



BMJ Open Concurrent chemoradiation and brachytherapy alone or in combination with nelfinavir in locally advanced cervical cancer (NELCER): study protocol for a phase III trial

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ABSTRACT

Introduction In locally advanced cervical cancer, nodal, local and distant relapse continue to be significant patterns of relapse. Therefore, strategies to improve the efficacy of chemoradiation are desirable such as biological pathway modifiers and immunomodulating agents. This trial will investigate the impact of nelfinavir, a protease inhibitor that targets the protein kinase B (AKT) pathway on disease-free survival (DFS).

Methods and analysis Radiosensitising effect of nelfinavir in locally advanced carcinoma of cervix is a single-centre, open-label, parallel-group, 1:1 randomised phase-III study. Patients aged over 18 years with a diagnosis of carcinoma cervix stage III are eligible for the study. After consenting, patients will undergo randomisation to chemoradiation and brachytherapy arm or nelfinavir with chemoradiation and brachytherapy arm. The primary aim of the study is to compare the difference in 3-year DFS between the two arms. Secondary aims are locoregional control, overall survival, toxicity and quality of life between the two arms. Pharmacokinetics of nelfinavir and its impact on tumour AKT, programmed cell death ligand 1, cluster of differentiation 4, cluster of differentiation 8 and natural killer 1.1 expression will be investigated. The overall sample size of 348 with 1 planned interim analysis achieves 80% power at a 0.05 significance level to detect a HR of 0.66 when the proportion surviving in the control arm is 0.65. The planned study duration is 8 years.

Ethics and dissemination The trial is approved by the Institutional Ethics Committee-I of Tata Memorial Hospital, Mumbai (reference number: IEC/0317/1543/001) and will be monitored by the data safety monitoring committee. The study results will be disseminated via peer-reviewed scientific journals, and conference presentations. Study participants will be accrued after obtaining written informed consent from them. The confidentiality and privacy of study participants will be maintained.

Strengths and limitations of this study

- This is the first large study investigating the role of protein kinase B pathway inhibitor nelfinavir in locally advanced cervical cancer in a randomised study.
- The statistical design of the study allows early analysis of drug activity at recruitment of 190/348 patients or 32/192 events.
- One of the key features of the study is the coexisting pharmacokinetic and translational research work which in future will be helpful in targeted treatment.
- The key limitations of the study include recruitment from one centre and expected delay in the trial completion.
- There is expected to be within group heterogeneity with regards to distribution of node positive disease and primary tumour extent.
- Based on revised International Federation of Gynecology and Obstetrics stage III cervical cancer 2018 staging the outcomes in the standard arm may be marginally different than expected due to relative distribution of patients with locally versus nodal advanced stage.

Trial registration number The trial is registered with Clinical Trials Registry-India (CTRI/2017/08/009265) and ClinicalTrials.gov (NCT03256916).

INTRODUCTION

Background and rationale

Cervical cancer is the fifth most common cancer globally and the fourth most common cancer in women, with an age standardised incidence of 13.3 per 100 000 and mortality of 7.3 per 100 000. In India, it is the second

most common cancer with an age standardised incidence of 18 per 100 000 and the second most common cause of cancer death with an age standardised rate of 11.4 per 100 000.¹ The most significant change in the treatment of locally advanced cervical cancer (LACC) was addition of concurrent cisplatin to radiotherapy,^{23–5} which became the standard treatment modality. Chemoradiation results in 5-year overall survival (OS) of approximately 50%–55% in stage III LACC.⁵ The 3-year disease-free survival (DFS) ranges from 61% to 74%.⁶ Since chemoradiation trials, further improvement in local control and DFS is also reported by integrating image-based brachytherapy and radiation dose escalation. Dose escalation through brachytherapy has led to a change in the patterns of failure, with 14%–21% of patients presenting with distant visceral relapse and 9%–12% with para-aortic nodal relapse. In addition, 11%–13% of patients still present with pelvic failure after primary treatment.^{7–11} As distant metastasis (including para-aortic nodal metastasis) forms the predominant form of failure, strategies to reduce relapses and improve OS include eliminating micrometastasis through the integration of systemic therapies have been tested.^{12–18} More recently, phase III studies are testing the role of immunotherapy agents in LACC. Ongoing trials are currently recruiting patients to test pembrolizumab and atezolizumab within concurrent and adjuvant setting.^{19 20}

