Clinical Trial Details (PDF Generation Date :- Wed, 24 Jul 2019 03:13:12 GMT)

CTRI Number	CTRI/2018/01/011353 [Registered on: 16/01/2018] - **Trial Registered Prospectively**
Last Modified On	21/05/2019
Post Graduate Thesis	No
Type of Trial	Interventional
Type of Study	Drug
Study Design	Randomized, Parallel Group Trial
Public Title of Study	Study to assess the efficacy of Durvalumab and/or Tremelimumab in Patients with Hepatocellular Carcinoma
Scientific Title of Study	A Randomized, Open-label, Multi-center Phase III Study of Durvalumab and Tremelimumab as First-line Treatment in Patients with Unresectable Hepatocellular Carcinoma (HIMALAYA)

Secondary IDs if Any

Secondary ID	Identifier
CTRI/2018/01/011353	ClinicalTrials.gov
Protocol No: D419CC00002 Version 1.0, dated 09 AUG 2017	Protocol Number

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

Details of Principal Investigator	
Name	
Designation	
Affiliation	
Address	
Phone	
Fax	
Email	

Details Contact Person (Scientific Query)

Details Contact Person (Scientific Query)	
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Source of Monetary or Material Support

Source of Monetary or Material Support
> AstraZeneca AB, 151 85 Södertälje, Sweden

Primary Sponsor

Primary Sponsor Details	
Name	AstraZeneca AB
Address	151 85 Sodertalje, Sweden
Type of Sponsor	Pharmaceutical industry-Global

Details of Secondary Sponsor

Name	Address
NIL	NIL

Countries of Recruitment

List of Countries
Brazil
Canada
China
France
Germany
Hong Kong
India
Italy
Japan
Republic of Korea
Russian Federation
Spain
Taiwan
Thailand
Ukraine
United States of America
Viet Nam

Sites of Study

Name of Principal Investigator	Name of Site	Site Address	Phone/Fax/Email
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Dr Subramanian Sundaram	V.S Hospital	Director Medical Oncology, Dept. of Medical Oncology, 13-East Spurtank Road Chetpet -600031 Chennai TAMIL NADU	9104442001000 subramanian.vsh@gmail.com

Details of Ethics Committee

Name of Committee	Approval Status	Date of Approval	Is Independent Ethics Committee?
Action Cancer Hospital Ethics Committee	Approved	12/03/2018	No
Artemis Health Sciences Institutional Ethics Committee	Approved	17/01/2018	No
Institutional Ethics Committee H. M. Patel Centre for Medical Care and Education	Approved	12/12/2017	No
Institutional Ethics committee – Clinical Studies, Apollo Hospitals	Approved	21/06/2018	No
Institutional Ethics Committee, Basavatarakam Indo American Cancer Hospital & Research Institute	Approved	21/06/2018	No
Institutional Ethics Committee, Kokilaben Dhirubhai Ambani Hospital & Medical Research Institute	Approved	15/05/2018	No
Institutional Ethics Committee, Netaji Subhash Chandra Bose Cancer Research Institute	Not Applicable	No Date Specified	No
Institutional Ethics Committee, Sparsh Hospital and Critical Care Pvt. Ltd.	Approved	27/06/2018	No
Institutional Ethics Committee, Tata Memorial Hospital	Approved	18/05/2018	No

Institutional Ethics Committee,The Karnataka Cancer Therapy & Research Institute	Approved	09/03/2018	No
Institutional Review Board (Ethics Committee), CMC	Submittted/Under Review	No Date Specified	No
Manavata Clinical Research Institute Ethics Committee	Approved	16/05/2019	No
Shetty's Hospital Ethics Committee	Approved	10/01/2018	No
Sri Venkateshwara Hospital Ethics Committee	Approved	18/01/2018	No
V.S Hospital Ethics Committee	Approved	11/02/2019	No

Regulatory Clearance Status from DCGI

Status	Date
Approved/Obtained	20/12/2017

Health Condition / Problems Studied

Health Type	Condition
Patients	Liver cell carcinoma
Patients	Men and women ?18 years of age with Unresectable Hepatocellular Carcinoma.

