Clinical Trial Details (PDF Generation Date :- Tue, 27 Jul 2021 08:38:48 GMT)

CTRI Number	CTRI/2020/08/027208 [Registered on: 18/08/2020] - **Trial Registered Prospectively**
Last Modified On	02/11/2020
Post Graduate Thesis	No
Type of Trial	Interventional
Type of Study	Drug
Study Design	Randomized, Parallel Group, Placebo Controlled Trial
Public Title of Study	Study of Durvalumab in Combination with Gemcitabine and Cisplatin in Patients with First Line Advanced Biliary Tract Cancers (TOPAZ-1)
Scientific Title of Study	A Phase III Randomized, Double-Blind, Placebo-Controlled, Multi- Regional, International Study of Durvalumab in Combination with Gemcitabine plus Cisplatin versus Placebo in Combination with Gemcitabine plus Cisplatin for Patients with First-Line Advanced Biliary Tract Cancers (TOPAZ-1)

Secondary IDs if Any

Secondary ID	Identifier
D933AC00001 Version 4.0, dated 17 APR 2020	Protocol Number
NCT03875235	ClinicalTrials.gov

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)	
Name	Tapankumar M Shah
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Affiliation	AstraZeneca Pharma India Ltd
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Source of Monetary or Material Support

Source of Monetary or Material Support
> AstraZeneca AB 151 85 Sodertalje, 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
AstraZeneca Pharma India Ltd	Block N1, 12th Floor, Manyata Embassy Business Park Rachenahalli, Outer Ring Road, Bangalore – 560045, India

Countries of Recruitment

List of Countries
Argentina
Brazil
Chile
China
France
Hong Kong
India
Italy
Japan
Poland
Republic of Korea
Russian Federation
Taiwan
Thailand
Turkey
United Kingdom
United States of America

Sites of Study

Name of Principal Investigator	Name of Site	Site Address	Phone/Fax/Email
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Dr Vineet Govinda Gupta	Artemis Hospitals	Dept. of Medical Oncology Sector-51, PIN-122001 Gurgaon HARYANA	01246767999 vineet.gupta@artemishospitals.com
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Dr Satheesh CT	Sri Venkateshwara Hospitals	Dept. of Medical Oncology #27th, 29th, Main Road, Rashtra Kuvempu Nagara, BTM 2nd Stage, BTM Layout, PIN-560076 Bangalore KARNATAKA	080-49730808 drsatheeshct@gmail.com
Dr Joydeep Ghosh	Tata Medical Centre Kolkata	Dept. of Medical Oncology 14 Major arterial road E-W, New Town, Rajarhat, PIN 700160 Kolkata WEST BENGAL	03366057000 dr.joydeep.ghosh@gmail.com
Dr Vikas Sureshchand Ostwal	Tata Memorial Hospital	3rd Floor, Room No. 323, Dr Ernest Borges Marg, Parel, PIN-400012 Mumbai MAHARASHTRA	02224177000 dr.vikas.ostwal@gmail.com

Details of Ethics Committee

Name of Committee	Approval Status	Date of Approval	Is Independent Ethics Committee?
Artemis Health Sciences Institutional Ethics Committee	Approved	08/06/2020	No
Institutional Ethics Committee TATA Memorial Hospital	Approved	05/10/2020	No
Institutional Ethics Committee - Clinical studies, Indraprastha Apollo Hospitals	Submittted/Under Review	No Date Specified	No
Institutional Ethics Committee, Action Cancer Hospital	Submittted/Under Review	No Date Specified	No
Institutional ethics committee, Tata Medical Center, Kolkata	Submittted/Under Review	No Date Specified	No
Institutional Review Board, Rajiv Gandhi Cancer Institute and Research Centre	Approved	02/07/2020	No

Shettys Hospital Ethics Committee	Approved	25/06/2020	No
Sri Venkateshwara Hospital Ethics Committee	Approved	30/06/2020	No

Regulatory Clearance Status from DCGI

Status	Date
Approved/Obtained	02/07/2020

Health Condition / Problems Studied

Health Type	Condition
Patients	Intrahepatic bile duct carcinoma
Patients	Malignant neoplasm of gallbladder

Intervention / Comparator Agent

Type	Name	Details
Intervention	Durvalumab (MEDI4736)	Durvalumab plus Cisplatin and Gemcitabine Frequency: every 03 weeks for first 8 cycles followed by every 4 weeks till progression Root of Administration: IV (Intravenous) Duration of therapy: until progression
Comparator Agent	Placebo	Placebo plus Cisplatin and Gemcitabine. Frequency: every 03 weeks for first 8 cycles followed by every 4 weeks till progression Root of Administration: IV (Intravenous) Duration of therapy: until progression