In cervix cancer, activation of the phosphoinositide-3-kinase–protein kinase B (PI3K–AKT) pathway is associated with radiation resistance through epidermal growth factor receptor signalling, enhanced tumour cell proliferation and cell survival.²¹ Phosphorylation of AKT (p-AKT) results in the overexpression of hypoxia-inducible factor 1-alpha and osteopontin, which modulates angiogenesis due to overexpression of vascular endothelial growth factor. Increased expression of these proteins results in increased resistance to radiation treatment.²² In vitro, preclinical studies have shown increased expression of p-AKT to be responsible for radiation resistance in many solid tumours.^{23–25} Phosphoinositide-3-kinase catalytic alpha (PIK3CA), involved in the PI3K–AKT-signalling pathway, is known to be an oncogene associated with cervical cancer.²⁶ Studies have demonstrated that the most common gene mutation is in the PIK3CA gene, seen in 14%–40% cancers.^{26–28}

Protease inhibitors (PIs) are a class of drugs that inhibit the AKT phosphorylation pathway and have been of recent interest in various malignancies. Nelfinavir has been found to be the most efficacious of all PIs.²⁹ Nelfinavir significantly decreases the phosphorylated AKT levels in the cancer cells and functions through other cancer pathways.^{30 31} Since nelfinavir has been used for over a decade to treat patients with HIV infection with an acceptable toxicity profile, it has the potential of being repurposed into clinical trials to be tested as a radiosensitizer. A phase-I trial of nelfinavir with escalating doses of gemcitabine and standard-dose cisplatin in locally advanced pancreatic cancer undergoing chemoradiation

demonstrated acceptable toxicity at 1250 mg two times per day dose of nelfinavir.³² Two phase-I studies reported from the University of Pennsylvania and Maastricht University Medical Centre evaluating toxicity and efficacy of escalating doses of nelfinavir with concurrent cisplatin and thoracic radiotherapy in advanced lung carcinoma and rectal cancer demonstrated that the dose of 1250 mg two times per day with cisplatin had acceptable toxicity (no dose limiting toxicities were observed) and good activity (metabolic response rate of 56%).^{33–35} Nelfinavir has also been administered along with hypofractionated stereotactic body radiation therapy (SBRT) in patients with pancreatic cancer. While concurrent SBRT with nelfinavir was deemed safe and feasible, five patients still presented with gastrointestinal bleeding. Median failure-free survival was 10 months.^{36 37} A recently published phase I study on determining the recommended dose of nelfinavir along with the standard of care chemoradiation in LACC reported that 1250 mg two times per day dose was safe and had an acceptable toxicity profile.³⁸

The present phase III randomised trial (radiosensitising effect of nelfinavir in locally advanced carcinoma of cervix (NELCER)), which is currently open to recruitment, is designed to test the role of nelfinavir in improving DFS when added to the therapeutic combination of chemoradiation and image-based brachytherapy.

Objective

The primary objective is to report on 3-year DFS in patients with stage III cervical cancer receiving standard chemoradiation and brachytherapy in combination with nelfinavir when compared with standard treatment (chemoradiation and brachytherapy). Secondary objectives are to report the effect of nelfinavir on loco-regional control, OS, toxicity and quality of life (QOL). In addition, pharmacokinetics and translational research studies are planned. The impact of nelfinavir on hypoxic status and efficacy of the drug in reference to cluster of differentiation 4 (CD4), cluster of differentiation 8 (CD8), programmed cell death ligand 1 (PD-L1) and natural killer 1.1 (NK1.1) expression will be studied.

METHODS AND ANALYSIS

Trial design

The trial is a single centre, open-label, parallel-group, 1:1 randomised phase-III study to evaluate the efficacy of an investigational drug (nelfinavir) in improving DFS in patients diagnosed with International Federation of Gynecology and Obstetrics stage III cervical cancer (FIGO 2018).

