A Post-Authorisation Safety Study Protocol

Title	Alvopem® (pemetrexed) safety assessment in patients with non-small cell lung cancer and malignant pleural mesothelioma
Protocol version identifier	Version 2.0
Date of last version of protocol	22.10.2019
Ethics Committee approval number	IR.SBMU.NRITLD.REC.1398.061
ClinicalTrials.gov ID	NCT04843007
Active substance	Pemetrexed (L01BA04)
Medicinal product	Pemetrexed (Alvopem®)
Research question and objectives	The objective of this PMS study is to monitor and assess the safety of Alvopem® in patients with non-small cell lung cancer and malignant pleural mesothelioma over a period of 4.5 to 9 months.
Country(-ies) of study	Iran
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2. List of abbreviations

Abbreviation or Specialist Term	Explanation
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Events of Special Interest
BSC	Best Supportive Care
CI	Confidence Interval
CTCAE	Common Terminology Criteria for Adverse Events
DC	Discontinued
DFS	Disease-Free Survival
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HR	Hazard Ratio
ICH	International Conference on Harmonization
IQR	Interquartile range
IRB	Institutional Review Board
IU	International Unit
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MOH	Ministry of Health
MPM	Malignant Pleural Mesothelioma
NCCN	National Current Comprehensive Network Guideline
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
PI	Principal Investigator
PMS	Post-Marketing Surveillance
PSC	Post-Study Chemotherapy
SAE	Serious Adverse Event
SCLC	Small Cell Lung Cancer
SCr	Serum Creatinine
SD	Standard Deviation
SOC	System Organ Class

Abbreviation or Specialist Term	Explanation
WBC	White Blood Cell

3. Responsible parties

3.1. Principal investigator

Roles and Responsibilities:

- Conducting the study according to the agreed protocol and ICH-GCP guidelines
- Setting up a team for this purpose
- Organizing training sessions for existing and newly recruited team members whenever necessary
- Supervising and approval of suitable places for patient visit
- Cooperation with monitors during the conduction of the study

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Signature:

3.2. Co-investigators

Roles and Responsibilities:

- Conducting the study according to the agreed protocol and ICH-GCP guidelines
- Setting up a team for conducting the study in study site
- Organizing training sessions for existing and newly recruited team members of study site whenever necessary
- Providing suitable place for patient visits
- Cooperation with Monitors during the conduction of the study

Names: Names of the collaborative investigators and study sites are presented in Table 1.

Table 1 Co-investigators and study sites

Center	Investigators
Dr. Masih Daneshvari Hospital, Tehran	Dr. Babak Salimi Dr. Sharareh Seyfi

3.3. Sponsor

Roles and Responsibilities:

- Study protocol preparation
- Preparing Case Report Forms (CRFs)
- Obtaining necessary approvals from external organizations for conducting the study
- Providing Standard Operational Procedures (SOP) for the investigators in study centers
- Funding provision for site staffs collaborating in data collection via signing contracts with the chief and principal investigators
- Providing necessary training for the staff
- Recruiting necessary workforce to conduct monitoring of the trial and the data management
- Planning and conducting the statistical analyses.
- Preparing required study reports.

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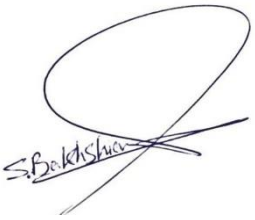

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4. Abstract

Title:

Alvopem® safety assessment in patients with non-small cell lung cancer and malignant pleural mesothelioma

Version 2.0

22.10.2019

Rationale and background:

Lung cancer is the leading cause of cancer deaths worldwide in both men and women. Non-small cell lung cancer (NSCLC) accounts for the majority (approximately 85 percent) of lung cancers with the remainder as mostly small cell lung cancer (SCLC) (1).