Inclusion Criteria

Inclusion Criteria	
Age From	18.00 Year(s)
Age To	99.00 Year(s)
Gender	Both
Details	Informed consent 1. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. 2. Provision of a signed and dated written ICF prior to any mandatory study-specific procedures, sampling, and analyses. 3. Provision of a signed and dated written informed consent prior to the collection of sample for optional genetic analysis Age 4. Age ?18 years at the time of screening Type of patient and disease characteristics 5. Histologically confirmed, unresectable advanced or metastatic adenocarcinoma of biliary tract, including cholangiocarcinoma (intrahepatic or extrahepatic) and gallbladder carcinoma. 6. Patients with previously untreated disease if unresectable or metastatic at initial diagnosis will be eligible. 7. Patients who developed recurrent disease >6 months after surgery with curative intent and, if given, >6 months after the completion of adjuvant therapy (chemotherapy and/or radiation) will be eligible. 8. A World Health Organization (WHO)/ECOG PS of 0 or 1 at enrollment. 9. At least 1 lesion that qualifies as a RECIST 1.1 Target Lesion (TL) at baseline. 10. No prior exposure to immune-mediated therapy, including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti-PD-L2 antibodies, excluding therapeutic anticancer vaccines. 11. Adequate organ and marrow function, as defined below: a. Hemoglobin ?9.0 g/dL. b. Absolute neutrophil count ?1.5 × 109 /L. c.

	Platelet count ?100 × 109/L. d. Serum bilirubin ?2.0 × the upper limit of normal (ULN); This will not apply to e. patients with confirmed Gilbert's syndrome. Any clinically significant biliary f. obstruction should be resolved before randomization. g. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ?2.5 × ULN; for patients with hepatic metastases, ALT and AST ?5 × ULN. h. Creatinine clearance (CL) >50 mL/min per 24hr urine or as calculated by Cockcroft-Gault 12. Patients must have a life expectancy of at least 12 weeks at the time of screening Sex 14. Male and/or female. Other 15. Patients must provide a recent tumor biopsy or an available unstained archived tumor tissue sample in a quantity sufficient to allow for analysis (taken ?3 years prior to screening). The tumor lesions to be used for biopsy should not be those used as RECIST TLs, unless there are no other lesions suitable for biopsy. 16. Patients with HBV infection (as characterized by positive hepatitis B surface antigen [HBsAg] and/or anti-hepatitis B core antibodies (anti-HBc) with detectable HBV deoxyribonucleic acid (DNA) [?10 IU/mL or above the limit of detection per local laboratory]) must receive antiviral therapy prior to randomization per institutional practice to ensure adequate viral suppression. Patients must remain on antiviral therapy for the study duration and for 6 months after the last dose of study treatment. Patients who test positive for anti-HBc with undetectable HBV DNA (<10 IU/mL or under the limit of detection per local laboratory) do not require antiviral therapy unless HBV DNA exceeds 10IU/mL or reaches detectable limits per local laboratory during the course of treatment. Patients with active co-infection of HBV and HCV as evidenced by positive anti-HCV antibody and actively co-infected with HBV and hepatitis D virus are not eligible.

Exclusion Criteria

Exclusion Criteria	
Details	Medical conditions 1. Ampullary carcinoma. 2. History of allogeneic organ transplantation. 3. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion: a. Patients with vitiligo or alopecia. b. Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement. c. Any chronic skin condition that does not require systemic therapy. d. Patients without an active disease in the last 5 years may be included but only after consultation with the Study Physician. f. Patients with celiac disease controlled by diet alone. 4. Uncontrolled intercurrent illness, including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, uncontrolled cardiac arrhythmia, active interstitial lung disease (ILD), serious chronic gastrointestinal 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. 5. History of another primary malignancy, except for: a. Malignancy treated with curative intent and with no known active disease ?5 years before the first dose of investigational product (IP)

and of low potential risk for recurrence.
b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
c. Adequately treated carcinoma in situ without evidence of disease.
6. History of leptomeningeal carcinomatosis.
7. History of active primary immunodeficiency.
8. Active infection, including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), or human immunodeficiency virus (positive HIV 1/2 antibodies).
9. Any unresolved toxicity NCI Common Terminology Criteria for Adverse Event (CTCAE) Grade ?2 from a previous anticancer therapy, with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria.
a. Patients with Grade ?2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
b. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Study Physician.
10. Brain metastases or spinal cord compression (including asymptomatic and adequately treated disease). Patients with suspected brain metastases at screening should have an MRI (preferred) or CT scan, each preferably with IV contrast, of the brain prior to study entry.
11. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.