Intervention / Comparator Agent

Type	Name	Details
Intervention	MEDI4736 monotherapy, MEDI4736 plus Tremelimumab combination therapy	Drug: Durvalumab Drug: Tremelimumab (Regimen 1) Drug: Tremelimumab (Regimen 2) Drug: Durvalumab (Regimen 1) Drug: Durvalumab (Regimen 2)
Comparator Agent	Sorafenib	Sorafenib

Inclusion Criteria

Inclusion Criteria	
Age From	18.00 Year(s)
Age To	99.00 Year(s)
Gender	Both
Details	1. Age greater than or equal to 18 years at the time of screening 2. Body weight >30 kg 3. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the US, European Union [EU] Data Privacy Directive in the EU) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations. 4. Confirmed HCC based on histopathological findings from tumor tissues 5. Must not have received prior systemic therapy for HCC 6. Must not be eligible for locoregional therapy for unresectable HCC. For patients who progressed after locoregional therapy for HCC, locoregional therapy must have been completed ?28 days prior to the baseline scan for the current study 7. Barcelona Clinic Liver Cancer (BCLC) stage B (that is not eligible for locoregional therapy) or stage C 8. Child-Pugh Score class A 9. ECOG performance status of 0 or 1 at enrollment 10. Patients with HBV infection (as characterized by positive

	hepatitis B surface antigen [HBsAg], detectable HBV DNA, or hepatitis B core antibodies [anti HBc Ab]) and are eligible for inclusion must be treated with antiviral therapy, per institutional practice, to ensure adequate viral suppression (HBV DNA ?2000 IU/mL) prior to enrollment. Note: HBV-positive patients must remain on antiviral therapy for the study duration and must continue therapy for 6 months after the last dose of study medication. 11. Patients with HCV infection must have confirmed diagnosis of HCV characterized by the presence of detectable HCV RNA or anti-HCV antibody upon enrollment (management of this disease is per local institutional practice). 12. At least 1 measurable lesion, not previously irradiated, that can be accurately measured at baseline as ?10 mm in the longest diameter (except lymph nodes, which must have a short axis ?15 mm) with CT or MRI, and that is suitable for accurate repeated measurements as per RECIST 1.1 guidelines 13. Adequate organ and marrow function, as defined below. Criteria “a,” “b,” “c,” and “f” cannot be met with transfusions, infusions, or growth factor support administered within 14 days of starting the first dose a. Hemoglobin ?9 g/dL b. Absolute neutrophil count ?1000/µL c. Platelet count ?75000/µL d. Total bilirubin (TBL) ?2.0×ULN e. AST and ALT ?5×ULN f. Albumin ?2.8 g/dL g. International normalized ratio (INR) ?1.6 h. Calculated creatinine clearance ?50 mL/minute as determined by Cockcroft Gault (using actual body weight) or 24 hour urine creatinine clearance a. Hemoglobin ?9 g/dL b. Absolute neutrophil count ?1000/µL c. Platelet count ?75000/µL d. Total bilirubin (TBL) ?2.0×ULN e. AST and ALT ?5×ULN f. Albumin ?2.8 g/dL g. International normalized ratio (INR) ?1.6 h. Calculated creatinine clearance ?50 mL/minute as determined by Cockcroft Gault (using actual body weight) or 24 hour urine creatinine clearance 14. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal as described in Section 3.8

Exclusion Criteria

Exclusion Criteria	
Details	1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site) 2. Previous study drug(s) assignment in the present study. 3. Concurrent enrollment in another clinical study, unless it is an observational (non interventional) clinical study or during the follow-up period of an interventional study. 4. Have received an investigational product within 28 days prior to the first dose of study drug(s) 5. Any unresolved toxicity National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) Grade ?2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria: - Patients with Grade ?2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician. - Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab may be