In February 2004, the FDA approved pemetrexed for treatment of malignant pleural mesothelioma, a type of tumor of the mesothelium, the thin layer of tissue that covers many of the internal organs, in combination with cisplatin for patients whose disease is either unresectable or who are not otherwise candidates for curative surgery (2,3). In September 2008, the FDA granted approval for pemetrexed as a first-line treatment, in combination with cisplatin, against locally advanced and metastatic non-small cell lung cancer (NSCLC) in patients with non-squamous histology (4-6).

Alvopem® is the generic product of the reference comparator Alimta® which is produced in NanoAlvand Company and it is available as 100 mg and 500 mg lyophilized powder for solution for intravenous infusion vials. Each box of Alvopem® contains one single-use vial (7).

According to the importance of pemetrexed in chemotherapy regimens, this observational cohort study, safety assessment of Alvopem® in patients with non-small cell lung cancer and malignant pleural mesothelioma is designed.

Research question and objectives:

The current outcome measure for this study is the safety evaluation of Alvopem® by monitoring adverse events.

Study design:

This study is a phase IV, post-marketing, observational, cohort study for safety evaluation of Alvopem® use in Iranian patients with non-small cell lung cancer and malignant pleural mesothelioma. No control groups are included in the study design.

Population:

Alvopem® will be given every 3 weeks with a dose of 500 mg/m^2. Data will be gathered in one booklet, containing information on six cycles of chemotherapy, which will be filled by the designated physician.

A population of 200 Iranian patients diagnosed with non-small cell lung cancer and malignant pleural mesothelioma under chemotherapy regimens with Alvopem®, will be enrolled in the study; and during 4.5 to 9 months period of study related data will be collected and analyzed.

Variables:

The primary objective of this study is safety assessment, including the incidence of AEs. The intensity of AEs will be graded according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) and terminology for AEs was chosen according to the MedDRA system organ class and preferred term (MedDRA Desktop Browser 4.0 Beta). Also, intensity, seriousness, onset of ADRs, and interventions for management of the adverse events will be documented in the booklet.

Exposure to Alvopem® in this study is defined as administration of 500 mg/m^2 from Alvopem® vials, once every 3 weeks during 4.5 to 9 months of the study period.

Variables in this study include: Patient's demographic information, patient's habit history, patient's medical history, cancer type**,** stage of cancer**,** patient's non-chemotherapy medication, patient's chemotherapy medication, laboratory tests, Alvopem® information, Alvopem® administration protocol checklist, premedication information, adverse drug events reporting, para-clinical actions due to adverse event, and clinical actions due to adverse event.

Data sources:

All adverse events and other required data will be collected through a comprehensive physical examination as well as a complete blood and urine test throughout the study by the specialists who visit the patients and is recorded in particular patient-specific case report forms specifically termed as PMS booklets.

Study size:

The planned sample size of this study is 200 patients.

Data analysis:

All Patients who will be included in the study will be analyzed. Safety evaluation will be reported using summary statistics. For each AE, data will be summarized using incidence according to system organ class and preferred term of AEs and SAEs. Moreover, causality assessment will be done and its results will be reported by frequency and percentage.

5. Rationale and Background

Lung cancer is the leading cause of cancer deaths worldwide in both men and women. Non-small cell lung cancer (NSCLC) accounts for the majority (approximately 85 percent) of lung cancers with the remainder as mostly small cell lung cancer (SCLC) (1).

In February 2004, the FDA approved pemetrexed for treatment of malignant pleural mesothelioma, a type of tumor of the mesothelium, the thin layer of tissue that covers many of the internal organs, in combination with cisplatin for

patients whose disease is either unresectable or who are not otherwise candidates for curative surgery (2,3). In September 2008, the FDA granted pemetrexed approval as a first-line treatment, in combination with cisplatin, against locally advanced and metastatic non-small cell lung cancer (NSCLC) in patients with non-squamous histology (4-6).

In 2003, a phase 3 clinical study evaluated the efficacy of pemetrexed when it is added to cisplatin. Chemotherapy-naive patients who were not eligible for curative surgery were randomly assigned to receive pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 on day 1, or cisplatin 75 mg/m^2 on day 1. Both regimens were given intravenously every 21 days. The results showed that the survival of patients, who have received Pemetrexed, is more than others. ($P = 0.02$) Mortality rate in patients, who received pemetrexed and cisplatin, was significantly less than the other group. ($P = 0.001$), and results showed the response to treatment in pemetrexed group was 44%, and the cisplatin group was 16.7% ($P <0.001$) (8).

