemotherapy. Both nivolumab and chemotherapy group included patients with all age groups (both young and old patients). However, nivolumab group included patients with good performance status (ECOF 0-1), while chemotherapy group included patients with both good and poor performance status. Therefore, nivolumab can be more effective than single chemotherapy for advanced NSCLC patients with different ages. However, nivolumab's efficacy may not be same for patients with poor performance status. Another meta-analysis by Khan, Lin (37)favours nivolumab over single chemotherapy for advanced NSCLC patients.

A study of chemotherapy (30) showed higher mOS(gemcitabine=18.8months,carboplatin/ paclitaxel= 17.4 months) than nivolumab. However, this study included all the patients who were either non-smoker or light smoker, while the patients of nivolumab group were regular smoker. This might be reason of higher mOS. One meta-analysis by Sheng, Zhu (35) found that smoking history favours mOS and mPFS. They (35) suggested that NSCLC patients with smoking history have higher mutational load. Therefore, either gemcitabine or carboplatin may not show the same efficacy in regular smoker patients.

TRAEs were higher with single chemotherapy (vinorelbine=69.2% and 51.7%, gemcitabine=28.6%, docetaxel=18%, 12.4%, 82.9%, 58%, 27.6% and 40.2%). The TRAE with pemetrexed were neutropenia and febrile neutropenia (31); with vinorelbine or gemcitabine were decreased haemoglobin and neutrophil concentration, febrile neutropenia and asthenia (24); with gefitinib acne, neutropenia, asthenic disorders, alopecia and rash (26). This suggests that nivolumab's TRAE are not fatal comparing to chemotherapy. Overall, nivolumab is more effective and safe than single chemotherapy for advanced NSCLC patients.

3.3 Nivolumab versus doublet-chemotherapy:

An impressive survival benefit and response rate were observed with nivolumab over doublet-chemotherapy. A phase-3 study (10) directly compared nivolumab with Investigator's choice of platinum doublet chemotherapy (ICC). The ORR was more than double (27% versus 10%) with nivolumab than ICC, while the TRAE was more than double (51% vs 18%) with ICC than nivolumab. Additionally, mOS (14.4 months versus 13.2 months) was higher with nivolumab. However, the mPFS was higher (5.9 months versus 4.2 months) with ICC. The patients of this study had no history of prior chemotherapy, and had good performance status (ECOG 0-1). Patient's performance status might affect the study outcome. The TRAE was higher with ICC (51%) than nivolumab (5.7%, 10%, 7% and 18%). Therefore, nivolumab can be more effective than ICC and the treatment outcomes may vary on different performance status.

Additionally, the mOS of nivolumab (14.4 months) was higher than other doublet-chemotherapies (Docetaxel+ cisplatin= 11.8 months, docetaxel+ carboplatin= 9.35 months, vinorelbine+ cisplatin= 10 months, carboplatin+ paclitaxel= 10.3 months, paclitaxel+ cisplatin= 9.9 months, etoposide+ cisplatin= 7.6 months). However, the mPFS was higher with carboplatin plus paclitaxel (6 months) (24) than nivolumab (4.2 months). The TRAE with nivolumab were low lymphocyte count, fatigue, decreased apatite, nausea, diarrhoea, pyrexia and arthralgia (21, 32); while with docetaxel plus cisplatin or docetaxel plus carboplatin or vinorelbine plus cisplatin were asthenia, pulmonary toxicities and infection (23). It seems that the TRAE of nivolumab were not serious compare with doublet chemotherapy. All of these patients of either nivolumab group or doublet-chemotherapy group had no history of previous chemotherapy. All the patients had good performance status except carboplatin plus paclitaxel group who were older (70-89 years) with poor performance status. Therefore, nivolumab shows higher efficacy and safety profile than doublet-chemotherapy for advanced NSCLC patients with good performance status and no prior chemotherapy. Moreover, it is not possible to say whether nivolumab will work better than doublet-chemotherapy in the patients with poor performance status (ECOGd"2) with less life expectance. In future, it is essential to conduct clinical trials on elderly patients

with poor performance status, which can show direct comparison between nivolumab and doublet chemotherapy.

