RESEARCH ARTICLE

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A Phase IV Efficacy Study of Formeta Plus Carboplatin as First-Line Treatment of Advanced Non-Squamous, Non-Small Cell Lung Cancer in Iran: An Affordable Price with Clinical Benefit

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Abstract

Background: This study performed to assess the efficacy and safety of Formeta (generic form of Pemetrexed) plus Carboplatin as first-line chemotherapy in advanced stage, non- squamous, non small cell lung cancer (NSCLC) in Iran. **Methods:** This was a post marketing single-arm phase IV efficacy study of Formeta (manufactured by Oncomed.,Czech Republic) and Carboplatin in chemo-naive advanced non-squamous NSCLC Iranian patients. Patients received up to six cycles of Formeta (500 mg/m^2) combined with Carboplatin (area under the curve: AUC 5) every 3 weeks. The primary endpoint was the progression free survival (PFS) and secondary endpoints were safety and overall survival (OS). **Results:** Fifty-two patients were enrolled between June 2014 to January 2016, and 44 patients were evaluable for both safety and efficacy. Partial and complete responses were achieved in 19 (36.5 %) and 2 (3.8%) patients, respectively as well as stable disease in 8 patients (15.3 %). Median of PFS and OS were 7.9 ± 1.1 months and 12.43±0.6 months, respectively. Anemia was the most prevalent adverse events of this regimen. Grades 3 or 4 of adverse events were not observed in any patients. Non-hematologic and other grades of hematologic toxicities were generally mild, and there were no treatment-related deaths. **Conclusion:** The combination of Formeta and Carboplatin was effective in advanced non-squamous NSCLC and can be a suitable candidate as first-line treatment in these patient's population.

Keywords: Non small cell lung cancer- carboplatin- pemetrexed- chemotherapy- safety

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Introduction

Lung cancer is the most leading cause of cancer-related death worldwide (Torre et al., 2015). With an incidence rate of 4.7-9.2 per 100,000 people, lung cancer ranks second in men and third in women as the cause of cancer related death in Iran (Mosavi et al., 2009). Eighty percent of lung cancer are non-small-cell (NSCLC) and at the time of diagnosis most of them are in advanced stages (stage IIIB or metastatic, stage IV) (Stewart, 1995; Adnan et al., 2016). Several efforts have been made to improve advanced stage NSCLC outcomes. One of the most significant improvements is the targeted therapies for patients harboring specific gene alterations, such as epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) translocations. In absence of these significant gene alternation, cytotoxic chemotherapy with ''third-generation'' drugs (Vinorelbine, Gemcitabine, Taxanes, Pemetrexed) in combination with platinum-based agents improved survival of patients with advanced NSCLC, with substantially similar results among the different drugs (Piccirillo et al., 2010; Liang et al., 2016). Pemetrexed (combined with Cisplatin or Carboplatin) is one of the recommended drugs for first-line treatment of these patients according to guidelines (Masters et al., 2015; Zhao et al., 2017). This drug is an antifolate agent that inhibits multiple enzymes involved in purine and pyrimidine synthesis. Primary and secondary targets of Pemetrexed are thymidylate synthase, dihydrofolate reductase and glycinamide ribonucleotide formyl, respectively (Ohe et al., 2008).

Medicine's access especially in cancer field varies from country to another and many patients in low and middle income countries, are not able to access many therapies which be needed . Some reasons for these differences are: drug costs, different regulatory and cultural barriers (Ruff et al., 2016). So, collaboration between academic centers and pharmaceutical companies

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is very necessary to facilitate patient's access to new cancer treatment agents. For many years, in Iran use of Pemetrexed as chemotherapy agent was limited due to the high drug cost. Recently, generic form of this agent as "Formeta"(manufactured by Oncomed., Czech Republic) has been released in Iran market by Cobel/Almagen Darou Company. "Generic drugs are equivalent to the brand formulation if they have the same active substance, the same pharmaceutical form, the same therapeutic indications and a similar bioequivalence respect to the reference medicinal product" (Gallelli et al., 2013). In order to reduce medication price and economic burden on national health systems; in many countries generic drugs are used. During switch from brand to generic drugs, clinical studies are necessary to test efficacy and safty profile of this agents. To best of our knowledge, there are no study investigating the efficacy of Pemetrexed (and or generic form: Formeta) as first-line chemotherapy in advanced stage of non-squamous NSCLC. Thus, we perform this study to assess the efficacy and safety of Formeta in combination with Carboplatin and compare them with other Pemetrexed- based studies which may reflect actual clinical practice, especially in Iran. Also, clinical benefit from generic substitution of Pemetrexed by Formeta had not been measured or was unclear in our countries, despite clear incentives to implement it.

