Randomized phase 3 open label study of quality of life of patients on Pemetrexed versus Erlotinib as maintenance therapy for advanced non squamous non EGFR mutated non small cell lung cancer

SUPPLEMENTARY MATERIALS

PROTOCOL

Title: Comparative study of QOL of patients on Pemetrexed versus Erlotinib in maintenance therapy for advanced NSCLC (other than squamous cell carcinoma)

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INTRODUCTION

Background

Lung cancer is the leading cause of death from cancer worldwide, with an estimated 1.8 million new cases in 2012 accounting for 13% of all cancer diagnosis [1]. In India, approximately 63,000 new lung cancer cases are reported each year [2]. More than 87% of the cases of lung cancer are non-small-cell lung cancer [3]. Forty percent of patients with newly diagnosed non-small cell lung cancer (NSCLC) have either stage IIIIB disease with malignant effusion or stage IV disease [4]. Treatment goals are to prolong survival, control disease-related symptoms and to improve quality of life (QOL), all of equal importance. Treatment options include cytotoxic chemotherapy and targeted agents. Radiation therapy and surgery are generally used in selective cases for symptom palliation. Despite significant advances in the treatment of advanced non-small cell lung cancer (NSCLC), overall prognosis remains poor. Maintenance therapy in advanced NSCLC has gained much recognition as a possible treatment strategy.

Standard treatment options for advanced NSCLC

Platinum-based chemotherapy represents the standard of care for patients with stage IIIIB or Stage IV NSCLC [5, 6]. The ASCO guidelines for the treatment of advanced NSCLC recommends platinum-based combination chemotherapy be administered for no more than six cycles as more cycles do not provide any survival benefit and have a higher risk of toxicity [7]. This recommendation was based on the results of randomized trials that compared shorter versus longer periods of administration of platinum-based chemotherapy [8–11]. New guidelines recommend maintenance therapy as a standard treatment for these patients post first-line therapy.

Randomized controlled trials of patients with stage IV disease and good PS have shown that platinum-based doublet chemotherapy improves survival and palliates disease-related symptoms. Patients with non-squamous cell histology, good PS, no history of hemoptysis or other bleeding, or recent history of cardiovascular events may benefit from the addition of bevacizumab to paclitaxel and carboplatin. Patients with tumors harboring mutations in EGFR, particularly those from East Asia, never smokers, and those with adenocarcinoma may benefit from EGFR tyrosine kinase inhibitors as an alternative to first- or second-line chemotherapy. The use of these combinations of drugs is based on tumour histology and genetic mutations along with patient factors like age, comorbidities and performance status. Molecular aberrations highly responsive to kinase inhibitors arise only in a minority of patient cases. For the majority of patients, cytotoxic chemotherapy is the mainstay of treatment, with response rates to platinum-based combinations ranging from 20% to 35%. After four to six cycles of first-line or induction chemotherapy, approximately two thirds of patients have non-progressive disease. Continuation of first-line platinum-based combination regimens beyond four to six cycles in the past have resulted in heightened toxicities and diminished quality of life without providing a survival advantage. Thus, the standard therapeutic approach has entailed stopping treatment at that point, close clinical and radiographic surveillance, and initiation of second-line treatment at the time of progression.

For non-responding or progressing patients, second-line chemotherapy with docetaxel, pemetrexed, erlotinib or gefitinib offers control of disease-related symptoms, improves quality of life, and prolongs overall survival (OS) [12-16]. However, only a select subgroup of patients (<50%) go on to receive second-line therapy due to side-effects of 1st line chemotherapy or low performance status. Therefore exploration of a maintenance strategy has been a sensible development.

Maintenance chemotherapy

The U.S. National Cancer Institute’s medical dictionary defines maintenance therapy as “any treatment that is given to keep cancer from progressing after it has been successfully controlled by the appropriate front-line therapy; it may include treatment with drugs, vaccines or antibodies, and it should be given for a long time”. In advanced NSCLC, it refers to the systemic therapy that may be given after 4-6 cycles of 1st line cytotoxic chemotherapy. Different approaches that might be classified as maintenance therapy in advanced NSCLC include: (1) continuing only the non-platinum or molecularly targeted component of the induction regimen, also known as ‘continuation maintenance’; and (2) switching to a different cytotoxic or molecularly targeted agent, often called ‘switch maintenance’. As per NCCN guidelines, maintenance therapy is an standard treatment option for select patients with partial or complete response to previous therapy or stable disease and is not considered standard of care for patients with ECOG PS 3-4 or with progressive disease [18].