Research setting

The NELCER study will be conducted at the Advanced Centre for Treatment Research and Education in Cancer (ACTREC) and Tata Memorial Hospital (TMH) of Tata Memorial Centre, Mumbai, India, a grant-in-aid

institution under the Department of Atomic Energy, Government of India.

Participant eligibility

Patients older than 18 years of age with a histologically proven diagnosis of cervical cancer and FIGO 2018 stage III (squamous, adenocarcinoma or adeno-squamous histology) will be included. Patients should have adequate bone marrow, liver and kidney function defined as neutrophil count ≥ 1500 , platelet count $\geq 100\,000$, total bilirubin < 1.5 times the upper limit of normal (ULN), aspartate transaminase and alanine aminotransferase $\leq 2.5 \times$ ULN and creatinine < 1.5 ULN or creatinine clearance > 60 mL/min/1.73 m². They should not have received prior chemotherapy or irradiation to the pelvis, should not have recent (< 3 months) severe cardiac disease (arrhythmia, congestive heart failure, infarction) and should have the ability to understand and sign an informed consent document. Extra biopsy for translational research and blood collection for pharmacokinetic studies exclusion criteria includes patients with newly diagnosed or uncontrolled diabetes mellitus with glycosylated haemoglobin $> 6.5\%$ or fasting blood sugar level of ≥ 126 mg/dL on primary evaluation. Patients who are taking any drugs which have pharmacological interaction with nelfinavir will be excluded from the study. These include terfenadine, cisapride, sildenafil, lovastatin or simvastatin and medication metabolised by the CYP3A4 isoenzyme. Antiarrhythmics (amiodarone, quinidine), neuroleptics (pimozide), sedative/hypnotic agents (midazolam, triazolam), ergot derivatives, β -Hydroxy β -methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (atorvastatin), rifampicin, rifabutin, felodipine, nifedipine). Patients with coexisting malignancy, HIV, haemophilia and those with reduced creatinine clearance (less than 50 mL/min), pregnant and lactating patients and those with a history of psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule, will not be taken for inclusion in the study.

Outcomes

Primary outcome measures is to evaluate improvement in 3-year DFS and 3-year OS by the addition of nelfinavir to patients with advanced carcinoma of cervix and receiving standard chemoradiation (cisplatin and radiotherapy). Secondary outcome measures are to evaluate change in locoregional control rates at 3-year, OS at 5-year in test and control arms, incidence of grade 3/4 adverse events in patients with advanced carcinoma of cervix and receiving nelfinavir along with standard chemoradiation (cisplatin and radiotherapy), changes in Akt levels in the tumour from pre-nelfinavir to post external beam radiotherapy (EBRT), change in tumour hypoxia using multifunctional positron emission tomography (PET)/MRI, interindividual variability of volume of distribution C_{max} (maximum concentration) will be estimated,

interindividual variability of clearance of nelfinavir clearance (litres per hour) and half-life (hours) will be estimated.

Study interventions

Standard arm (chemoradiation)

Patients will undergo contrast enhanced CT for radiation treatment planning. Target delineation will be performed to include uterus, cervix, vagina with at least 2 cm caudal margin from lower extent of palpable disease, parametrium and pelvic lymphnodes upto the bifurcation of common iliac. When involved paraaortic nodes will be included. No prophylactic paraaortic irradiation is planned. The total dose of pelvic EBRT will be 45–50 Gy/23–25 #/4.5–5 weeks. Pelvic EBRT will be delivered preferably by intensity-modulated external radiation with 6 MV/15 MV photon beams as per standard guidelines. Involved nodes will receive an EBRT dose of 55–60 Gy through simultaneous integrated boost. All patients will receive concurrent cisplatin, administered weekly with a dose of 40 mg/m² by intravenous infusion over 1 hour, 2–4 hours prior to starting EBRT.