Materials and Methods

Fifty and two chemo-naive patients (no previous history of chemotherapy, immune therapy, or biologic agents) were eligible for this prospective, unicenter, open-label, non-randomized and single-arm trial from June 2014 to January 2016 in patients whom referred to National Institute of Tuberculosis and Lung Disease (NRITLD), Masih Daneshvari Hospital. Informed written consent was obtained prior to participating patients in the study according to Shahid Beheshti Medical University's ethics and scientific committees (number: IR.SBMU.REC.1394.196) and was conducted in compliance with the Helsinki Declaration and Good Clinical Practice guidelines (GCP) (Handbook for good clinical research practice (GCP): Guidance for implementation., 2007). This trial registered in Iranian clinical trial registry (ID number:IRCT2016091322610N2).

Eligibility criteria

The patients with histologically confirmed non- squamous NSCLC, at Eastern Cooperative Oncology Group (ECOG) (Oken et al.,1982) performance status (PS) 0-2 and stages IIIB and IV (by AJCC, 7th edition) (Edge and Compton, 2010) were enrolled in this study. Other eligibility criteria included the following: age ≥ 18 years old, at least one unidimensionally measurable or assessable disease, adequate bone marrow reserve, serum creatinine less than or equal to 1.5 mg/dL or a calculated creatinine clearance greater than or equal to 60 mL/min, bilirubin level less than or equal to 2.0 mg/dL, aspartate transaminase (AST) less than or equal to twice the institutional upper limits of normal, or less than or equal to four times the institutional upper limits of normal if the patient had liver metastasis. Neither of patients had prior chemotherapy, biologic therapy or radiotherapy less than 14 days ago. Patients with significant mutation of EGFR or ALK translocation were excluded.

Eligible patients assigned to receive Formeta (manufactured by Oncomed.,Czech Republic) 500 mg/m^2 1 and Carboplatin area under curve (AUC) 5 on day1, every 3 weeks. One to three weeks prior to start of therapy with Formeta, substitution with 1,000 µg Folic acid orally daily and Vitamin B12/ 1,000 µg IM once every 9 weeks till 3 weeks after therapy completion was done. Dexamethasone 8 mg i.v. used on the day before, day of, and day after Formeta administration. Notably, in this real world study the dosage of cytotoxic agents was permitted to be modified by clinicians' discretion based on patient's age, alteration on PS, or adverse events in the course of treatment for each individual case. The study's efficacy parameters included disease assessments by CT scans within 30 days prior to the first dose of study drugs and every 12 weeks for the first 24 weeks of treatment followed by every 12 weeks thereafter. Response rate was evaluated according to "Response Evaluation Criteria in Solid Tumors" (RECIST) criteria (Green and Weiss, 1992). Objective response rate (ORR) defined as the sum of the number of complete response (CRs) and partial response (PRs). In the absence of progressive disease or intolerable toxicity, the patients were treated for a minimum of four cycles. Patients who achieved a CR or PR could receive two additional cycles of therapy, for a maximum of 6 cycles.

During treatment all patients had a complete blood cell (CBC) count, one week after each chemotherapy cycle. Dose modification and concomitant granulocyte-colony stimulating factor (G-CSF) were allowed during treatment course according to the encountered toxicity in respect to the grade of neutropenia. The dose of cytotoxic agents were attenuated by 25% if patients experienced neutropenia 1,000-1,500/dL and/or platelets 75,000-100,000/dL or grades 3 or 4 adverse event except mucositis. If neutrophil or platelet count was less than 1,000/dL and 75,000/dL, respectively, or grades 3 and 4 mucositis the dose of both drugs adjusted to 50% of previous dose. Toxicity assessment was based on "Common Terminology Criteria for Adverse Events" (CTCAE) version 3.0 (Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, 2003). Criteria for withdrawal from study were unacceptable toxicity as determined by the treating physician in consultation with the study coordinator, a delay in treatment greater than 2 weeks, requirement for palliative radiotherapy, or patient refusal.

