Clinical Trial Details (PDF Generation Date :- Sun, 27 Nov 2022 11:52:57 GMT)

CTRI Number	CTRI/2019/02/017548 [Registered on: 08/02/2019] - **Trial Registered Prospectively**
Last Modified On	18/03/2021
Post Graduate Thesis	No
Type of Trial	Interventional
Type of Study	Drug
Study Design	Single Arm Study
Public Title of Study	Liquid biopsy for treatment guidance in cancer
Scientific Title of Study	To evaluate the efficacy of therapy administered based on guidance obtained from integrative molecular analysis of cell free nucleic acids and in vitro chemosensitivity analysis of circulating tumor cells, aimed at improving availability of therapy options and treatment outcomes in relapsed/refractory metastatic solid organ tumors with unavailability of de novo tissue biopsies.

Secondary IDs if Any

Secondary ID	Identifier
NIL	NIL

Details of Principal Investigator or overall Trial Coordinator (multi-center study)

Details of Principal Investigator	
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Source of Monetary or Material Support

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> 1) Datar Cancer Genetics Limited, F-8, D Road, MIDC, Ambad,Nasik, Maharashtra 422 010
> 2) Canconnect Foundation, Flat No.12, Ameya Sankul, B Wing, Sharanpur Road, Nasik, Maharashtra 422 005

Primary Sponsor

Primary Sponsor Details	
Name	Datar Cancer Genetics Limited
Address	F-8, D Road, MIDC, Ambad, Nasik, Maharashtra 422 010
Type of Sponsor	Other [Molecular Laboratory and Research Centre]

Details of Secondary Sponsor

Name	Address
Canconnect Foundation	Flat No.12, Ameya Sankul, B Wing, Sharanpur Road, Nasik, Maharashtra 422 005

Countries of Recruitment

List of Countries
India

Sites of Study

Name of Principal Investigator	Name of Site	Site Address	Phone/Fax/Email
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Dr Raj Nagarkar	HCG Manavata Cancer Centre	Ground Floor, Behind Shivang Auto, Mumbai Naka, Nashik 422001 Nashik MAHARASHTRA	9823061929 drraj@manavatacancercentre.com

Details of Ethics Committee

Name of Committee	Approval Status	Date of Approval	Is Independent Ethics Committee?
Datar Cancer Genetics Limited Ethics Committee	Approved	01/11/2018	Yes
Manavata Clinical Research Institute Ethics Committee	Approved	30/01/2019	Yes

Regulatory Clearance Status from DCGI

Status	Date
Not Applicable	No Date Specified

Health Condition / Problems Studied

Health Type	Condition
Patients	Neoplasms

Intervention / Comparator Agent

Type	Name	Details
Intervention	FDA approved off-label and repurposed drugs	This trial is not for any new drug or molecule. In this trial chemotherapy and nonchemotherapy drugs currently approved by FDA and available in the market will be administered at the standard recommended dose to the study

		participants.These drugs will be selected based on results of in-vitro and molecular analysis of patients blood sample. In case of toxicity the dose may be reduced.
Comparator Agent	Not Applicable	Not Applicable

