Study Title: Feasibility, safety, and efficacy of concomitant curcumin in patients undergoing palliative radiotherapy for FIGO stage IIIB–IVA cervical cancer: An open-label pilot trial

Short title: CuPRAC

Phase of the trial: Phase I

CTA Number: ET-CT-0036

Protocol No.: 001/21/SoP

Version No.: 6

National Principal Investigator (NPI): Dr. Wondimagegegn Tigneh

Trial Site: Tikur Anbesa Specialized Hospital

Sponsor: Addis Ababa University, College of Health Science

Ethics Approval date: NA

Submission Date to EFDA: 11/11/2022

EFDA Status of trial (Approval or Rejection): Approved **Date:** 24/07/2024

Study Rationale

The rationale for combining curcumin with radiotherapy in the context of treating stage IIIB-IVA cervical cancer aims to enhance therapeutic efficacy while mitigating treatment related toxicities. Envisaged synergies between curcumin and radiotherapy, coupled with the potential reduction in radiation-induced toxicities, offer a promising pathway to advance treatment strategies and enhance patient care standards in these challenging clinical situations. To enhance the bioavailability, novel curcumin formulation, CurQfen™ or curcumagalactomannoside (CGM), is used.

General objective / Study aims

- The primary goal is to assess the preliminary efficacy of curcumin in conjunction with standard of-care palliative radiotherapy in patients with locally advanced cervical cancer (International Federation of Gynecology and Obstetrics (FIGO) IIIB-IVA)

Primary objectives

Objective
• To assess the efficacy of curcumin in combination with palliative radiation therapy of FIGO stage IIIB-IVA cervical cancer patients as determined by the objective response rate • To assess the feasibility of the trial as determined by the concomitant curcumin palliative radiation fidelity rate
Outcome measures
• Trial Feasibility: Treatment fidelity rate: proportion of participants who received the study treatment as planned • Efficacy: Objective response rate (ORR): proportion of participants having a complete response (CR) or partial response (PR) as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Secondary Objectives and Outcome Measures

Objective
• To evaluate the efficacy of curcumin in combination with palliative radiation therapy of FIGO stage IIIB-IVA cervical cancer patients as estimated by the disease control rate • To evaluate the efficacy of curcumin in combination with palliative radiation therapy of FIGO stage IIIB-IVA cervical cancer patients as estimated by the rates of applicable treatment outcome measures routinely used in the local clinical practice setting (provided that such outcome measures are available) • To assess the safety of concomitant curcumin administration in patients undergoing palliative radiation therapy for FIGO stage IIIB-IVA cervical cancer • Assess the tolerability of concomitant curcumin administration in patients undergoing palliative radiation therapy for FIGO stage IIIB-IVA cervical cancer • To determine the pharmacokinetic (PK) characteristics of CGM curcumin in patients with advanced cervical cancer

- To assess the change in health-related quality of life (QoL) from baseline in FIGO stage IIIB-IVA cervical cancer patients treated with concomitant curcumin palliative radiotherapy
- To assess trial feasibility proposed trial
- To compare the safety and efficacy between concomitant curcumin palliative radiotherapy and a matched external control group of palliative radiotherapy (provided that adequate historical/external control as well as trial data is available)

Outcome measures

- Efficacy: Disease control rate (DCR): proportion of participants having a complete response (CR) or partial response (PR) or stable disease (SD) as defined by the RECIST 1.1 criteria
- Safety: Treatment-emergent adverse event (TEAE): any event not present prior to the initiation of the study treatment or any event already present that worsens in either intensity or frequency following exposure to the study treatment. TEAEs are characterized by type, frequency, severity (as graded by the National Cancer Institute Common Terminology. Criteria for Adverse Events (NCI CTCAE) v.5), timing, seriousness, and relationship to study treatment, including laboratory and vital sign abnormalities.
- Tolerability:
    - Dose interruption: a zero dose given on one or more days on which the protocol specified dose is non-zero, followed by resumption of dosing
    - Dose reduction: a decrease in dose from the protocol planned starting dose or a decrease from the previous non-zero dose, even if this decrease has been directly preceded by an interruption
    - Dose intensity (DI): cumulative dose divided by the treatment duration in weeks.
    - Relative dose intensity (RDI): dose intensity (actual DI) divided by the protocol weekly dose (planned DI), expressed as a percentage