Statistical analysis

The primary end point of study was progression free survival (PFS). Secondary objectives were overall survival (OS) and adverse events.

The mean ± standard deviation (SD) was calculated for continuous variable. All confidence intervals (CIs) for parameters to be estimated were constructed with a significance level of alpha=0.05 (a 95% confidence level). The sample size was determined to test the hypothesis that an 18 months survival rate would

be expected. Current study was used to test the null hypothesis (H0) that the true response rate is 25 % versus the alternative hypothesis (Ha) that the true response rate is at least 40 %. Assuming an accrual period of 3years, a potential follow up 1 years for last patients and a type I error rate of 0/5, 50 patients to be randomized. Kaplan Meier's survival curves were obtained for PFS and OS. PFS was calculated from date of registration in study to date of progression or death. OS was calculated from date of registration in study to date of death. Patients who were alive or lost of follow up at time of data analysis, censored for PFS and /or OS analysis. Never smoker defined to person who has smoked less than 100 cigarettes in his/her lifetime (DiFranza et al., 2002).

Our study was a postmarketing and efficacy approach to determine efficacy of Formeta as chemotherapy agent.

The analysis was "intention to treat" and includes all enrolled patient regardless of subsequent withdrawal from treatment or deviation from the protocol. A P -value of less than 0.05 was considered statistically significant. IBM SPSS statistical software version 19 for Windows (IBM, Armond, NY, USA) was used for data analysis.

Results

A total of 52 eligible patients (36 men and 16 women) were enrolled. The median age of patient' population was 58 years old. There was no deviation from assigned treatment in our trial and also, no exclusion occurred. Female/ male ratio was 0.44. Fifteen (15.3 %) patients