Central to the evolution of the maintenance treatment strategy is the Goldie Coldman hypothesis [19], which dictates that even the smallest detectable cancers contain at least one drug-resistant hypothesis that even the smallest detectable cancers contain at least one drug-resistant clone and that increasing numbers of resistant clones emerge as tumours grow and progress. To overcome this phenomenon, the use of different non-cross-resistant chemotherapy regimens in alternating or sequential fashion has been employed [20, 21]. This same hypothesis underpins the design of maintenance trials in which NSCLC patients are switched to a new, potentially non-cross-resistant agent if they respond to or remain stable on initial therapy. This ‘switch maintenance’ therapy is the most closely examined and has become the most debated [22]. Potential rationales for maintenance therapy include increased exposure to effective therapies, decreasing chemotherapy resistance,
optimizing efficacy of chemotherapeutic agents, anti-angiogenic effects, and altering antitumor immunity. With switch maintenance, effective drugs are delivered to a substantially higher proportion of patients, generally more than 90% as compared to <50% when a second-line approach is used [21].

Maintenance therapy after 4-6 cycles of platinum doublet chemotherapy has shown an improvement in PFS and OS too. The JMEN study compared maintenance chemotherapy with pemetrexed with placebo in stable and responding patients treated initially with one of three platinum-based regimens [24]. Stable and responding patients were randomized 2:1 to receive pemetrexed or placebo. There were 660 patients randomized and an analysis by histology was a pre-specified endpoint. Of the patients randomized to pemetrexed, 48% received 6 cycles and 23% - 10 cycles. There was a significant PFS advantage seen in the group as a whole (HR 0.6, p¼0.00001). Subgroup analysis revealed that patients with non-squamous histology had a HR of 0.47 (p¼0.00001, interaction p-value 0.036). When OS was examined, there remained a significant advantage in the entire treatment group (HR 0.79, p¼0.012). Furthermore, patients with non-squamous tumour had a median survival advantage of 5 months (15.5 versus 10.3 months) with a significant OS benefit (HR 0.7, p¼0.002, interaction p-value 0.033). This finding that pemetrexed improves survival in maintenance setting in non-squamous carcinoma was confirmed in the next study called PARAMOUNT study [32, 33]. Regulatory bodies have approved pemetrexed as maintenance chemotherapy in non-squamous NSCLC.

The strategy of maintenance therapy with targeted agents has been evaluated in a number of phase III trials. Three studies have used the EGFR inhibitor erlotinib [25, 26, 28] and three have used the EGFR inhibitor gefitinib [29–31]. The sequential Tarceva in unresectable non-small cell lung cancer trial (SATURN) was a large international study in which 1949 patients were treated initially with four cycles of platinum-based chemotherapy [25]. Stable and responding patients (n=889) were randomized to receive maintenance erlotinib or placebo. The primary endpoint was PFS and patients were stratified by a number of clinical factors as well as by EGFR protein expression (assessed by immunohistochemistry [IHC]) and EGFR gene copy assessed by fluorescent in-situ hybridization (FISH). Both PFS and OS were significantly longer in the erlotinib arm (HR for PFS 0.71, p<0.0001; HR for OS 0.81, p = .0088) in the erlotinib group as compared to placebo. The ATLAS trial compared bevacizumab and erlotinib with bevacizumab and placebo in advanced NSCLC [26, 27]. The primary endpoint was PFS and patients were stratified by a number of clinical factors as well as by EGFR protein expression (assessed by immunohistochemistry [IHC]) and EGFR gene copy assessed by fluorescent in-situ hybridization (FISH). Both PFS and OS were significantly longer in the bevacizumab and erlotinib arm (HR for PFS 0.72, p = .0012; HR for OS 0.9, p = .2686) as compared to bevacizumab and placebo. The IFCT trial compared erlotinib with placebo in advanced NSCLC [28]. The primary endpoint was PFS and patients were stratified by a number of clinical factors as well as by EGFR protein expression (assessed by immunohistochemistry [IHC]) and EGFR gene copy assessed by fluorescent in-situ hybridization (FISH). Both PFS and OS were significantly longer in the erlotinib arm (HR for PFS 0.69, p = .003; HR for OS 0.87, p = .3) as compared to placebo. The INFORM trial compared gefitinib with placebo in advanced NSCLC [29]. The primary endpoint was PFS and patients were stratified by a number of clinical factors as well as by EGFR protein expression (assessed by immunohistochemistry [IHC]) and EGFR gene copy assessed by fluorescent in-situ hybridization (FISH). Both PFS and OS were significantly longer in the gefitinib arm (HR for PFS 0.42, p<0.0001; HR for OS 0.84, p = .2608) as compared to placebo.