Inclusion Criteria

Inclusion Criteria	
Age From	18.00 Year(s)
Age To	70.00 Year(s)
Gender	Both
Details	For Inclusion, an individual must meet all of the following criteria: 1.Age – 18 to 70 years (male or female); 2.Refractory/relapsed, advanced/unresectable/metastatic histologically documented solid organ malignancy 3.Should have ECOC score of maximum 2 and a life expectancy of at least 3 months 4.Patient should have progressed on at least one SOC lines of therapy OR have no further SOC option/ option is beyond financial reach OR there must not be other approval/standard therapy available that has been shown to prolong overall survival OR therapy naïve patients where no agreed upon standard of care (SOC) options exist OR patients who cannot receive other standard therapy that has been shown to prolong overall survival due to medical issues will be eligible. (SOC lines would include surgery / RT / Cytotoxic therapy / targeted therapy) 5.If the patient is currently receiving therapy, the clinician must have assessed that the current therapy is no longer benefitting the patient prior to enrolling 6.Patient should be willing and fit for requisite blood or body fluid sampling required for study purpose e.g. ascitic fluid / pleural fluid/ CSF etc. as the case may be; 7.Patient should be physically and financially able to undertake treatment as may be advised after the analysis by DCGL with good compliance history in the past; 8.Patient should be willing and ready for baseline PET Scan and/or CT and/or USG and/or MRI and follow-up scans (usually the first follow-up scan is after 30 days followed by further scans at 75 days and 120 days); 9.Patient is willing and can tolerate cytotoxic and targeted therapy (labelled / off-label / repurposed / natural tumor inhibiting supplements); 10.Female patient is not pregnant / lactating; 11.Provision of signed and dated informed consent form 12.Stated willingness to comply with all study procedures 13.Patients must have measurable disease on radiological imaging post biopsy to monitor treatment response 14.Adequate organ function defined as: a)Absolute neutrophil count ? 1,000/?L b)Platelet count ? 50,000/?L c)Total bilirubin ? 1.5x institutional upper limit of normal (IULN) d)AST and ALT ? 2x IULN e)Creatinine ? 2x IULN f)Creatinine clearance ? 45 mL/min/1.73m2 for participants with creatinine levels above IULN g)Albumin ? 2.5 g/dL h)Prothrombin time (PT) and PTT 80% to 120% of institutional normal range i)Left Ventricular Shortening Fraction (LVSF) ? 28% confirmed by echocardiogram (ECHO), or Left Ventricular Ejection Fraction (LVEF) ? 45% confirmed by echocardiogram or Multiple Uptake Gated Acquisition (MUGA).

Exclusion Criteria

Exclusion Criteria	
Details	1.Patients who fail to meet all of the iclusion criteria will be excluded. Failing to meet any single criteria would be sufficient grounds for exclusion. 2.Prior malignancy other than types included in study

	3.Active or latent hepatitis B or active hepatitis C (test within 8 weeks of screening), or any uncontrolled infection at screening 4.Human Immunodeficiency Virus (HIV) positive test within 8 weeks of screening. 5.Serious co-morbidities such as, but not limited to severe cardiac failure severe pulmonary compromise or severe and active infections, HIV, HPV, HBV, HCV, Tuberculosis etc. 6.Patient has an investigational medicinal product within the last 30 days prior to screening. 7.Pregnant or nursing women. 8.Psychiatric illness with potential to affect study compliance

Method of Generating Random Sequence	Not Applicable
Method of Concealment	Not Applicable
Blinding/Masking	Open Label

Primary Outcome

Outcome	Timepoints
Objective Response Rate (ORR): To evaluate the proportion of patients exhibiting objective response (OR) study guided therapy approach. OR includes Complete Response (CR) as well as Partial Response (PR). ORR is evaluated in compliance with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria for solid tumors.	First after minimum two lines of therapy or one month, whichever is earlier. Therapy and follow up will be continued further

Secondary Outcome

Outcome	Timepoints
1. Clinical Benefit Rate (CBR): 2. Time to Tumor Progression (TTP): 3. Progression Free Survival (PFS): 4. Overall Survival (OS): 5. Event Free Survival (EFS): 6. Quality of Life (QOL): 7. Any other incidental or significant observation or finding relevant for the science or clinical management of cancer.	Dependent on each parameter

Target Sample Size	**Total Sample Size=**66 **Sample Size from India=**66 **Final Enrollment numbers achieved (Total)=**Applicable only for Completed/Terminated trials **Final Enrollment numbers achieved (India)=**Applicable only for Completed/Terminated trials
Phase of Trial	Phase 2/ Phase 3
Date of First Enrollment (India)	11/02/2019
Date of First Enrollment (Global)	No Date Specified
Estimated Duration of Trial	**Years=**1 **Months=**0 **Days=**0
Recruitment Status of Trial (Global)	Not Applicable
Recruitment Status of Trial (India)	Open to Recruitment
Publication Details	No publication yet out of this study
Brief Summary	**Introduction:**