In another study in 2003 the use of supplements for reduction of adverse effects of pemetrexed was assessed. In this study, a total of 64 patients were enrolled. In these patients, 500 mg/m² Pemetrexed was administered intravenously over 10 minutes every 3 weeks. Forty-three patients received vitamin supplementation for all courses of therapy, and 21 patients did not. Finally, Patients who received supplements such as folic acid and vitamin B_{12} tolerated treatment better (less toxicity and more cycles of treatment) and had more 5-month median overall survival than patients who have not been received supplements (9).

In 2005, a study was conducted on patients with malignant plural mesothelioma. This retrospective analysis was conducted using data from patients with MPM who had received post-study chemotherapy (PSC) following participation in the phase III study of pemetrexed plus cisplatin versus single-agent cisplatin. Eighty-four patients from the pemetrexed plus cisplatin arm and 105 patients from the single-agent cisplatin arm received PSC. The results showed the pemetrexed plus cisplatin treatment group had a statistically significant survival advantage even though fewer patients from that arm of the trial received PSC ($P <0.01$) (10).

In 2008, a phase 3 study was conducted to evaluate the therapeutic effect of cisplatin plus gemcitabine and cisplatin plus pemetrexed. In this study, 1725 patients with advanced NSCLC cancer has no cure before, were examined. In advanced NSCLC, cisplatin/pemetrexed provided similar efficacy with better tolerability and more convenient administration than cisplatin/gemcitabine (11).

In 2008 phase III study compared overall survival (OS) of second-line pemetrexed plus best supportive care (BSC) versus BSC alone in patients with advanced malignant pleural mesothelioma (MPM). In this study 123 patients for 21 days received of 500 mg/m² pemetrexed and 121 received supportive treatments, such as analgesics and antibiotics and their thoracentesis. In this study, survival was not different between the two groups significantly, but recurrence after treatment and the need for secondary treatment were significantly lower in the group that received pemetrexed ($P <0.001$) (12).

In 2008, one study evaluated pemetrexed use as maintenance therapy versus placebo in patients with NSCLC. Overall, 663 patients were enrolled (Pemetrexed =441; placebo =222). Pemetrexed at a dose of 500 mg/m² was administered in 21-day cycles. The results showed that PFS in patients who have received pemetrexed was

significantly higher. (P <0.00001) The occurrence of adverse events did not differ significantly between two groups and only 4.3% patients who received pemetrexed showed side effects (13).

In 2009, Phase III study by the Norwegian lung cancer was conducted to compare efficacy of pemetrexed plus carboplatin with gemcitabine plus carboplatin as first-line chemotherapy in advanced non-small-cell lung cancer. Overall, 436 patients for treatment of advanced lung cancer received one of the regimes as first-line therapy. At the end of the study, pemetrexed/carboplatin provides similar health-related quality of life and survival when compared with gemcitabine/carboplatin with less hematologic toxicity and less need for supportive care (P <0.001) (14).

In 2010 the first evaluation on the pemetrexed effect of treatment on brain metastases in patients with NSCLC was performed. 39 patients were included in this study. The cerebral response to pemetrexed was interesting with a cerebral radiological benefit obtained in 32 patients (82%), while 7 patients only showed brain progressive disease. Overall median survival was 10 months (15).

In 2011 the safety and efficacy of pemetrexed–cisplatin in patients with metastatic NSCLC, with brain metastases were examined. The reason for this study was the high incidence of brain metastases in patients with lung cancer. Overall, 43 patients were enrolled in this study. These patients were eligible to receive up to six cycles of cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 every 3 weeks. In these patients, grade 3–4 hematological toxic effects were neutropenia at 11 patients (febrile neutropenia, 1 patient but only one person was neutropenia with fever), and anemia at 6 patients. Non-hematologic side effects were occurred in one person who was suffering from pneumonia. Pemetrexed could increase patient survival to 7 months (16).