### Table 1: Clinical experience with maintenance therapy in advanced NSCLC: summary of selected phase III trials

| Author/Year | Agent Vs Control | Patient no. | Progression free survival | Salvage Rx % | Overall survival |
|-------------|-----------------|-------------|---------------------------|--------------|-----------------|
| Fidias et al. in 2009 [23] | Docetaxel 75 mg/m2 every 3 Weeks for up to 6 cycles Vs. Observation | 153 Vs. 156 | 5.7 m Vs. 2.7 m HR: 0.63, P<.001 | 63 | 12.3 m Vs. 9.7 m HR: 0.80, P=.085 |
| JMEN (Ciuleanu et al.) in 2009 [24] | Pemetrexed 500 mg/m2 every 3 weeks + BSC Vs. Placebo + BSC | 441 Vs. 222 | 4.0 m Vs. 2.0m HR: 0.60, P < .001 | 67 | 13.4 m Vs. 10.6 m, HR: 0.79, P = .012 |
| SATURN (Capuzzo et al.) in 2010 [25] | Erlotinib 150 mg PO daily Vs. Placebo | 438 Vs. 451 | 12.3 wks Vs. 11.1 wks HR: 0.71 P < .001 | 72 | 12 m Vs. 11 m HR: 0.81 P = .0088 |
| ATLAS (Miller et al.) in 2009 [26, 27] | Bevacizumab 15 mg/kg every 3 wks + erlotinib 150 mg PO daily Vs. Bevacizumab 15 mg/kg every 3 wks + placebo | 373 Vs. 370 | 4.8 m Vs. 3.8 m HR: 0.72 P = .0012 | 55.5% | 15.9 m Vs. 13.9 m, HR: 0.9 P = .2686 |
| IFCT (Perol et al.) in 2010 [28] | Erlotinib 150 mg PO daily Vs. Observation | 155 Vs. 155 | 2.9 m Vs. 1.9 m HR: 0.69 P = .003 | 81.9% | 11.8 m Vs. 10.7 m, HR: 0.87 P = .3 |
| INFORM (Zhang et al.) in 2011 [29] | Gefitinib 250 mg PO daily Vs. Placebo | 148 Vs. 148 | 4.8 m Vs. 2.6 m HR: 0.42 P < .0001 | 58.8 | 18.7 m Vs. 16.9 m, HR: 0.84 P = .2608 |
0.81, \( p=0.0088 \) resulting in its regulatory approval for this indication. Erlotinib approval for maintenance therapy has not been linked to any EGFR marker in either the United States or Europe.

In advanced stage NSCLC where systemic palliative therapy has limited survival benefit, to maintain or improve patients’ quality of life (QOL) represents one of the main treatment goals. Several tools have been developed for measuring quality of life in cancer patients, such as the Functional Living Index–Cancer (FLIC) [34], Functional assessment of cancer therapy (FACT) scale [35], lung cancer symptom scale (LCSS) [36], and the European Organization for Research and Treatment of Cancer (EORTC) QLQ questionnaires which will be used in the present study [37]. The EORTC QLQ is a reliable, valid and clinically relevant tool for assessing lung cancer patients [38] and is efficacious for use in clinical trials as seen in comparative studies [39]. The EORTC QLQ-C30 includes five functional scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, nausea or vomiting, and pain), global health status, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) [40]. The QLQ LC-13 is a supplementary, lung cancer specific questionnaire with 13 items addressing symptoms associated with lung cancer and its standard treatment [41].

Studies with QOL analysis in patients of advanced NSCLC as a primary outcome are limited and some have shown benefit in patients treated in first line setting [42]. Quality of life has also been studied in maintenance therapy. Belani et al. (2012) prospectively analyzed QOL of patients treated in JMEN study and found that patients receiving maintenancepemetrexed had significantly longer time to worsening of pain and hemoptysis symptoms[43]. The PARAMOUNT study also reported similar results [44]. Patients on the SATURN study showed significant delay in the time to pain and analgesic use in those receiving erlotinib maintenance[45]. Based on these multiple QOL analyses accompanying their respective trials, it appears that maintenance therapy in NSCLC delays the worsening of QOL and is beneficial in terms of QOL.