For majority of advanced/metastatic solid organ malignancies the survival rates become dismal with relapse /recurrence. In the U.S., pancreatic cancer is 9th or 10th most commonly diagnosed cancer (depending on gender), but the fourth leading cause of cancer death in men and women. Patients with metastatic pancreatic cancer have been considered incurable and rarely survived more than one year. The 5-year survival rate for stage III pancreatic cancer is about 3% while that of Stage IV is about 1%. Similar dismal survival rate of 3% is observed for advanced stage cancers of the liver and intrahepatic bile duct. For advanced esophageal cancer the 5-year survival rates are 5%. Stage IV stomach cancer is the most advanced form of the disease where the cancer has metastasized beyond the stomach into other areas of the body. About four out of five stomach cancers in the United States are diagnosed after the cancer has spread to other areas of the body. The five-year survival rate for those diagnosed with stage IV stomach cancer is 4 percent.

Esophageal cancer is the fourth common cause of cancer-related deaths in India. It is prevalent among both men and women. Squamous cell carcinoma (SCC) accounts for up to 80% of these cancers, although adenocarcinoma is on the increase due to changing lifestyles. Approximately 47,000 new cases are reported each year and the reported deaths reach up to 42,000 each year in India. The 5-Year relative survival rate for disease with distant spread is 5%

In glioblastoma, the most common length of survival following diagnosis is 12 to 15 months, with fewer than 3% to 5% of people surviving longer than five years. Without treatment survival is typically 3 months.

Background:

The most crucial aspect of a successful treatment of a cancer is selection of effective therapy. For patients with advanced refractory solid organ malignancies, therapy is limited by fewer treatment options and therapy resistance. Eventually, most of these patients run out of beneficial treatment options.

Responses to cancer therapy and outcome are governed by various factors which may either be genetic, epigenetic or environmental. Genetic alterations and differential regulations in metabolic pathways contribute to chemo resistance in tumor cells whereas pharmacogenetics, lifestyle and health status contribute to safety, activity and metabolism of drugs. Owing to various combinations of intrinsic and extrinsic factors, both in hosts and in malignancies, therapy safety and efficacy are not universally constant. Due to these reasons, selection of chemotherapeutics based on anecdotal or empirical basis are reported to be associated with risks of failure.

Molecular profiling can provide diagnostic, prognostic, or treatment-related information to guide cancer patient management. Large-scale research projects have elucidated genomic landscapes of many cancers but have provided limited insight into the clinical utility of genomic testing. Still, these efforts have led to development of precision oncology approach in which treatment is tailored as per molecular characteristics of the tumor. This approach has potential to improve patient outcomes by selecting appropriate therapy, reducing side effects and reducing treatment with therapies from which clinical benefit is unlikely.

Impact of molecular analysis-based therapy has been clearly established in malignancies like non-small cell lung cancer (NSCLC), colorectal cancer and breast cancer. Multiple studies have indicated encouraging outcomes from therapy selected based on molecular profiling.

A pilot study has shown that comprehensive molecular profiling can be used to find molecular targets in patients with refractory metastatic cancer. In 18 of 66 patients treated with a molecularly guided therapy, the approach resulted in a longer PFS on a molecular profiling suggested regimen than on the prior regimen on which the patient had just experienced progression. Exploratory analysis demonstrated that this PFS ratio correlated with the clinical parameter of overall survival.[1]

Another study in patients with refractory breast cancer showed that tumor profiling resulted in a revision of the original treatment decision for all patients and tumor profiling-based therapy resulted in a clinical benefit in 52% of heavily pretreated patients.[2]

Similar outcomes were reported in pancreatobiliary cancer (clinical benefit in 37.5%) and adenoid cystic carcinoma (response in 4/11) patients treated in line with tumor profiling results.[3, 4]

However, such precision oncology-based approach is currently implemented only for labelled or limited off-label targeted therapy selection and not for cytotoxic chemotherapy. And as patients fail on multiple lines of therapies, availability of established molecular biomarkers to act on declines. For example, NSCLC with sensitizing EGFR mutation gets treated with first or second generation TKI. After failure of this first line targeted therapy, third generation EGFR TKI becomes available for

patients with new mutation EGFR T790M. However, after failure of this therapy, current approved biomarker list has no next line of targeted therapy to offer.

