Short-Course Radiation Followed by mFOLFOX-6 Plus COMPOUND 2055269 for Locally-Advanced Rectal Adenocarcinoma

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Main Information

Primary registry identifying number
LBCTR2018120174

Protocol number
BIO-2017-0422

MOH registration number
20796/2018

Study registered at the country of origin
Yes

Study registered at the country of origin: Specify

Type of registration
Retrospective

Type of registration: Justify
This is because the trial was initiated prior to the activation of this registry

Date of registration in national regulatory agency
16/05/2018

Primary sponsor
American University of Beirut

Primary sponsor: Country of origin
Lebanon

Date of registration in primary registry
29/12/2018

Date of registration in national regulatory agency
16/05/2018

Public title
Short-Course Radiation Followed by mFOLFOX-6 Plus COMPOUND 2055269 for Locally-Advanced Rectal Adenocarcinoma

Acronym
NA

Scientific title
Short-Course Radiation Followed by mFOLFOX-6 Plus COMPOUND 2055269 for Locally-advanced Rectal Adenocarcinoma

Acronym
NA

Brief summary of the study: English

The purpose of this research trial is to investigate a new drug, COMPOUND 2055269, in the treatment of locally advanced rectal adenocarcinoma.
COMPOUND 2055269 is a fully human antibody directed against programmed death ligand-1 (PD-L1) blocking antibody that results in the restoration of anti-tumor immune responses.
COMPOUND 2055269 is already available in the market for treatment of bladder cancer and Merkel-Cell carcinoma, an aggressive type of skin cancer.
COMPOUND 2055269is still being tested for safety and effectiveness in different types of cancer, including rectal cancer.
The standard treatment for participants' condition involves radiation to the rectum followed by chemotherapy then surgery.
In this clinical trial, we will be adding COMPOUND 2055269 to the chemotherapy treatment for 6 doses for all patients before surgery.

Brief summary of the study: Arabic

تهدف هذه الدراسة البحثية إلى التحقق من مفعول دواء جديد، COMPOUND 2055269 في علاج سرطان المستقيم المتقدم محلياً.
فيعمل على تعطيل آلية تستخدمها الأورام للاختباء من جهاز1 (بي دي آل 1الأفيلوماب مضادّ مناعيّ بشريّ يستهدف خلايا الموت المبرمج-1) المناعة.
لعلاج سرطان المثانة وسرطان خليّة مركل، وهو نوع شرس من أنواع سرطانات الجلد. ولا تزال الاختبارات جارية على هذا الدواء للتحقق من مدى سلامته وفعاليته في علاج أنواع مختلفة من السرطان، بما في ذلك سرطان المستقيم.
يتمثل العلاج النموذجي المناسب لحالتك الصحية بالخضوع لعلاج إشعاعي للمستقيم، يتبعه علاج كيميائي، وتأتي الجراحة في المرحلة النهائية. في هذه التجربة السريرية، سنقوم بإضافة الأفيلوماب على العلاج الكيميائي لـ6 جرعات لجميع المرضى قبل خضوعهم للجراحة.

Health conditions/problem studied: Specify

Locally-Advanced Rectal Adenocarcinoma

Interventions: Specify

Visit 1
1.Informed consent
2.Baseline laboratory tests including free T4, TSH, Hepatitis B virus surface antigen, and Hepatitis C virus antibodies
3.Tissue blocks or at least 7 slides of the baseline biopsy specimen upon which diagnosis was based
4.PD-L1 expression on tumor cells and TILs will be assessed by the pathologist at AUBMC. Also, CD4+, CD8+ and CD3+ T cell infiltration will be quantified in mm2 in the most abundant tumor-infiltrating area in both, the stroma and the tumor, of the baseline biopsy. Microsatellite instability, MSI or MMR status, will be evaluated once on either the baseline biopsy or day 10 (D10) biopsy, and the predictive markers to be assessed are: MLH-1, MSH-2, MSH-6, and PMS-2.

VISITS 2-6 (Week 1 ± 3 days; Day 1-5)
1.SCRT will be administered for 5 days from day 1 (D1) to D5 during week 1 (Either 3D conformal or in intensity-modulated radiotherapy (IMRT) treatment planning may be used. The daily dose will be 5 Gy to a total dose of 25 Gy.)

