# Ceritinib nanoparticle composition for the treatment of non-small-cell lung cancer

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**Abstract:** The present work relates to a process to prepare Ceritinib formulation in the form of nanoparticles and the use of nanoparticle composition for the treatment of non-small-cell lung cancer. In this study Anticancer compositions comprising anticancer agents in the form of surface modified nanoparticles as obtained through the process according to the invention exhibit reduced toxicity and/or enhanced efficacy. It is a particularly advantageous feature of this invention that a process for obtaining anticancer compositions is provided, which compositions exhibit reduced toxicity and/or improved efficacy.

**Keywords:** Cancer, Nanoparticle, Lung cancer, Toxicity, NSCLC

## Introduction

Cancer is a type of disease where cells of the body grow uncontrollably and spread to other parts of the body. Cancer is characterized by the development of abnormal cells that divide uncontrollably and have the ability to infiltrate and destroy normal body tissue. Now a days Cancer is a leading cause of death in the world, accounting around 9.6 million deaths in 2018. The most common cancers are: Cancer arises from the transformation of normal cells into tumour cells in a multistage process that generally progresses from a pre-cancerous lesion to a malignant tumour. Treatment of cancer involves the chemotherapy which is a drug treatment that uses powerful chemicals to kill fast-growing cells in your body. Cancer cells grow and multiply much more quickly than most cells in the body and chemotherapy used to treat cancer. Many drugs are available for chemotherapy and the scientist are developing new drugs for the cancer. Chemotherapy is a very effective way to treat many types of cancer, chemotherapy treatment also carries a risk of side effects. Some chemotherapy side effects are mild and treatable, while others can cause serious complications. More than one kind of treatment is often used, depending on the stage of the cancer, the individual's overall health, age, response to chemotherapy, and other factors such as the likely side effects of the treatment.[1] After full staging, the NSCLC patient can typically be classified in one of three different categories: patients with early, nonmetastatic disease (stages I and II, and select type III tumors), patients with locally advanced disease confined to the thoracic cavity (e.g., large tumors, tumors involving critical chest structures, or patients with positive mediastinal lymph nodes), or patients with distant metastasis outside of the thoracic cavity.[2]

Non-small cell lung cancer (NSCLC) is a type of lung cancer that contains a variety of different lung cancers, most notably adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Adenocarcinoma is the most common type of lung cancer in this category and includes one-half of all lung cancer cases.[3]

NSCLC accounts for about 85% of all lung cancers. As a class, NSCLCs are relatively insensitive to chemotherapy, compared to small-cell carcinoma. As possible, they are primarily treated by surgical resection with curative intent, although chemotherapy has been used increasingly both preoperatively (neoadjuvant chemotherapy) and postoperatively (adjuvant chemotherapy).[4]

Ceritinib is a second-generation anaplastic lymphoma kinase (ALK) inhibitor.[5] It is a prescription-only drug used for the treatment of non-small cell lung cancer (NSCLC).[6] It was approved by the FDA on April 29, 2014.[7]

Ceritinib is a tyrosine kinase inhibitor that selectively and potently inhibits anaplastic lymphoma kinase (ALK). [8]In normal physiology, ALK functions as a key step in the development and function of nervous system tissue. However, chromosomal translocation and fusion give rise to an oncogenic form of ALK that has been implicated in progression of NSCLC.[9] Ceritinib thus acts to inhibit this mutated enzyme and stop cell proliferation, ultimately halting cancer progression. Because ceritinib is considered a targeted cancer therapy, an FDA-approved test is required to determine which patients are candidates for ceritinib. This test, developed by Roche, is the VENTANA ALK (D5F3) CDx Assay and is used to identify ALK-positive NSCLC patients who would benefit from ceritinib treatment.

A nanoparticle with a large number of surface functional groups provides an avenue for the attachment of multiple kinds of biomolecules for targeted drug delivery and diagnostic applications for lung cancer.[10]

Lung cancer is the most common cause of cancer-related death in humans worldwide. Various cancer therapies are available to treat cancer but the main causes of concern with most are the toxic effects as well as diagnosis at an advanced stage. These factors lead to high mortality in a majority of patients. These shortcomings can be overcome up to some extent by either reducing the dose of drug or by early diagnosis. Recently nanotechnology is being explored extensively toward early diagnosis and detection of cancer. Many effective nanomedicines have been developed with advance treatment regimens.[11] Various nanosystems have been developed to enhance the therapeutic effect of drugs as well as selective targeting and delivery of drugs to specific sites of tumor. Nanoparticle-based medicines and therapeutics is becoming more important in the treatment of different forms of cancers, especially lung cancer.[12]

## Materials and Methods

Ceritinib was received as a gift sample from MSN Labs (Hyderabad, India). zirconium oxide was purchased from Sigma Aldrich (New Delhi, India), and Tween-20 was supplied by S. D. Fine Chemicals (New Delhi, India). All other chemicals were of analytical grade and used as received.

## Method of preparation

Coarse particles of Ceritinib were dispersed in water and milled for 120 hours in a roller mill under the following milling conditions:

Grinding vessel: 250 ml; Media: 1.0 mm pre-cleaned zirconium oxide beads; media volume: 120 ml; milling time: 120 hours; Slurry volume: 60 ml, RPM: 92

Approximately 18 ml precleaned zirconium oxide media (1 mm) was added to a 30 ml amber jar. To it was added 240 mg Ceritinib and 180 mg Tween 20. Finally, 12 ml water for injection was added to the jar, it was sealed and mounted on a roller mill for 11 days. The final particle size was 327 nm.

Nanoparticle formulation was evaluated in two separate efficacy studies in pancreatic ductal adenocarcinoma #03 (PANC #03). Control C was a 2% non-aqueous certinib solution.

**Results and Discussion**

The surface modifier is adsorbed on the surface of the certinib in an amount sufficient to maintain an effective average particle size of less than 400 nm. The surface modifier does not chemically react with the anticancer agent or itself.

Antitumor activity was assessed by monitoring tumor weight from experimental and control animals. These studies demonstrate that the etoposide compositions when prepared according to the process of this invention provide a means to deliver high doses of the drug without evidence of severe toxic reaction. Refer Table 1 for results.

It is a particularly advantageous feature that the anticancer compositions obtained with the method of this study exhibit reduced toxicity and/or enhanced efficacy. The formulation was stable when exposed to PBS (pH 7.4) and rat plasma. Further, the particles obtained with the method of this invention exhibit prolonged circulation in the blood pool.

**Table 1: Efficacy studies for Nanoparticle composition in PANC murine tumor model**

| Example | route | Dose mg/kg | % wt loss | Drug Deaths | T/C % |
|---|---|---|---|---|---|
| Control C | IV | 120 | -24.0 | 0/5 | 04.0 |
| | IV | 25 | -4.0 | 0/5 | 20.0 |
| 20 | IV | 160 | -12.0 | 0/5 | 18.0 |
| | IV | 100 | 0.0 | 0/5 | 32.0 |
| | IV | 62 | 2.0 | 0/5 | 42.0 |
| 21 | IV | 160 | -12 | 0/5 | 26.0 |
| | IV | 100 | +2 | 0/5 | 35.0 |
| | IV | 62 | +4 | 0/5 | 35.0 |
| 22 | IV | 170 | -18 | 0/5 | 16.0 |
| | IV | 85 | -2 | 0/5 | 35.0 |
| | IV | 43 | +2.5 | 0/5 | 41.0 |

**Conflict of Interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

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