In 2011, a study was performed on patients with malignant pleural mesothelioma who were previously treated with pemetrexed and they had recurrence. During 5 years 31 patients were studied that survive least 3 months after first-line treatment. Re-treatment with pemetrexed could increase overall survival (OS) for 10.5 months. Toxicity was mild and grade 3 or 4 hematological toxicity was occurred in 9.7% of patients (17).

In 2014, a systematic review and meta-analysis was conducted to compare the efficacy and safety of pemetrexed and docetaxel for non-small cell lung cancer (NSCLC). Six RCTs involving 1,414 patients were identified. We found that there were no statistically significant differences in overall response rate, survival time, progression-free survival, disease control rate, and 1–2-year survival rate (p>0.050) but it is worthy of mention that patients in the pemetrexed arms had significantly higher 3-yr survival rate (P=0.002). As for safety, pemetrexed led to lower rate of grade 3-4 febrile neutropenia, neutropenia, leukocytes, diarrhea and alopecia toxicity. However, it was associated with a higher rate of grade 3-4 thrombocytopenia (18).

In 2014, safety and effectiveness of pemetrexed in patients with non-small cell lung cancer (NSCLC) were reviewed using data from post-marketing surveillance. Among 699 patients registered in Japan from June 2009 to May 2010, 683 patients were analyzed (343, first-line therapy: 340, second-line therapy or beyond). The surveillance results showed no apparent difference in total ADRs in this current study compared to the safety profile established in clinical trials previously conducted in Japan and overseas. These results demonstrate the safety and effectiveness of pemetrexed treatment for NSCLC patients in daily clinical settings (19).

Alvopem® is the generic product of the reference comparator Alimta® which is produced in NanoAlvand Company and it is available as 100 mg and 500 mg lyophilized powder for solution for intravenous infusion vials. Alvopem® is supplied as a sterile lyophilized powder for solution for intravenous infusion available in single-dose vials. The product is a white to either light yellow or green-yellow lyophilized solid. Each box of Alvopem® contains one single-use vial (7).

Post-marketing surveillance (PMS) is one of the methods for evaluating drug safety in clinical use. Thus, in this phase IV, post-marketing, observational, cohort study, we will aim to investigate safety of Alvopem® use in patients with non-small cell lung cancer and malignant pleural mesothelioma. Safety will be assessed by collecting and processing all the AEs happening during the study.

6. Research question and objectives

The objective of this PMS study is to monitor and assess the safety of Alvopem® use in patients with non-small cell lung cancer and malignant pleural mesothelioma over a period of 4.5 to 9 months. In this safety assessment study, the incidence and intensity of all reported adverse events (AEs), adverse events of special interest (AESI) and serious adverse events will be assessed.

7. Research methods

7.1. Study design

This study is a phase IV, post-marketing, observational, cohort study for safety evaluation of Alvopem® use in Iranian patients with non-small cell lung cancer and malignant pleural mesothelioma. No control groups are included in the study design.

PMS studies are of significant value in developing drugs and leading to the evaluation of safety. Safety monitoring of medicines that are already marketed is one of the endpoints of these studies. One of the main advantages of PMS studies is the enrollment of a large number of patients.

The objective of this PMS study is to monitor and assess the safety of Alvopem® in patients with non-small cell lung cancer and malignant pleural mesothelioma over a period of 4.5 to 9 months.

7.2. Setting

A population of 200 Iranian patients diagnosed with non-small cell lung cancer and malignant pleural mesothelioma under chemotherapy regimens with Alvopem® (with a dose of 500 mg/m^2), will be enrolled in the study. Study will start recruitment on October 2016; and during 4.5 to 9 months period of study related data will be collected and analyzed.

Inclusion Criteria

Patients with non-small cell lung cancer and malignant pleural mesothelioma will be included in the study.

Exclusion Criteria

There are no exclusion criteria for this study.