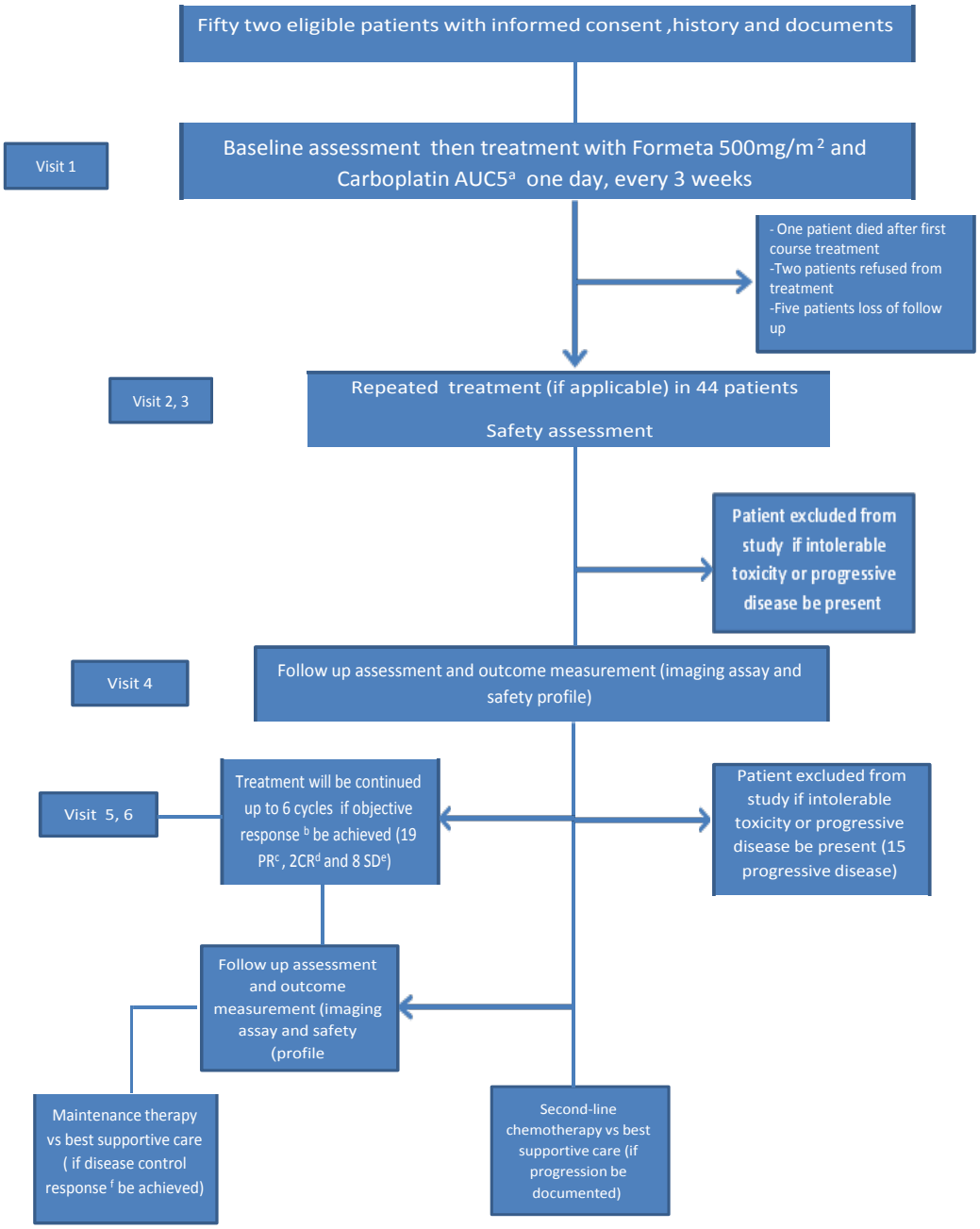

Figure 1. Diagram of the Study; Clinical Trial Flow Chart. A total of 52 patients received study treatment consisting of at least 1 cycles first-line chemotherapy with Formeta and Carboplatin. Abbreviation, a AUC, area under curve; b objective response as defined partial and complete response; c PR: partial response; CR, complete response; e SD, stable disease; f Disease control, as defined partial, complete response and stable disease.

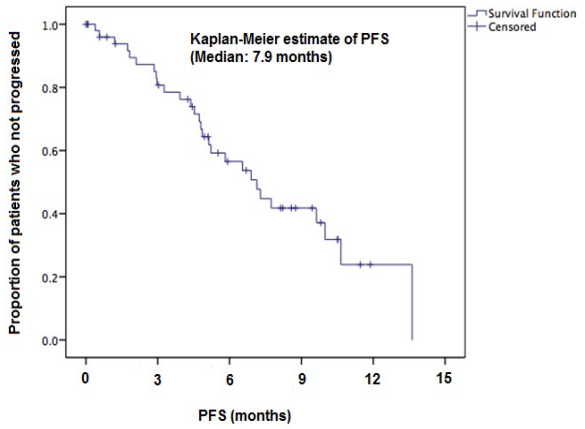

Figure 2. Progression Free Survival (PFS) in Intention to Treatment Population Formeta Plus Carboplatin. Kaplan-Meier survival curve from onset of recurrence for the effect of Formeta plus Carboplatin chemotherapy on progression free survival.

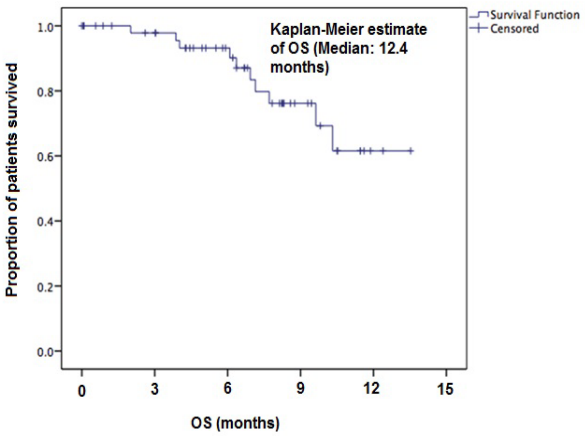

Figure 3. Overall Survival (OS) in Intention to Treatment Population Formeta Plus Carboplatin. Kaplan-Meier survival curve for overall survival (OS) in patints treated by Formeta plus Carboplatin.