To summarize, there are two drugs approved in the maintenance setting in non-small cell lung cancer-pemetrexed and erlotinib. These two drugs have different side effect profile. Usually oral treatment is considered safer and more convenient than IV chemotherapy but this has not been compared in the maintenance setting. We want to compare the effect of these two drugs which are both standard of care, on the quality of life of the patients.

**AIMS AND OBJECTIVES**

**Outcomes**

Primary: Study the QOL in these two regimes at 3 months.

Secondary: Safety and Toxicity of these two regimen PFS and OS in these two regimens.

**MATERIALS AND METHODS**

**Study design**

This is a prospective randomized open label study comparing Pemetrexed and Erlotinib in maintenance therapy of Non-squamous NSCLC. The protocol is required to be approved by Institutional Review Board at Tata Memorial Hospital.

**Study population**

**Inclusion criteria shall be:**

1. TKI-naive patients with documented Stage III OR Stage IV NSCLC who experience stable disease/ partial response/ complete response after 4-6 cycles of Pemetrexed + Cisplatin/Carboplatin chemotherapy.
2. ECOG Performance status (PS) from 0 to 2
3. Age ≥ 18yrs
4. Adequate bone marrow tests (absolute neutrophil count >1500/IL, hemoglobin > 8 g/dL, and platelet count >100,000/IL), renalfunction tests (creatinine<2 mg/dl), and liver function tests (total bilirubin <1.5 times the institutional upperlimit of normal [ULN], aspartate aminotransferase and alanine aminotransferase levels <2 times the institutional ULN);
5. Life expectancy ≥ 3 months
6. Clinically stable brain metastases if any

**Exclusion criteria shall be:**

1. Prior therapy with TKI
2. Squamous cell Histology
3. A second primary tumor
4. Uncontrolled infection
5. Uncontrolled co-morbidities
6. Premenopausal women will be required to practice a suitable method of birth control and have a negative pregnancy test.

**Treatment drugs**

**Pemetrexed:** Dose - 500mg/m2 IV once in every 3 weeks

It is a pyrrolyrimidinedeantifolate analog which acts mainly by inhibition of folate dependent enzyme thymidylatesynthetase (TS) resulting in inhibition of DNA synthesis and function. It also inhibits dihydrofolate reductase and two formyltransferases. It is metabolized intracellularly to more potent polyglutamates. It is principally excreted by kidneys. Its dose-limiting toxicity is myelosuppression. Other toxicities include skin rashes and hand-foot syndrome, nausea, vomiting, diarrhea, mucositis, fatigue, muscle or joint ache, motor or sensory neuropathy and transient derangement of liver function tests.

**Erlotinib:** Dose - 150mg PO once daily

It is a potent and selective EGFR tyrosine kinase inhibitor causing inhibition of critical mitogenic and anti-apoptotic signals involved in proliferation, growth,
metastasis, angiogenesis and response to chemotherapy and/or radiation therapy. Oral bioavailability is up to 100% after food. It is 90% bound to plasma proteins. Erlotinib is primarily metabolized in liver by the microsomal enzyme system and excreted in feces. Side effects of erlotinib treatment includes diarrhea, nausea, vomiting, oral ulcers, skin rashes with itching, acne and pustules, painful fissures or cracking of skin of hands and feet, alopecia and hair growth abnormalities, nail changes including paronychia and brittle or loose nails, fatigue, loss of appetite, conjunctivitis, abnormal LFTs, elevated INR and bleeding events, and rarely breathlessness, fever, cough and interstitial lung disease.

Concomitant drugs

Concomitant medications are allowed in the study patients as per their co-morbidities and symptomatic management. Vitamin B12 1000 mcg 1 week prior to beginning pemetrexed and every 9 weeks thereafter, daily folic acid supplementation and dexamethasone for 3 days starting 1 day before pemetrexed will be given in the pemetrexed arm. GCSF may be needed in pemetrexed arm. Zoledronic acid for bony metastatic lesions and palliative radiation for painful or symptomatic metastasis will be given.