The study consists of 6 visits, including a baseline visit and 5 additional follow-up visits. The follow-up visits will be conducted every 3 weeks.

This study consists of one booklet, which has 6 different periods (each period covers 3 weeks). The patients' information will be assessed after each injection, every 3 weeks. The duration of this study is 4.5 to 9 months per patient. These booklets will be completed by physicians.

At the baseline visit, information of the patients' demographic data, patients' habit histories (including cigarette smoking and alcohol consumption) and past medical histories (allergic history, renal and hepatic impairments, respiratory impairment, radiotherapy history), patients' medications (including chemotherapy drugs or other non-chemotherapy drugs), type of cancers (malignant pleural mesothelioma or NSCLC or other cancer types) and stage of cancers will be provided.

Patients at baseline (before starting treatment with Alvopem®) and the beginning of each cycle will have a complete blood and urine test.

At the start of the study and the beginning of each cycle the physicians have to determine which setting should be prescribed according to patients` conditions including first line, second line, or adjuvant/neoadjuvant.

In each period below items will be recorded by a specialist:

- The duration of infusion
- The solvent used for infusion
- The type of premedication
- The dose of Alvopem®
- The dosage form of Alvopem®
- The adverse events related to Alvopem®
- Actions done for adverse events
- The withdrawal reason should be specified in case of drug discontinuation.

Timeline of the study including the type and the visit number of each assessment is as follows:

Evaluations visit	1st visit	2nd visit	3rd visit	4th visit	5th visit	6th visit
Patient's Demographic Information	√					
Patient's Habit History (smoking,	√					

alcohol, …)						
Patient's Medical History	√					
Patient's Non-Chemotherapy Medication	√					
Patient's Chemotherapy Medication	√					
Cancer Type	√					
Stage of Cancer	√					
Laboratory Tests	√	√	√	√	√	√
Alvopem® Information	√	√	√	√	√	√
Premedication Information	√	√	√	√	√	√
Alvopem® Administration Protocol Checklist	√	√	√	√	√	√
Adverse Drug Events Reporting	√	√	√	√	√	√
Para-clinical Actions Due to Adverse Event	√	√	√	√	√	√
Clinical Actions Due to Adverse Event	√	√	√	√	√	√

7.3. Variables

Exposure to Alvopem® in this study is defined as administration of 500 mg/m^2 from Alvopem® vials, once every 3 weeks during 4.5 to 9 months of the study period.

The objective of this study is safety assessment, including the incidence of AEs. The intensity of AEs will be graded according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) and terminology for AEs was chosen according to the MedDRA system organ class and preferred term (MedDRA Desktop Browser 4.0 Beta). Also, intensity, seriousness, onset of ADRs, and interventions for management of the adverse events will be documented in the booklet.

Variables in this study include: Patient's demographic information, patient's habit history, patient's medical history, patient's non-chemotherapy medication, patient's chemotherapy medication**,** cancer type**,** stage of cancer**,** laboratory

tests**,** Alvopem® Information, premedication information, Alvopem® administration protocol checklist, adverse drug events reporting, para-clinical actions due to adverse event, clinical actions due to adverse event

7.4. Data sources

AEs will be monitored through a comprehensive physical examination as well as a complete blood and urine test throughout the study period. Each patient will be followed up for a maximum of six cycles and the cycle intervals are defined on the physician's discretion. AEs will be recorded according to the MedDRA system organ class and preferred term. Intensity and seriousness will be reported for each AE. All the assessment procedures will be done regularly at each visit. During each visit, all data will be collected by a designated physician and recorded in particular patient-specific booklets consist of six visits from baseline to the end of the follow-up duration.

7.5. Study size

In a cohort study with no background incidence of a particular adverse reaction, the probability that 1 or more adverse reactions will not occur in a sample of 190 patients with an anticipated incidence rate of 0.0085 is 0.19889. Assuming a 5% dropout rate and 80% power, 200 patients will be required.

$$\boldsymbol{\beta = \sum_{i=0}^{A-1} \frac{N^i (D)^i e^{-N(D)}}{i!}}$$

Report Definitions:

Power is 1 - Beta.