Prior/concomitant therapy

12. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable.
13. Radiation therapy, including palliative radiation, is not allowed before the study, with an exception of radiation given in an adjuvant setting.
14. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note that patients, if enrolled, should not receive live vaccine while receiving IP and up to 30 days after the last dose of IP.
15. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note that minor surgery of isolated lesions for palliative intent is acceptable if performed more than 14 days prior to the first dose of IP.
16. Patients who have received prior immune-mediated therapy, including, but not limited to, other anti-PD-1, anti PD-L1, or anti CTLA-4.
17. Prior locoregional therapy such as radioembolization.
18. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:
a. Intranasal, inhaled, or topical steroids or local steroid injections (eg, intra-articular injection).
b. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent.
c Steroids as premedication for hypersensitivity reactions (eg, CT scan
premedication).

Prior/concurrent clinical study experience
19. Participation in another clinical study with an IP administered in the last 3 months.

	20. Previous IP assignment in the present study. 21. 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. 22. Prior randomization or treatment in a previous durvalumab clinical study, regardless of treatment arm assignment. Other exclusions 23. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to use effective birth control from screening to 180 days after the last dose of gemcitabine/cisplatin or 90 days after the last dose of durvalumab/placebo monotherapy. 24. Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements. 25. Genetic research study (optional). Exclusion criteria for participation in the optional (deoxyribonucleic acid [DNA]) genetic research component of the study include the following: a. Previous allogeneic bone marrow transplant. b. Non-leukocyte-depleted whole blood transfusion in 120 days of genetic sample collection. 26. Active infection of hepatitis C as evidenced by detectable HCV RNA per local laboratory. Patients who test positive for hepatitis C (HCV) antibody may be enrolled if HCV RNA is undetectable.

Method of Generating Random Sequence	Stratified block randomization
Method of Concealment	Centralized
Blinding/Masking	Double Blind Double Dummy

Primary Outcome

Outcome	Timepoints
To assess the efficacy of Arm A compared to Arm B in terms of OS (overall survival) in patients with first-line advanced BTC	It will be assessed at the following time points: 1. Interim Analysis-2: Approximately 347 OS events have occurred across Arm A and Arm B (52% maturity) and 2. Final Analysis: Approximately 496 OS events have occurred across Arm A and Arm B (74% maturity).

Secondary Outcome

Outcome	Timepoints
To further assess the efficacy of Arm A compared to Arm B in terms of ORR and DoR in patients with first-line advanced BTC	Interim Analysis -1: When at least 200 patients (100 patients in the each arm) have had the opportunity to be followed for at least 32 weeks or the last patient has been randomized to the global cohort whichever comes later.
For interim analysis 1: to summarise the efficacy of Arm A compared to Arm B in terms of ORR and DoR in patients with first-line advanced BTC	Interim Analysis -1: When at least 200 patients (100 patients in the each arm) have had the opportunity to be followed for at least 32 weeks or the last patient has been randomized to the global cohort whichever comes later.
To assess the efficacy of Arm A compared to Arm B by PD-L1 expression	It will be assessed at the following time points: 1. Interim Analysis-2: Approximately 347 OS events have occurred across Arm A and Arm B (52% maturity) and