3.4 Nivolumab versus gefitinib for EGFR non-mutant NSCLC:

A comparison between nivolumab and gefitinib for EGFR non-mutant NSCLC (table-2) favours nivolumab over gefitinib. The ORR was more than four times greater (26% vs 6%) with nivolumab than gefitinib, while the mOS was more than double (8.2 months vs 3.7 months) with nivolumab. The mPFS was also higher (1.9 month vs 43 days) with nivolumab. Gefitinib is EGFR's mutant amino acid specific (38), therefore it seems to be less effective for NSCLC with the absence of EGFR mutation. Additionally, TRAE was more than double (36% vs 17%) with gefitinib than nivolumab. Both of the studies (17, 33) on nivolumab and gefitinib were phase-2 clinical study. The study (33) on gefitinib was conducted on more patients (201 versus 117), while the study (17) on nivolumab assessed the tumour response (RECIST 1.0 versus RECIST) and TRAE (CTCAE 4.0 versus CTCAE 3.0) with more updated scale. Overall, nivolumab shows higher efficacy and safety for EGFR non-mutant NSCLC patients than gefitinib.

3.5 Nivolumab versus gefitinib for EGFR mutant NSCLC:

The studies (9, 13) of nivolumab and gefitinib on EGFR mutant NSCLC favours gefitinib over nivolumab. The ORR (73.7% versus 39%), mPFS (10.8 months versus 2.3 months) and mOS (30.5 months versus 12.2 months) were higher with gefitinib than nivolumab. Gefitinib is a selective EGFR-TKI, therefore it directly inhibits EGFR tyrosine kinase domain (38). This potential mechanism leads to a better survival outcome for EGFR mutant NSCLC patients by gefitinib. However, the TRAE was apparently four times greater (41.2% versus 10%) with gefitinib than nivolumab. Overall, gefitinib is more effective than nivolumab for EGFR mutant NSCLC patient, although the TRAE is higher with gefitinib than nivolumab. Another study Paez, Jänne (39) also highlighted gefitinib's dramatic effect for EGFR-mutant NSCLC patients.

3.6 Limitations:

Despite of encouraging results, the included studies have some limitations. Three of the studies (17, 28, 32) have small sample size such as 35, 182 and 117 respectively in comparison to other included studies. A study with small size can be associated with false-positive results, difficulties in results interpretation and overestimation of the extent of an association (40). Therefore, the results of the study with small sample size may not be applicable for large population. Individual studies have some limitations too. The study by Carbone, Reck (10) is an exploratory analysis and the presented data were hypothesis-generating. Therefore, prospective analysis is essential for the validation of the results. Moreover, the age of the participants was limited between 29 to 89 years with a median age of 64 years. The study by Brahmer, Reckamp (21) assessed the PD-L1expression in the storage tissue sample which was collected at the beginning of the therapy. Therefore, the study does not state the effect of nivolumab on PD-L1 expression. Hida, Nishio (32) conducted the study on Japanese population only and there was an absence of the comparator on that study. Additionally, this study and a study by Schuette, Nagel (27) included predominately male (91.4%) and older patients with a median age of 65 years. Overall, there was a lack of heterogeneity in these studies. The study by Belani and Fossella (23) analysed the patient's data retrospectively and included older patients mainly. There is a risk of recall and selection bias with retrospective studies as the data are collected from medical database (41). Therefore, there might be possibility of missing key statistical data, and the results might be biased. Total four studies (9, 17, 26, 33) included mainly white patients, while two studies (13, 30) included predominantly Asian patients. Therefore, the results of these studies may not be applicable to black or other racial population. Additionally, Kim, Hirsh (26) identified the EGFR-gene-copy number in the primary tumour from storage samples. This suggests that it is unidentified whether the gene-copy number has changed or not after the chemotherapy. The study by Quoix, Zalcman (24) was conducted on elderly (70 to 89 years) and fit patients. Therefore, the results may not be applicable for elderly unfit patients with a poor performance status. The leading prognostic indicator of this study was performance status score. They used Charlson's co-morbidity index score that failed to correlate with survival. Therefore, the assessment method was inadequately sensitive for the study. Another study by

Fidias, Dakhil (29) was not powered to identify changes lower than four months. Therefore, the progress in overall survival failed to reach statistical significance. All the included studies of nivolumab assigned nivolumab's dose of 3 mg/kg, so it is unpredictable to state whether other doses of nivolumab (0.3 mg/kg, 1 mg/kg, 5 mg/kg or 10mg/kg) works better or not for NSCLC patients. Overall evidence suggest that insufficient patient numbers, bias selection, insensitive method and heterogeneity in above mentioned studies may lead to achieve inappropriate and limited results that may not be applicable for worldwide population.