N is the number of patients monitored.

D is the expected incidence rate of adverse reactions.

A is the number of adverse reactions.

Beta is the probability that A reactions will not be found in the N patients.

Based on the PASS® output, the sample size required is 190.

Table 1: PMS Power Analysis Numeric Results (Cohort Study with No Background Incidence)

Power	Sample size (N)	Additional Incidence Rate (D)	Number of Occurrences(A)	Beta
0.80	190	0.0085	1	0.19889

7.6. Data management

Case report forms are designed in the form of booklets termed as *PMS booklets* consists of six cycles from baseline to the end of the follow-up duration. The duration of Alvopem® treatment, as well as the interval between cycles, will be determined at the physicians' discretion based on the patient's condition.

Recorded data in booklets will be monitored regularly on a periodic basis. Then, data will be entered into an electronic data registry specifically designed for this study for further data extraction and analysis (Access app version 2016, Microsoft Corporation, USA). Process of data cleaning including assessing the range of data and determining out layer data will be done. After that, data will be analyzed according to study endpoints using STATA version 14.

7.7. Data analysis

All Patients who will be included in the study will be analyzed. Analysis for continuous variables will be based on mean and standard deviation. Frequency and percentage of categorical variable will be described.

Adverse events will be reported as incidence. In other words, patients with any number of AEs will be counted only once in the incidence calculation. The safety data will be analyzed primarily using summary statistics. Summary statistics are included the number of subjects (number and percentages) and then classified according to system organ class and preferred term for AEs and SAEs. The incidence of the preferred term for grades 3 and 4 of AEs will be reported. Moreover, causality will be assessed and its results will be reported by frequency and percentage.

7.8. Quality control

Nanoalvand Co. conducts all studies according to procedures that incorporate the ethical principles of Good Clinical Practice (GCP). The investigators participated in this study are amongst the most professional oncologists in Iran. All labs involved in this study are under MOH of Iran supervision.

Prior to run the study, the PMS booklet is checked and confirmed by the principal investigator regarding conformity with the study protocol. It will be further approved by co-investigators during an investigator meeting. An electronic data registry will be developed based on the approved PMS booklet and its conformity with the PMS booklet is confirmed by investigators correspondingly. The instruction manual will also be provided for training the personnel involved in filling the booklets. Patients' recorded data in PMS booklets are regularly monitored in terms of verification and validity while the study is progressing. Recorded data in the data registry is also regularly exported and checked by a certified statistician in terms of outlier determination to verify if data entry error has occurred and will be rechecked if needed.

7.9. Limitations of the research methods

As this study is a phase IV study, the setting is open-label and this might be a confounding factor. In addition, data will be gathered in booklets, therefore monitoring process is harder and some out-layer data may not be corrected, and may cause deviations in results.

7.10. Other aspects

There are no other aspects to be mentioned in this section and all contents are described in other sections.

8. Protection of human subjects

The study data is monitored periodically and the investigators are responsible to report the AEs to the pharmacovigilance team. In case that the study team question the risk-benefit balance of the study, either for a single patient or all patients, the sponsor is responsible for organizing an investigators' meeting.
Also, if a SUSAR occurs or the incidence of a particular AE is higher than expected, unscheduled meetings will be held based on the request of the principal investigator or the sponsor.

9. Management and reporting of adverse events/adverse reactions

AEs will be recorded for primary endpoint evaluation according to the MedDRA system organ class and preferred term. The booklets will be filled by the designated physicians. Intensity and seriousness will be reported for each AE. There are questionaries' presented in patient's booklets in order to gather all the adverse events reported in this study. This data will be collected and analyzed in order to present the incidence, seriousness and interventions of all adverse events occurring during this study. The intensity of AEs will be graded according to the CTCAE v5.0, and terminology for AEs will be chosen according to the MedDRA system organ class and preferred term.

10. Plans for disseminating and communicating study results

The results from this study will be reported to regulatory authorities and also an article will be written based on results.

11. References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: a cancer journal for clinicians. 2015 Mar;65(2):87-108.