Also, targeted therapy selected based on a single biomarker testing may not always be effective due to additional molecular alteration in other genes. RNA gene expression analysis may prove to have additive clinical utility as it can potentially indicate cell cycle pathway dysregulations.

For such extensive molecular and in vitro chemosensitivity analysis, it is imperative to have de novo and adequate fresh tissue biopsy sample. As for tissue biopsy, though recognized as the current gold standard for tumor diagnosis and molecular analysis, it also has its disadvantages due to the severe clinical complications resulting from sampling and the result bias caused by tumor heterogeneity. The most important, sometimes it is very difficult to obtain tissues, especially from terminal cancer patients.

The poor performance status of patients e.g. many advanced NSCLC patients, limits the role of uncomfortable interventional biopsy procedures. Moreover, a significant barrier to molecular testing is the availability of an adequate amount of tissue (e.g., tumor cellularity and size of the specimen) due to increasing diagnostic demands and declining amounts of tissue delivered per patient. Up to 80% of NSCLC patients with advanced disease will only have tissue from small biopsies or cytology, limiting the ability to perform additional tests, and as many as 31% of patients do not have accessible tissue. Even when tissue can be collected, preservation methods such as formalin fixation can display high levels of C > T/G > A transitions in the 1–25% allele frequency range, potentially leading to false positive results for molecular assays. Although this has improved for

individual gene mutations, there are still limitations for next generation sequencing (NGS) analyses.

Thus, it is necessary to have noninvasive modality with high specificity and sensitivity for providing molecular blueprint of tumor and to dynamically and timely monitor tumor progression.

Tumor tissue will release tumor cells, DNA and exosomes into the body fluid, which offers a test approach called “liquid biopsy”. It means diagnosis and monitoring tumor initiation and progression by capturing and detecting biomarkers (eg. cell, DNA, RNA and protein) in body fluid (eg. blood, ascitic fluid, pleural fluid). The greatest strength of liquid biopsy is to allow doctors to noninvasively take repeated tumor samples. Other advantages include fewer side effects, ease of operation, rapid testing speed, decreasing the diagnosis bias from tumor heterogeneity and dynamically reflecting tumor progression. With these advantages, liquid biopsy has a wonderful future in the field of detection of actionable molecular artefacts, elucidating drug resistant mechanism, judging prognosis and guiding treatment plan.

We propose a novel approach of precision oncology therapy selection which encompasses not only analysis of DNA alterations in tumor but implements a far more comprehensive approach of integrative simultaneous molecular analysis of tumor DNA and RNA alterations of multiple genes along with chemosensitivity testing of cytotoxic and targeted drugs on patient’s live tumor cells – from only a peripheral blood sample.

Cell free DNA, exosomal RNA, circulating tumor cells will be utilized for unraveling actionable molecular artefacts and chemosensitivity testing to

develop a personalized treatment plan for advanced relapsed/refractory cancer patients with lack of optimal tissue sample.

We anticipate better clinical outcomes of such treatment approach as it is based on comprehensive insight into tumor profile.

Purpose:

Current study aims to achieve the goal of ‘Personalized Therapy’ by customizing the therapy choice as well as the treatment plan based on two factors, viz, the unique molecular biomarker profile of the malignancy in each patient, as well as the in vitro sensitivity of the tumor cells to a panel of approved and off-label therapies.

Analysis of tumor DNA reveals abnormalities such as point mutations, gene amplifications as well as translocations of genome segments which are linked to altered functions – therapies targeted at these alterations are associated with higher rates of success and may be beneficial to the patients. Analysis of tumor RNA provides evidence on differential expression of key genes (e.g., cell cycle regulation, cell-surface receptors, signaling molecules), the polypeptide products of which may be potential druggable targets for therapies, contributing to higher rates of success.