included only after consultation with the Study Physician.
6. Any concurrent chemotherapy, study drug, or biologic or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable.
7. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
8. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 28 days of the first dose of study drug(s).
9. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of study drug(s). Note: Local surgery of isolated lesions for palliative intent is acceptable
10. History of allogeneic organ transplantation (eg, liver transplant).
11. History of hepatic encephalopathy within past 12 months or requirement for medications to prevent or control encephalopathy (eg, no lactulose, rifaximin, etc if used for purposes of hepatic encephalopathy).
12. Ascites that require ongoing paracentesis, within 6 weeks prior to the first scheduled dose, to control symptoms.
13. Main portal vein thrombosis present on imaging
14. Active or prior documented GI variceal bleed or history of upper GI bleeding, ulcers, or esophageal varices with bleeding within 12 months; adequate endoscopic therapy according to institutional standards is required for patients with history of esophageal variceal bleeding or assessed as high risk for esophageal variceal by the treating investigator
15. Patient currently exhibits symptomatic or uncontrolled hypertension defined as diastolic blood pressure >90 mmHg or systolic blood pressure >140 mmHg
16. Any condition interfering with swallowing pills, uncontrolled diarrhea, or other contraindication to oral therapy.
17. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease, systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome (granulomatosis with polyangiitis, Graves isease, rheumatoid arthritis, hypophysitis, uveitis, etc)). Patients without active disease in the last 5 years are excluded unless discussed with the Study Physician and considered appropriate for study participation
The following are exceptions to this criterion:
- Patients with vitiligo or alopecia
- Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement
- Any chronic skin condition that does not require systemic therapy
- Patients with celiac disease controlled by diet alone
18. Confirmed HBV infection must not be co-infected with HCV (as indicated by the absence of anti-HCV antibodies) or hepatitis D virus (HDV; as indicated by the absence of anti-HDV antibodies).
19. Confirmed HCV infection must not be co-infected with HBV as defined by negative HBsAg. Patients with confirmed HCV infection who are negative for HBsAg, but positive for anti-HBc with detectable HBV DNA, are eligible but must be started on active antiviral therapy (for HBV) prior to enrollment to ensure adequate viral suppression (HBV DNA ?2000 IU/mL).
20. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, ILD, serious chronic GI conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase the risk of incurring AEs, or compromise the ability of the patient to give written

	informed consent 21. History of another primary malignancy except for: ? Malignancy treated with curative intent and with no known active disease ?5 years before the first dose of study drug(s) and of low potential risk for recurrence ? Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease ? Adequately treated carcinoma in situ without evidence of disease 22. History of leptomeningeal carcinomatosis. 23. Brain metastases or spinal cord compression. Patients with suspected brain metastases at screening should have an MRI (preferred) or CT, each preferably with IV contrast of the brain prior to study entry. 24. Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC. 25. History of active primary immunodeficiency. 26. Active infection including tuberculosis (TB) (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), or human immunodeficiency virus (positive human HIV 1/2 antibodies). 27. Current or prior use of immunosuppressive medication within 14 days before the first dose of study drug(s). The following are exceptions to this criterion: ? Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra articular injection) ? Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent ? Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication) 28. Receipt of live attenuated vaccine within 30 days prior to the first dose of study drug(s). Note: Patients, if enrolled, should not receive live vaccine while receiving study drug(s) and up to 30 days after the last dose of study drug(s). 29. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab plus tremelimumab combination therapy. Not engaging in sexual activity, as per the patient's preferred and usual lifestyle, for the total duration of the treatment and washout periods is an acceptable practice. 30. Prior randomization or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment arm assignment. 31. Patients who have received anti-PD-1, anti PD-L1, or anti CTLA-4 prior to the first dose of study drug(s)

Method of Generating Random Sequence	Stratified block randomization
Method of Concealment	Centralized
Blinding/Masking	Open Label

Primary Outcome

Outcome	Timepoints
To assess the efficacy of durvalumab 1500 mg plus tremelimumab 75 mg×4 doses compared with sorafenib 400 mg BID	Overall Survival (OS) (Time frame-Approximately 4 years)

Secondary Outcome

Outcome	Timepoints
To assess the efficacy of durvalumab 1500 mg plus tremelimumab 300 mg×1 dose combination therapy compared with sorafenib 400 mg BID	Overall Survival (OS) (Time frame-Approximately 4 years)