	2. Final Analysis: Approximately 496 OS events have occurred across Arm A and Arm B (74% maturity).
To assess the PK of durvalumab when used in combination with cisplatin / gemcitabine	It will be assessed at the following time points: 1. Interim Analysis-2: Approximately 347 OS events have occurred across Arm A and Arm B (52% maturity) and 2. Final Analysis: Approximately 496 OS events have occurred across Arm A and Arm B (74% maturity).
To investigate the immunogenicity of durvalumab	It will be assessed at the following time points: 1. Interim Analysis-2: Approximately 347 OS events have occurred across Arm A and Arm B (52% maturity) and 2. Final Analysis: Approximately 496 OS events have occurred across Arm A and Arm B (74% maturity).
PROs (secondary):	It will be assessed at the following time points: 1. Interim Analysis-2: Approximately 347 OS events have occurred across Arm A and Arm B (52% maturity) and 2. Final Analysis: Approximately 496 OS events have occurred across Arm A and Arm B (74% maturity).
Safety objective: To assess the safety and tolerability profile of Arm A compared to Arm B in patients with first-line advanced BTC	It will be assessed at the following time points: 1. Interim Analysis-2: Approximately 347 OS events have occurred across Arm A and Arm B (52% maturity) and 2. Final Analysis: Approximately 496 OS events have occurred across Arm A and Arm B (74% maturity).
Exploratory objectives: 1. To investigate the efficacy of Arm A compared to Arm B by candidate biomarkers (for example but not limited to TMB and MSI) that may correlate with drug activity or identify patients likely to respond to treatment	It will be assessed at the following time points: 1. Interim Analysis-2: Approximately 347 OS events have occurred across Arm A and Arm B (52% maturity) and 2. Final Analysis: Approximately 496 OS events have occurred across Arm A and Arm B (74% maturity).
2. To evaluate circulatory-based biomarkers and associations with efficacy parameters, including, but not limited to, ctDNA	It will be assessed at the following time points: 1. Interim Analysis-2: Approximately 347 OS events have occurred across Arm A and Arm B (52% maturity) and 2. Final Analysis: Approximately 496 OS events have occurred across Arm A and Arm B (74% maturity).
3. To explore the impact of treatment and disease on healthcare resource use	It will be assessed at the following time points: 1. Interim Analysis-2: Approximately 347 OS events have occurred across Arm A and Arm B (52% maturity) and 2. Final Analysis: Approximately 496 OS events have occurred across Arm A and Arm B (74% maturity).
4. PROs (exploratory): To assess patient-reported treatment tolerability using PRO-CTCAE and global assessment of treatment tolerability	It will be assessed at the following time points: 1. Interim Analysis-2: Approximately 347 OS events have occurred across Arm A and Arm B (52% maturity) and 2. Final Analysis: Approximately 496 OS events have occurred across Arm A and Arm B (74% maturity).

To assess the patients' global impression of the severity of cancer symptoms	It will be assessed at the following time points: 1. Interim Analysis-2: Approximately 347 OS events have occurred across Arm A and Arm B (52% maturity) and 2. Final Analysis: Approximately 496 OS events have occurred across Arm A and Arm B (74% maturity).
To explore the impact of treatment and disease state on health state utility using the EQ-5D-5L	It will be assessed at the following time points: 1. Interim Analysis-2: Approximately 347 OS events have occurred across Arm A and Arm B (52% maturity) and 2. Final Analysis: Approximately 496 OS events have occurred across Arm A and Arm B (74% maturity).

Target Sample Size	**Total Sample Size=**672 **Sample Size from India=**32 **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)	21/08/2020
Date of First Enrollment (Global)	16/04/2019
Estimated Duration of Trial	**Years=**3 **Months=**4 **Days=**0
Recruitment Status of Trial (Global)	Open to Recruitment
Recruitment Status of Trial (India)	Open to Recruitment
Publication Details	NIL
Brief Summary	This is a Phase III Randomized, Double-Blind, Placebo-Controlled, Multi-Regional, International Study of Durvalumab in Combination with Gemcitabine plus Cisplatin versus Placebo in Combination with Gemcitabine plus Cisplatin for Patients with First-Line Advanced Biliary Tract Cancers (BTC) Approximately 672 patients with previously untreated, unresectable locally advanced or metastatic BTC will be randomized in a 1:1 ratio to receive either Durvalumab plus Gemcitabine and Cisplatin or Placebo plus Gemcitabine and Cisplatin. The primary objective of the study is to confirm the superiority of Arm A compared to Arm B in terms of overall survival (OS) in patients with first-line advanced BTC. Patients will be stratified by disease status (initially unresectable versus recurrent) and primary tumour site (intrahepatic cholangiocarcinoma versus extrahepatic cholangiocarcinoma versus gallbladder cancer). Patients will receive Durvalumab plus cisplatin and gemcitabine (Arm A) or placebo plus cisplatin and gemcitabine (Arm B) via IV infusion q3w, starting on Cycle 1, for up to 8 cycles. After treatment with gemcitabine/cisplatin is complete, the patients will receive durvalumab (Arm A) or placebo (Arm

B) via IV infusion q4w until clinical progression or RECIST 1.1-defined radiological PD, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

During the treatment period, patients who are clinically stable at an initial RECIST 1.1-defined radiological PD may continue to receive study treatment at the discretion of the Investigator and patient. A follow-up scan is to be collected after the initial RECIST 1.1-defined radiological PD, preferably at the next (and no later than the next) scheduled imaging visit and no less than 4 weeks after the prior assessment of PD.

Patients with RECIST 1.1-defined radiological PD who continue to receive their assigned treatment at the discretion of the Investigator and patient (following consultation with sponsor) can receive treatment until no longer having clinical benefit, and imaging for tumour assessments should continue on their regular imaging schedule for the duration of treatment.

All randomized patients should be followed up for survival.