Table 1. Baseline Patient and Disease Characteristics of Patients for Study

Characteristics	N= 52 (%)
Age(yrs)	
Mean ±SD [a]	58.2 ± 10.4
Range	34-83
Disease stage [b]	
IIIB	5 (9.6)
IV	47 (80.4)
Smoking status	
Smoker	25 (48.1)
Non-smoker	27 (51.9)

a SD, standard deviation; b disease staging was done according to AJCC, 7th edition

completed four cycles, and 45 (45.9 %) completed six cycles of chemotherapy. Patient and disease baseline characteristics were shown in Table 1. Mean administered cycles and of treatment duration was 3.88 (range 1-6) and3.31 months (range 0.9-8.7), respectively.

Table 2. CTCAE Grade 1 or 2 vs Grade 3 or 4 Toxicities, Safety Population

Toxicity	CTCAE [a] Grade 1 or 2 n (%)	CTCAE Grade 3 or 4
Thrombocytopenia	2 (3.8)	-
Neutropenia	3 (5.7)	-
Anemia	8 (15.3)	-
Fatigue	4 (7.6)	-
Sensory neuropathy	6 (11.5)	-
Alopecia	-	-
Mucositis	3 (5.7)	-
Vomating	4 (7.6)	-
Constipation	2 (3.8)	-

a CTCAE, common toxicity criteria for adverse events.

Treatment response and efficacy

Of the 52 patients treated with Formeta plus Carboplatin, 44 were assessable for response evaluation.

The reasons of not assessing were

-One patient died very soon after first course of treatment.

-Two patients refused from treatment continuation.

Five patients were lost of follow up after first course of therapy. Nineteen patients (36.5%) achieved PR response and CR response was seen in 2 cases (3.8%), while in another 8 patients (15.3%) there was stable disease. ORR and disease control rate were seen in 29 (55.7%) and 25 (48.07) patients, respectively. In 15 cases (28.8%)-after first assessment for response-progressive disease was documented.

The median PFS was 7.9 ± 1.1 months and median of OS was 12.43±0.6 months. Figures 2 and 3 show the Kaplan-Meier curve for PFS and OS.

Safety

In all patients, Formeta plus Carboplatin was well tolerated and demonstrated a consistent safety profile. Eight patients were not assessable for toxicity. Main toxicity and adverse effect of Formeta plus Carboplatin was shown in Table 2. Anemia with incidence of 15.3% was the most common adverse event in our study. The other significant toxicity was thrombocytopenia which observed in 2 cases (3.8%). No patients developed febrile neutropenia nor dosage adjustment / treatment delay.

Post discontinuation therapy

Decisions regarding post study therapy were at the discretion of the individual investigators. Docetaxel was the most commonly used chemotherapeutic agent as second line after disease progression (in 11 patients). For 5 patients maintenance therapy with Formeta was administrated. Two patients received Gemcitabine as salvage chemotherapy and Vinorelbine was used in 1 patient as salvage chemotherapies. Palliative brain

radiotherapy was performed in 2 patients.

Discussion

Substitution innovator brand products with generic drugs is partially common to facilitate access to essential drugs and also save life-years for many patients. However, using generic drugs instead of innovator brand -especially in cancer- is often met with patients or their relatives' resistance. Despite highlighting the need for efficacy and safety assessments of pharmaceutical generic drugs in order to compare same efficacy and side effects with reference medicinal product, the quality of many pharmaceutical products is not clear. Although trusting in to a single arm study to determine a generic drug efficacy may be hard but to best of our knowledge, this study is the first investigation of the safety and effectiveness of a generic chemotherapy agent (Formeta manufactured by Oncomed.,Czech Republic) as first-line chemotherapy in advanced stage, non- squamous NSCLC in Iran. Our survey, demonstrated a well-tolerated safety profile of Formeta plus Carboplatin that is consistent with that of previous innovator brand (Pemetrexed) studies (Lu et al., 2016; Scagliotti et al., 2008; Rodrigues-Pereira et al., 2011). In regard to the median PFS and OS, good efficacy and ORR of this protocol with a generic drug, this study successfully met its primary and secondary end-points. Importantly, the regimen exhibited an acceptable toxicity profile, too.