3.7 Strength of this systematic review:

This systematic review has several advantages alongside some limitation. The review addresses a clearly focused issue with sufficient information on study population, intervention and outcomes. This review includes 17 clinical trials with 9284 patients of advanced NSCLC, while another systematic review (42) included 15 clinical trials. Most relevant papers on phase-3 and phase-2 clinical trials are included in this review. However, this study includes papers published in English language only. The search was performed on the database of 3 websites, while the study by Ellis, Vella (42) also searched on 3 websites. The quality of the studies were assessed by modified Jadad scale (20). All the included studies scored four or more in modified Jadad score which favours the inclusion of good quality studies. The results of this study are clearly displayed in two tables similar to other two systematic reviews (42, 43). However, no statistical analysis was conducted in this review while other systematic review conducted statistical analysis (43). The results are not displayed with the confidence interval; however, the efficacy analysis is stratified by various control interventions. The review clearly highlights the comparators. Two included studies (25, 30) do not show results on ORR, mPFS and TRAES, while one included study (22) do not highlight results on mOS and mPFS. The review includes a wide range of patients' characteristics such as age, race, gender etc. Therefore, nivolumab therapy can be applied to local population. The review includes all the important outcomes regarding to efficacy and safety similar to other systematic reviews (42, 43). The nivolumab clearly displays efficacy and safety over single or doublet chemotherapy for both EGFR mutant and non-mutant NSCLC patients. A Markov model study by Matter-Walstra, Schwenkglenks (44) on Swiss population showed that nivolumab and docetaxel mean cost were 66,208 Swiss franc(CHF) and 37,618 CHF, while the quality-adjusted life-years (QALYs) were 0.69 QALYs and 0.53 QALYs, respectively. Nivolumab is more preferable than chemotherapy in terms of efficacy, safety and patients' comfort although it is expensive. Therefore, the benefits worth the cost. Gefitinib shows superior efficacy, but lower safety profile than nivolumab for EGFR mutant NSCLC. A Markov model study by Piha, Barbosa (14) suggests that total cost of gefitinib is $6,916.67 per year for NSCLC, while a study Aguiar Jr, Perry (45) suggests that total cost of nivolumab is $104453 and $100791 per year for squamous and non-squamous NSCLC, respectively. The cost of nivolumab is nearly 15 times greater than gefitinib. Therefore, gefitinib is more preferable than nivolumab for EGFR mutant NSCLC patients, especially in the developing countries where patients bear their treatment expenses.

Conclusion:

This systematic review concludes that nivolumab can be an effective and safe treatment option for advanced NSCLC patients. Nivolumab therapy is more expensive than chemotherapy, however the efficacy and safety profile are higher than chemotherapy. Therefore, the efficacy and patients' comfort worth the expenses. Nivolumab will not be able to replace gefitinib for EGFR mutant NSCLC, as nivolumab's efficacy was inferior to gefitinib. Moreover, the treatment related cost was also higher with nivolumab than gefitinib. In future, it is essential to conduct double-blinded randomised phase-3 trials that directly compares nivolumab and gefitinib. Currently, there are no prognostic biomarkers for nivolumab (46), and the treatment response is assessed by ORR, mPFS and mOS. Henceforth, it is necessary to develop biomarker for accurate results. Despite excellent results, nivolumab fails to guarantee mOS more than 16 months. Hence, it is essential to develop curative medicine for advanced NSCLC patients. Most of the current clinical trials are heterogeneous as they are focused on specific characteristics of the participants (specific age group or race, gender or performance status). Therefore, more clinical trials are needed that involve patients with wide range of age, gender and races.

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