Biopsies will be performed at two different time points—one before treatment initiation and another at first brachytherapy. Patients will be evaluated by the concerned investigators every week during radiation therapy, and all the toxicities will be documented according to the Common Terminology Criteria for Adverse Events (CTCAE) V.4.0. All patients will undergo image-based brachytherapy with an aim to receive a total cumulative dose to 90% vol of high risk clinical target volume (D90) > 85 Gy₁₀ with 2 cm³ bladder, rectum, sigmoid and bowel doses not exceeding 90 Gy₃, 75 Gy₃, 75 Gy₃ and 75 Gy₃. The use of brachytherapy technique, that is, intracavitary or intracavitary-interstitial will be guided by the tumour response and organ at risk dose. Standard guidelines for reporting or prescription will be followed and all treatment will be completed in 56 days (8 weeks).

Intervention arm (nelfinavir plus chemoradiation)

Nelfinavir (Pfizer) will be administered orally to a dose of 1250 mg two times a day, 7–10 days before the start of chemoradiation and will continue for the entire duration of EBRT. Nelfinavir will be administered with food to increase bioavailability. Chemoradiation and brachytherapy will be delivered as in the standard arm. The study drug will continue for a total of 42 days until the completion of EBRT. The trial schema is summarised on [figure 1](#).

Study investigations

All patients will undergo a baseline MRI of the abdomen and pelvis. Extra sequence acquisition of MRI and PET scan as part of research (like blood oxygen level dependent MRI) will be performed on 60 patients (30 in each arm). As MRI will be used for response assessment and brachytherapy planning, in addition to axial images, sagittal and coronal images will be obtained at