2. Manegold C. Pemetrexed (Alimta, MTA, multitargeted antifolate, LY231514) for malignant pleural mesothelioma. InSeminars in oncology 2003 Aug 1 (Vol. 30, pp. 32-36). WB Saunders.

3. National Cancer Institute: FDA Approval for Pemetrexed Disodium

4. Cohen MH, Justice R, Pazdur R. Approval summary: pemetrexed in the initial treatment of advanced/metastatic non-small cell lung cancer. Oncologist. 2009 Sep 1;14(9).

5. Rossi A, Ricciardi S, Maione P, de Marinis F, Gridelli C. Pemetrexed in the treatment of advanced non-squamous lung cancer. Lung cancer. 2009 Nov 1;66(2):141-9.

6. ealthcare Professional Website". *ALIMTA.com*. Eli Lilly and Company. Archived from the original on 7 January 2009. Retrieved 1 December 2008.

7. Vogelzang, Nicholas J., et al. "Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. " Journal of clinical oncology 21.14 (2003): 2636-2644

8. Scagliotti, Giorgio V., et al. "Phase II study of pemetrexed with and without folic acid and vitamin B12 as front-line therapy in malignant pleural mesothelioma." Journal of clinical oncology 21.8 (2003): 1556-1561.

9. Manegold, C., et al. "Second-line (post-study) chemotherapy received by patients treated in the phase III trial of pemetrexed plus cisplatin versus cisplatin alone in malignant pleural mesothelioma." Annals of oncology 16.6 (2005): 923-927.

10. Scagliotti, Giorgio Vittorio, et al. "Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non–small-cell lung cancer." Journal of Clinical Oncology 26.21 (2008): 3543-3551.

11. Jassem, Jacek, et al. "Phase III trial of pemetrexed plus best supportive care compared with best supportive care in previously treated patients with advanced malignant pleural mesothelioma." Journal of Clinical Oncology26.10 (2008): 1698-1704.

12. Ciuleanu, T. E., et al. "Maintenance pemetrexed plus best supportive care (BSC) versus placebo plus BSC: A phase III study." ASCO Annual Meeting Proceedings. Vol. 26. No. 15_suppl. 2008.

13. Grønberg, Bjørn H., et al. "Phase III study by the Norwegian lung cancer study group: Pemetrexed plus carboplatin compared with gemcitabine plus carboplatin as first-line chemotherapy in advanced non–small-cell lung cancer." Journal of clinical oncology 27.19 (2009): 3217-3224.

14. Bearz, Alessandra, et al. "Activity of pemetrexed on brain metastases from non-small cell lung cancer." Lung Cancer 68.2 (2010): 264-268.

15. Barlesi, F., et al. "Pemetrexed and cisplatin as first-line chemotherapy for advanced non-small-cell lung cancer (NSCLC) with asymptomatic inoperable brain metastases: a multicenter phase II trial (GFPC 07-01)." Annals of oncology (2011): mdr003.

16. Ceresoli, Giovanni L., et al. "Retreatment with pemetrexed-based chemotherapy in patients with malignant pleural mesothelioma." Lung Cancer72.1 (2011): 73-77.

17. Zhang QY, Yang KH, Ge L, Huang WH, Zhang FW. Effectiveness and safety of pemetrexed versus docetaxel as a treatment for advanced non-small cell lung cancer: a systematic review and meta-analysis. Asian Pacific Journal of Cancer Prevention. 2014;15(8):3419-24.

18. Okubo S, Kobayashi N, Taketsuna M, Kaneko N, Enatsu S, Nishiuma S. Safety and effectiveness of pemetrexed in patients with non-small cell lung cancer in Japan-analysis of post-marketing surveillance. Gan to Kagaku ryoho. Cancer & Chemotherapy. 2014 Apr 1;41(4):475-81.
19. https://www.nanoalvand.com/products/detail/Pemetrexed/115/view/

Annex 1. List of stand-alone documents

There are no stand-alone documents on this protocol.

Annex 2. Additional information

There is no additional information on this protocol.