Appropriate systemic chemotherapy for patients with lung cancer have been selected based on factors such as age, PS status, histology, clinician's experience, presence of comorbid disease, as well as drug anticipated toxicity, pharmacogenomics markers and also, flexibility in the administration schedule. Since limited number of treatment options existed for patients with EGFR-wild-type NSCLC, still needs to prompt a search for new chemotherapeutic agents to improve NSCLC prognosis. Some investigators believed that for chemo-naive patients with non-squamous NSCLC in advanced stage, Pemetrexed in combination with Platinum (Cisplatin vs Carboplatin) have comparable efficacy and better tolerability rather than other platinum-based doublet chemotherapy. Schuette et al., (2013) demonstrated that Pemetrexed plus Carboplatin had a good efficacy profile, with an OS of 8.9 months and a PFS of 4.7 months in patients with locally advanced or metastatic disease. Also Zukin et al., (2013) showed Pemetrexed + Carboplatin PFS 5.8 and OS 9.3 months in advanced stage disease. The median PFS of 5.4 and the median OS of 12.7 months was demonstrated in Kimura et al., (2016) study. In summary, different assays showed an OS ranging between 8.9 and 13.5 months (Tomasini et al., 2016). These results are partially similar to result of current study and may reflect same therapeutic indications of Formeta with reference medicinal product. The difference between OS in different studies may be due to patient population selection (Grønberg et al., 2009). For example lower PS has a negative impact on survival and in some surveys patients with Poorer PS has been excluded.

In terms of efficacy, the ORR=40.3% was in accordance with those derived from a randomized phase III trial for non-squamous NSCLC (ORR=34.0%) Schuette et al., (2013) and the other study performed by Kimura et al., (2016) with ORR=36%. It is notable that our results compared favorably to those reported in previous large studies (Schuette et al., 2013; Tomasini et al., 2016; Grønberg et al., 2009). It was established that tumors without significant EGFR mutations are heterogeneous groups regarding to driver mutations, such as KRAS mutation. KRAS mutation has been known as a negative predictor of response to first-line platinum-based chemotherapy (Metro et al., 2014) and thus treatment response may be influenced by such molecular alteration and can explain different response rate in different studies. Also, there may be also ethnic difference between different surveys. Our study was a post marketing and efficacy approach to determine efficacy of Formeta as chemotherapy agent. Efficacy studies examine the impact of a defined treatment on clinical outcomes (Möller., 2011).

Some investigators had reported myelosuppression as the predominant dose-limiting toxicity of Pemetrexed (Mc Donald et al., 1998)but substitution of corticosteroids, folic acid and vitamin B12 supplementation during Pemetrexed treatment has removed pretty this problem. The others adverse effects are fatigue, nausea, vomiting, mucositis, and rash. In our study, no grade 3 or 4 drug-related adverse event was seen and can be reflecting good safety profile of this regimen. Furthermore, there was no treatment-related death either. Judging about drug safety needs to larger studies with enough sample size.

At the recommended dose and submitted price (when the study was in progress), the main brand of Pemetrexed (Alimta, Indianapolis, IN. Lilly USA) costs $515 and $2,145 per 100mg and 500mg vial in Iran compared to$95.238 and $321.42 per 100mg and 500mg vial for Formeta (Oncomed.,Czech Republic). It seems that Formeta is affordable for more patients in Iran.

One limitation of the present trial was the lack of quality of life data. Also, this study is limited by the possibility that post discontinuation therapy influenced the outcome of the patients and that the study design did not allow separate evaluation of the contribution of either post discontinuation therapy or maintenance therapy to the efficacy outcomes. This study was run from a referral lung disease center in Iran and may be reflect a prospective of generic drug efficacy, adverse events and response monitoring of lung cancer patients. Because of our population health care facilities (such as different insurance coverage) were very heterogeneous and also was very different from health care characteristics in other countries, this study may be valuable as a cost-effective treatment in Iran.

In conclusion, the Formeta in combination with Carboplatin exhibited favorable efficacy in patients with advanced stage non-squamous NSCLC. Therefore, Formeta plus Carboplatin is a suitable candidate as first-line treatment for non-squamous NSCLC instead of other high cost regimens.

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