Study Schema

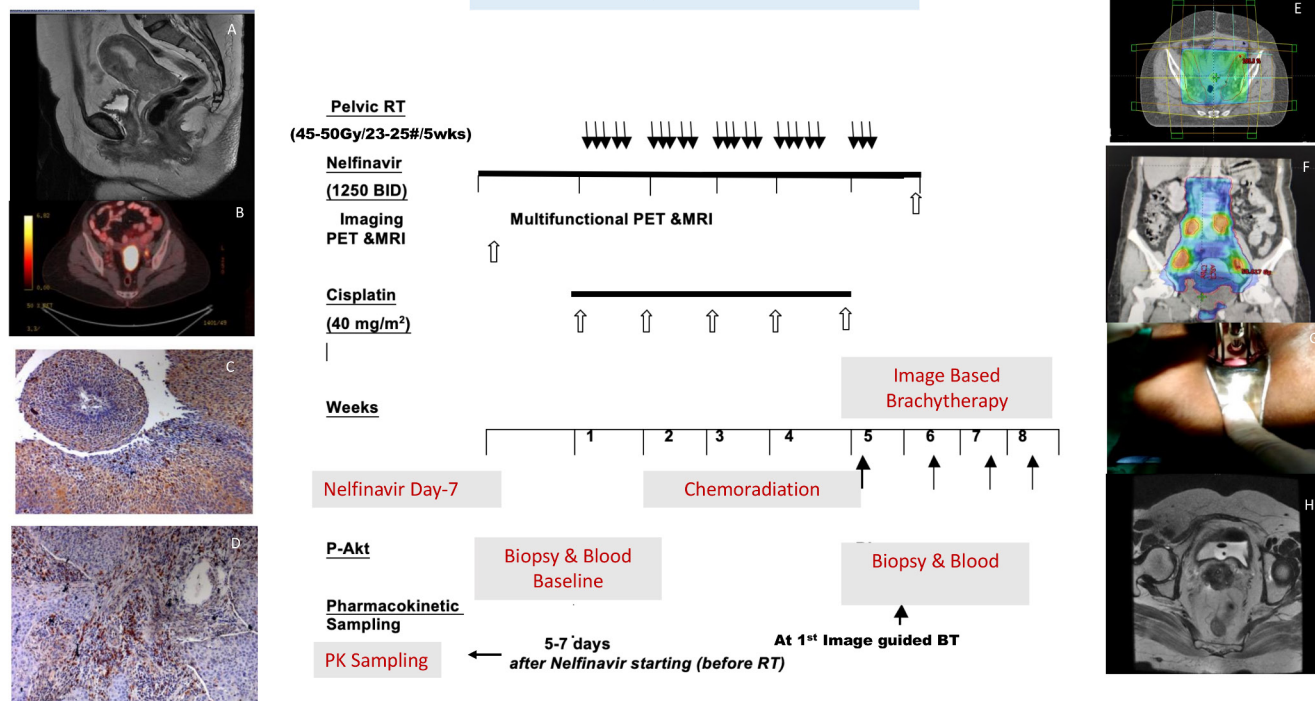


Figure 1 Figure depicting the workflow of the clinical trial. At baseline patients undergo (A) MRI of the pelvis and (B) positron emission tomography (PET) scan for clinical staging. Additional research biopsy is obtained for performing immunohistochemistry (C, D). Following this patients are started on allocated intervention. Panel E and F demonstrate the clinical treatment provided to the patients with radiation along with weekly concurrent cisplatin following which patients undergo image guided brachytherapy. Panel E and F depicts the brachytherapy procedure and imaging. P-Akt, phosphorylation of protein kinase B. RT, radiotherapy; PK, pharmacokinetic; BT, brachytherapy.

each examination. All patients will undergo blood sugar evaluation, ECG and lipid profile at baseline, treatment completion and 6 months of follow-up. Blood sugars and liver function will also be monitored every 2 weeks while on chemoradiation.

Follow-up

Response assessment will be done clinicoradiologically at 6 months. MRI of the abdomen and pelvis will be performed at 6 months to demonstrate loco-regional response. This will include (T1W, T1W+contrast, T2W, diffusion and perfusion scan, obtained in axial, coronal and sagittal sequences). Three-dimensional measurements will be accepted of residual tumour. For nodal disease, residual size will be documented. Patients with suspicion of residual disease in the cervix will undergo a biopsy. Subsequently, patients will be followed up with an abdominopelvic MRI at 1 and 2 years from treatment completion. All patients with local recurrence will undergo a biopsy for confirmation. Annual chest X-ray will also be performed to rule out distant metastasis.

Translational research studies

5 mL blood sample and tumour biopsies will be taken before nelfinavir use and after EBRT on the day of first intracavity radiation therapy (ICRT). Phosphorylated Akt and total Akt will be determined. Multifunctional

PET and MRI will be done in the first 30 patients of each arm (total of 60 patients) to gain insight into changes in tumour maximum standardized uptake value (SUV max) and hypoxia following treatment with nelfinavir. In addition, PDL-1, CD4, CD8 and NK 1.1 will be estimated semiquantitatively in biopsies obtained at baseline and brachytherapy.

Pharmacokinetic studies

Population pharmacokinetics of nelfinavir will be studied in the group of patients receiving nelfinavir. For this, a sparse sampling strategy will be followed. Four blood samples will be collected from each patient at a steady state (7–10 days after the start of nelfinavir). A random grouping table will be used to allot patients to one of the groups for pharmacokinetic sampling. The sampling time points are so selected to cover the interval of drug administration. In addition, one blood sample will be collected before the last dose of administration of cisplatin.

Efficacy and Safety assessments

The use of nelfinavir is associated with an increase in the frequency of stools, nausea, vomiting, rash, tingling, numbness in hand and feet and tiredness. Nelfinavir is also known to cause minor muscle pain, inflammation, tingling, numbness in the hands and feet. The study drug nelfinavir may also cause low blood counts, mandating

blood transfusions. In a small proportion of patients, low blood counts may cause fever and infection. These side effects are caused by standard treatment (concurrent chemoradiation) and hence will be listed as adverse events irrespective of arm allocation. However, any hospitalisation because of the above side effects will constitute serious adverse events (SAE).

Accrual and duration of study

The estimated rate of accrual for this study is 5–7 patients a month. Thus, patient accrual is expected to be completed in 5 years. The total duration of the study is for 8 years, as the patients will be followed up for three more years after the accrual of the last patient to study the 3-year DFS. The study had initiated recruitment in January 2018.

Randomisation

Randomisation is based on a 1:1 allocation ratio generated using Stata 14 software and uses permuted block randomisation technique. All randomisation will be done through the epidemiology and clinical trials unit at Tata Memorial Centre, ACTREC. Once randomised, patients will be treated according to the allocated arm.