Characterization of molecular biomarkers thus not only helps oncologists better characterize the malignancy, but also presents relevant therapy choices, including off-label use of existing chemotherapeutic drugs. To exemplify, a minor population of NSCLCs carry a deletion in Exon 19 of Epidermal Growth Factor Receptor (EGFR), that renders the tumor chemosensitive to EGFR-Tyrosine Kinase Inhibitors (EGFR-TKI) such as Gefitinib. A proportion of EGFR-mutated NSCLC also exhibit amplification

of the MET gene leading to Gefitinib resistance in these tumors. Such information is vital in selection of relevant efficacious therapy.

Subsequently, the other arm of precision oncology, i.e., in vitro chemo-sensitivity testing, offers direct evidence of action of chemotherapeutics drugs against the patient's own cancer cells. Cancer cells isolated from tumor biopsy are maintained in vitro in culture medium and treated with various drugs (single agents as well as combinations). Analysis of the proportion of apoptotic cancer cells, following treatment, is a direct measure of drug efficacy since cytotoxic chemotherapeutics induce cell killing by apoptosis.

This assay may be used for testing of approved drugs, off-label activities, as well as for evaluating repurposed drugs. Indeed, several repurposed drugs have been reported to potentiate the activity of chemotherapeutics, when used in combination. Repurposed drugs also offer advantages of minimal or no toxicity to the host. Identification of genetic and metabolic signatures, via tumor DNA and RNA, and selection of potential therapy choices, followed by in vitro evaluation of therapy options on tumor derived cells is expected to contribute to a quantum leap in terms of safety, efficacy and probability of favorable prognosis. Several studies have reported the merits of both approaches, when used individually as well as in combination. These approaches may potentially benefit patients with advanced refractory tumors, in whom conventional treatment approaches have failed and no other approved or experimentally described approaches exist.

Aim:

To evaluate the efficacy of therapy administered based on guidance obtained from integrative molecular analysis of cell free nucleic acids and in vitro chemosensitivity analysis of circulating tumor cells, aimed at improving availability of therapy options and treatment outcomes in relapsed/refractory metastatic solid organ tumors with unavailability of de novo tissue biopsies.

Primary Objective:

Objective Response Rate (ORR)

Objective Response Rate (ORR): To evaluate the proportion of patients exhibiting objective response (OR) study guided therapy approach. OR includes Complete Response (CR) as well as Partial Response (PR). ORR is evaluated in compliance with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria for solid tumors.

Secondary Objectives:

1. **Clinical Benefit Rate (CBR):** The proportion of patients whose best response is complete response, partial response or stable disease with study-based therapy approach. CBR is evaluated in compliance with

Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria for solid tumors.

2. **Time to Tumor Progression (TTP):** The length of time from the date of start of study-based treatment until the disease progression with exclusion of death as an event.

3. **Progression Free Survival (PFS):**

The length of time from the date of start of study-based treatment until the disease progression or death from any cause.

4. **Overall Survival (OS):**

The length of time from the date of start of study-based treatment until death from any cause.

5. **Event Free Survival (EFS):**

The length of time from the date of start of study-based treatment till the patient remains free of certain complications or events that the treatment was intended to prevent or delay.

6. **Quality of Life (QOL):**

Evaluation of quality of life on study-based treatment as evaluated with EORTC QLQ-C30 (version 3) and FACT (Functional Assessment of Cancer Therapy).

7. **Any other incidental or significant observation** or finding relevant for the science or clinical management of cancer.

Study Milestones and Schedule:

OUTLINE:

STEP 0 (Screening): Patients undergo evaluation for study eligibility. Consenting patients also undergo collection of blood samples for research purposes. After adequate sample availability and study eligibility compliance, patient enters study.

STEPS 1, 3, 5, 7...(Treatment): Patients are assigned to study- based treatment protocol

STEPS 2, 4, 6.... (Screening): Patients undergo periodic screening and patients experiencing disease progression on the prior Step treatment or who could not tolerate the assigned treatment undergo review of their previous results or fresh sample analysis to determine if another treatment is available.

STEP 8 (Optional Research): Consenting patients undergo end-of-treatment collection of blood samples for research purposes.

After completion of study treatment, patients are followed up every 3 months for 1 years and then every 6 months for 1 year.