Dose modification and treatment interruption

Pemetrexed needs to be withheld when creatinine clearance is reduced to less than 45ml/min from baseline. There is no recommended dose reduction for hepatic dysfunction. In case of Grade III/IV neutropenia or thrombocytopenia, dose reduction is required as per standard practice.

For Erlotinib, dose reduction is considered in patients with severe hepatic dysfunction and/or in those with a bilirubin > 3 times the upper limit for normal or AST/ALT > 5 times the upper limit for normal. No dose reduction is required for renal dysfunction. Erlotinib dose reduction or temporary interruption may be needed in Grade III/IV diarrhea and skin reactions. It should be withheld if ILD is suspected and discontinued if proven.

Discontinuation of treatment

Treatment will be discontinued any time when progression is detected, quality of life or performance scale deteriorates during therapy, serious or intolerable side-effects occur as a result of treatment or if the participant wishes as such due to any reason.

Tumour assessment

Tumour response assessment post 1st line chemotherapy before starting maintenance therapy and during the maintenance phase as per routine practice would be done radiologically with scan as when needed by the treating physician.

Efficacy, safety and toxicity assessment

Patients will be followed up in OPD as per standard care. QOL (Quality of Life) assessment will be done at baseline and at 3 months using the EORTC-QLQ-C30 and LC13 questionnaire for lung cancer. Any adverse event whether related or unrelated to treatment would be recorded in the Adverse events form with grade as per CTCAE 4.3. Number of days of hospitalization required during the therapy will also be noted.

STATISTICAL ANALYSIS

Randomization

The patients shall be stratified into Pemetrexed and Erlotinib treatment arms by block randomization so that the two groups are comparable.

Sample size

Primary outcome is change in the score of QOL at 3 months We estimate that with 200 patients, the study will have 80% power to detect a significant difference between the two groups with an alpha error of 5%, when the effect is 0.3 [46].

STATISTICAL METHODS

Changes in HRQOL scores during the study will be calculated as the difference between baseline and 3 months’ value and compared using the paired t test. Effect sizes will be calculated by dividing the changes in each HRQOL score by the standard deviation (SD) of that score estimated at baseline on the entire sample. Analysis of the study variables will be done using simple percentages, log rank test, cox proportional regression analysis and Kaplan Meir Curves.

PRIMARY END POINT: 3 months

Quality of life of patients in the two arms of the study shall be determined using the EORTC-QLQ-C30 and LC13 questionnaire for lung cancer. QOL assessment shall be done at every OPD visit.

SECONDARY END POINTS: Discontinuation of treatment or death due to any cause

Any serious adverse event occurring after the patient has provided informed consent and until four weeks after the patient has stopped study participation shall be reported to the ethics committee. Information about all serious adverse events will be collected and recorded on the Adverse Events Report Form. All the adverse events shall be graded as per the CTCAE Version 4.03. Adverse events recorded in the two study arms shall be compared.

Overall survival in these two arms shall be compared during the period of study. Overall survival will be calculated from the date of diagnosis to date of death from any cause.
Feasibility of the study

We register approximately 1300 patients of lung cancer at TMH. Approximately 1000 patients is planned for palliative systemic therapy. 700 patients are non-squamous NSCLC. We expect 25% of the patients to enroll in the study. We expect to complete the study in 2 years.

Ethical considerations

Both the study arms are standard of care at TMH. Both the drugs are approved for NSCLC. Patients in both arms will receive standard of care.

Informed consent

Each participant shall be informed of the objectives, benefits, risks and requirements of the study. The participants shall be provided with an information sheet in clear, simple language that they understand. The informed consent will be obtained from the patient after the patient clearly reads and understands the informed consent and the patient’s doubts and queries are answered. Since patient will be receiving standard of care in both arms, if complications arise from the trial, they will be managed routinely and the patient will bear the cost. All patient information collected will be confidential and will be available only to the investigators and treating physicians.
1. **SCHEME OF STUDY**

Advanced NSCLC (non-squamous) Post 4-6 cycles of Pemetrexed + Platinum with stable disease or response to therapy and willing for switch maintenance therapy

- Fit for study + willing for study

- Informed Consent

- Randomization into two treatment arms

- Continuation of treatment till decline in QOL or Poor PS or disease progression or significant toxicity or death

- **Primary:** Quality of Life in 2 arms at 3 months

- **Secondary:** Adverse Events in 2 arms, OS in 2 arms
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