Data collection and management

All study related data of the participants will be collected on physical case report form (CRF) and transferred to eCRF (REDCap). All data entry will be performed by authorised personnel. European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C-30), and its Quality-of-Life questionnaire cervical cancer module (Cx-24) will be used to document the patient's QOL at each visit.

Statistical considerations and sample size calculation

The study's primary endpoint is 3-year DFS which will be defined as time in months from date of randomization to date of any recurrence/relapse/death due to any cause. This is a superiority trial design that intends to demonstrate a 3-year improvement in DFS from 65%^{6 9 39} to 75%. Using a group sequential design, considering a HR of 0.66, 1:1 randomisation is planned. A safety analysis report is scheduled at 50% recruitment. Safety will be assessed in terms of the following: diarrhoea > grade 3, which does not settle with optimal use of antidiarrheal medication for more than 3 days or any ≥ grade 4 haematological toxicity. The test regimen will be deemed to be associated with higher toxicity if the incidence of the above toxicities is different with a p value of <0.01. An interim analysis is planned for futility at 32 events (or 190 patients), and the final analysis is planned at 192 events. With two-sided type I error of 0.05 and type II error of 0.20, a total sample size of 348 patients is planned. The details of statistical assumption are provided in online supplemental appendix A.

Data monitoring

The study will be monitored by the Institutional Data Safety Monitoring Sub-Committee, independent from

investigators and the sponsor, and a report will be submitted to Institutional Ethics Committee (IEC). A continuing review application will be submitted by PI at a regular interval (annually) to the IEC to continue the trial.

Events reporting

All adverse events occurring during the study will be recorded using CTCAE V.4.0. All SAE will be reported to the IEC within 24 hours of the occurrence. SAE's related to disease progression post 6 months of study treatment, administration of salvage treatment and death due to disease progression will be exempted from reporting to the IEC.

Patients and public involvement

This trial was planned without patient and public involvement at any stage of the study design, initiation, and conduct.

ETHICS AND DISSEMINATION

Research ethics approval

The IEC-I of TMH, Mumbai has approved the study (reference number: IEC/0315/1543/001).

Informed consent

The principal investigator (PI) or personnel delegated by the PI before study-related investigations will obtain written informed consent from the eligible patients. Patients will be given appropriate time to decide regarding study participation. Randomisation will be performed after consent. The study does not involve minors, pregnant mothers and neonates. Additional consent for research on tumour tissue and blood will be obtained. English version of the participant information sheet and informed consent form, and additional consent for biological tissue sampling or banking for research can be found as the supplemental material of the manuscript

Confidentiality

Each participant will receive a study number allocated for identification purposes. No personal information of the participants will be shared with anyone other than the study team members. All forms will be confidentially maintained and will be signed by the principal or coprincipal investigator. The final responsibility of data handling will be the responsibility of the PI of the study.

Access to data: All study-related clinical data of the participants will be securely maintained and will be available to study investigators only.

Dissemination policy

The results obtained from the study will be available to healthcare professionals and the public through open peer-reviewed scientific journals, conference presentations .

Ancillary and post-trial care

The study has been budgeted to provide patient costs of medical treatment in case of severe adverse events during study participation.

In summary, this phase III trial is designed to investigate the impact of addition of repurposed drug nelfinavir in improving 3-year DFS in women with LACC.

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manuscript preparation and final approval. LN contributed in executing protocol, review of contents of the protocol, manuscript preparation and final approval. ShS contributed in drafting final protocol, review of contents of the protocol, manuscript preparation and final approval. PrP contributed in drafting final protocol, review of contents of the protocol, manuscript preparation and final approval. PaP in drafting final protocol (radiology), review of contents of the protocol, manuscript preparation and final approval. JG contributed in drafting final protocol, review of contents of the protocol, manuscript preparation and final approval. SR contributed in drafting final protocol, review of contents of the protocol, manuscript preparation and final approval. SG contributed in drafting final protocol, review of contents of the protocol, manuscript preparation and final approval. RE contributed in review of contents of the protocol, manuscript preparation and manuscript review and submission. UM contributed in drafting final protocol, review of contents of the protocol, manuscript preparation and final approval. SG contributed in drafting final protocol, review of contents of the protocol, manuscript preparation and final approval.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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