To assess the efficacy of durvalumab 1500 mg monotherapy compared with sorafenib 400 mg BID	Overall Survival (OS) (Time frame-Approximately 4 years)
To assess the efficacy of all immunotherapy arms compared with sorafenib 400 mg BID	Overall Survival (OS) (Time frame-Approximately 4 years)
To assess the efficacy of combination immunotherapies compared with durvalumab monotherapy in the overall population and in the population defined by programmed cell death ligand 1 (PD-L1) expression	Overall Survival (OS) (Time frame-Approximately 4 years)
To assess the efficacy of all immunotherapy arms compared with sorafenib 400 mg BID by PD-L1 expression	Overall Survival (OS) (Time frame-Approximately 4 years)
To assess disease-related symptoms and health-related quality of life (HRQoL) in patients treated with all immunotherapy arms compared with sorafenib 400 mg BID	Overall Survival (OS) (Time frame-Approximately 4 years)
To investigate the immunogenicity of all immunotherapy arms	Overall Survival (OS) (Time frame-Approximately 4 years)
To evaluate the population PK and pharmacodynamics of all immunotherapy arms	Overall Survival (OS) (Time frame-Approximately 4 years)
To assess the safety and tolerability profile of all immunotherapy arms with sorafenib 400 mg BID	Overall Survival (OS) (Time frame-Approximately 4 years)
To assess the efficacy of all immunotherapy arms compared with sorafenib 400 mg BID using immune-related Response Evaluation Criteria in solid tumors (irRECIST) and modified Response Evaluation Criteria in Solid Tumors (mRECIST) for HCC	Overall Survival (OS) (Time frame-Approximately 4 years)
To investigate the relationship between the progressive changes in alpha-fetoprotein (AFP) level and efficacy parameters	Overall Survival (OS) (Time frame-Approximately 4 years)
To investigate the efficacy of all immunotherapy arms and sorafenib 400 mg BID by baseline gene expression	Overall Survival (OS) (Time frame-Approximately 4 years)
To investigate efficacy of all immunotherapy arms and sorafenib 400 mg BID by candidate biomarkers that may correlate with drug activity or identify patients	Overall Survival (OS) (Time frame-Approximately 4 years)
To assess physician-reported patient outcome in patients treated with all immunotherapy arms and sorafenib 400 mg BID	Overall Survival (OS) (Time frame-Approximately 4 years)

Target Sample Size	**Total Sample Size=**1200 **Sample Size from India=**90 **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 3
Date of First Enrollment (India)	25/01/2018
Date of First Enrollment (Global)	11/10/2017
Estimated Duration of Trial	**Years=**4 **Months=**0 **Days=**0
Recruitment Status of Trial (Global)	Open to Recruitment

Recruitment Status of Trial (India)	Open to Recruitment
Publication Details	None Yet
Brief Summary	This is a randomized, open-label, multi-center, global, Phase III study to assess the efficacy and safety of durvalumab plus tremelimumab combination therapy and durvalumab monotherapy versus sorafenib in the treatment of patients with no prior systemic therapy for unresectable HCC. The patients cannot be eligible for locoregional therapy. Patients will be randomized in a 1:1:1:1 ratio to durvalumab 1500 mg monotherapy (Arm 1), combination therapy with durvalumab 1500 mg plus tremelimumab 75 mg×4 doses (Arm 2), combination therapy with durvalumab 1500 mg plus tremelimumab 300 mg×1 dose (Arm 3), and sorafenib 400 mg twice daily (BID; Arm 4). Patients will be stratified according to macrovascular invasion (yes versus no), etiology of liver disease (hepatitis B virus [HBV] versus hepatitis C virus [HCV] versus others), and performance status (Eastern Cooperative Oncology Group [ECOG] 0 versus 1). Durvalumab and tremelimumab will be administered via intravenous (IV) infusion every 4 weeks (Q4W). Sorafenib will be administered orally BID. Patients in all treatment arms, should, wherever possible, continue to receive their initially assigned treatment to disease progression. Patients in all treatment arms may continue receiving their originally assigned treatment, at the Investigator’s discretion, after the first overall time point assessment of progressive disease (PD) by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) until PD is confirmed on a follow-up scan (confirmed PD). A confirmatory scan is required following the assessment of PD by RECIST 1.1, preferably at the next scheduled visit and no earlier than 4 weeks after the previous assessment of PD. Patients in all arms with confirmed PD who, in the Investigator’s opinion, continue to receive benefit from their assigned treatment and meet the criteria for treatment in the setting of PD may continue to receive their assigned treatment. However, patients who develop progression in a target lesion after a clear response to therapy as defined by RECIST?1.1 will not be permitted to continue therapy.