- Pharmacokinetics (PK): Plasma concentrations and derived PK parameters (depending on the sufficiency of available data) of CGM curcumin including
    - Maximum plasma concentration (Cmax): highest observed drug concentration observed in plasma over all PK sample concentrations.
    - Time to maximum plasma concentration (Tmax): time when the Cmax occurs.
    - Area Under Curve (AUCτ): area under the concentration-time curve from time zero to the time of the end of dosing interval.
    - Half-life (T1/2): time required for the drug concentration to decrease by a factor of one-half in the terminal phase.
- QoL: QoL scores based on European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire—Cervical Cancer (EORTC QLQ-CX24) & EORTC core quality of life questionnaire (EORTC QLQ-30)
- Trial Feasibility:
    - Recruitment rate: proportion of those who participate in the trial who were approached as potential participants
    - Assessment completion rates: proportion of assessments that could be completed as planned
    - Attrition rate: proportion participants who withdraw from the study.
- Comparative safety and efficacy assessment
    - Safety: Type, frequency and severity of adverse events laboratory and vital sign abnormalities
    - Efficacy: clinical benefit rates as per available treatment outcome measures used in the standard clinical practice in the local setting

Study Design

- The trial is a prospective open-label, single-arm, single-center exploratory trial.

Study Population

- Adult International Federation of Gynecology and Obstetrics (FIGO) Stage IIIB-IVA cervical cancer patients receiving standard-of-care (SOC) palliative radiation therapy as per the local treatment guideline

Eligibility Criteria

Inclusion Criteria:

- Age >18 years old (Adult, Older Adult)
- Histologically confirmed squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma of the cervix, FIGO stage IIIB-IVA
- Undergoing for standard of care palliative radiotherapy without chemotherapy as per the local treatment guideline
- Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, 2
- Adequate liver function (aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN (Upper Limit of Normal); total serum bilirubin ≤1.5 x ULN), blood cell counts (absolute neutrophils count ≥1.500/mm3; platelet count ≥100.000/mm3; hemoglobin ≥10.0 g/dL), renal function (serum creatinine ≤1.5 x ULN; estimate creatinine clearance (Cockroft-Gault) ≥60 mL/min)
- Participants must have measureable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) V1.1.
- Agree to use an effective form of contraception (e.g., true abstinence (not periodic abstinence), barrier contraception, highly effective hormonal contraception) if the participant is of child bearing age
- Give informed consent

Exclusion criteria:

- Cervical cancer patients who are candidates for single dose palliative radiotherapy
- Patients with severe or bilateral hydronephrosis
- Evidence of distant metastases
- Receiving any other investigational agent concurrently or within the last 4 weeks before enrollment
- Received any previous pelvic radiation or chemotherapy for cervical cancer
- Underwent surgery in the four weeks prior to the enrolment date or scheduled to undergo surgery within eight weeks after end of treatment
- Currently using of any chemotherapy or scheduled to receive within eight weeks after end of treatment
- Known allergy to turmeric or its derivatives (ginger, curry, cumin, or cardamom)
- Known allergy to fenugreek, peanut, soy, lentil, pea, bean, and chickpea
- Presence of conditions that precludes the safe administration of the trial intervention and/or prohibit adequate compliance to study requirements.
- Pregnant and breastfeeding women
- Participants with circumstances that will not permit completion of the study or required follow-up. For instance, if travel to and from treatment site is an issue.

Study Duration

- 12 months

Investigational Medicinal Product

CGM - a patented and registered curcumin formulation

Intervention(s)

- Formulation: Curcumin (CGM) capsules, manufactured in a GMP (good manufacturing practices) facility
- Dose: A daily dose of 1000 mg of CGM curcumin will be given orally in four divided doses (250 mg four times a day) beginning one week prior to the start of the standard palliative radiotherapy for locally advanced cervical cancer patients available at TAHRC.
- Route of administration: Oral

Sample size

- 19 adult patients

Evaluator's Risk/Benefit Assessment:

- When considering the potential benefit compared to the risk of the intervention, the possible improvement in the patient and the limited side effect of natural product with a good safety history outweighs the chance of disease exacerbation and hence the current trial is approved, with due consideration given to the safety of the participants. and the trial will follow the principles of Good Clinical Practice.