VISIT 7 (Week 2 ± 3 days; Day 10)
2.Sigmoidoscopy will be performed and a biopsy taken
3.Slides of the corresponding specimen will be provided
4.PD-L1 expression on tumor cells and TILs will be assessed by the pathologist at AUBMC. Also, CD4+, CD8+ and CD3+ T cell infiltration will be quantified in mm2 in the most abundant tumor-infiltrating area in both, the stroma and the tumor, of the baseline biopsy. Microsatellite instability, MSI or MMR status, will be evaluated once on either the baseline biopsy or day 10 (D10) biopsy, and the predictive markers to be assessed are: MLH-1, MSH-2, MSH-6, and PMS-2.

VISITS 8-13 (Week 3 ± 3 days to week 13 ± 3 days; Day 15+)
1.mFOLFOX-6 chemotherapy plus avelumab will be administered every 2 weeks for 6 cycles.
2.Avelumab at a dose of 10mg/kg is administered, followed 30 minutes later by mFOLFOX as follows: 85 mg/m2 of oxaliplatin in a 2-hour infusion, 400 mg/m2 of leucovorin over 2 hours, followed by a 48-hour infusion of fluorouracil 2,400 mg/m2.
3.Hematologic and biochemical laboratory tests are ordered prior to every cycle. D
4.Visit 13 is the end of treatment visit which includes, in addition to the procedures mentioned above, an assessment of tumor markers (CEA and CA 19-9).

Visit 14 (Week 16 or 17 ± 3 days)
1.2 to 3 weeks after last cycle of mFOLFOX-6 plus avelumab, an open, laparoscopic, or robotic TME is performed at the corresponding site.
2.An optional pelvic MRI might be ordered prior to surgery to evaluate the patient's disease status.
3.All TME procedures will be video recorded and the corresponding videotapes and images of the resected specimens are to be provided to AUBMC.
4.All specimens are to be processed and graded using the recommendations of the College of American Pathologists
5.PD-L1 expression on tumor cells and TILs will be assessed.
6.CD4+, CD8+ and CD3+ T-cell infiltration will be quantified in mm2 in the most abundant tumor-infiltrating area in both, the stroma and the tumor, of the tumor excision specimen.

Follow-up Visits
1.Follow-up laboratory tests including tumor markers (CEA, Ca19-9) are to be performed every 3 months for 3 years after the surgical procedure.

Key inclusion and exclusion criteria: Inclusion criteria

Inclusion Criteria
1)Signed informed consent form.
2)Patients aged ≥18 years.
3)Locally-advanced rectal cancer cT2 N1-3, cT3 N0-3
4)< 12 cm from anal verge.
5)Histologically proven rectal adenocarcinoma.
6)ECOG performance score ≤ 1.
7)Have adequate organ function by meeting the following:
•Absolute neutrophil count (ANC) ≥ 1.5 × 109/L;
•Platelet count ≥ 100 × 109/L;
•Hemoglobin ≥ 9 g/dL;
•Total bilirubin level ≤ 1.5 × the upper limit of normal (ULN) range;
•AST and ALT levels ≤ 2.5 × ULN or AST and ALT levels ≤ 5 x ULN (for subjects with documented metastatic disease to the liver);
•Estimated creatinine clearance ≥ 30 mL/min according to the Cockcroft-Gault formula (or local institutional standard method).
8)Negative serum or urine pregnancy test at screening for women of childbearing potential.

Key inclusion and exclusion criteria: Gender

Both

Key inclusion and exclusion criteria: Specify gender

Key inclusion and exclusion criteria: Age minimum

18

Key inclusion and exclusion criteria: Age maximum

100

Key inclusion and exclusion criteria: Exclusion criteria

Exclusion Criteria
1)Distant metastasis (M1).
2)Patients with T2 N0 or T4.
3)Recurrent rectal cancer.
4)Symptoms or history of peripheral neuropathy.
5)Prior radiotherapy or chemotherapy.
6)Current use of immunosuppressive medication except for the following:
-Intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection);
-Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent;
-Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).
7)Concurrent treatment with a non-permitted drug.
8)Active autoimmune disease that might deteriorate when receiving an immuno-stimulatory agent.
9)Vaccination within 4 weeks of the first dose of avelumab and while on trials is prohibited except for administration of inactivated vaccines.
10)Active infection requiring systemic therapy.
11)Known history of testing positive for the human immunodeficiency virus or known acquired immunodeficiency syndrome.
12)Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive).
13)Known prior severe hypersensitivity to investigational product or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v4.03 Grade ≥ 3).
14)Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.
15)Persisting toxicity related to prior therapy (NCI CTCAE v. 4.03 Grade > 1); however, alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable.
16)Prior organ transplantation including allogenic stem-cell transplantation.
17)Any psychiatric condition that would prohibit the understanding or rendering of informed consent.

Type of study

Interventional

Type of intervention

Pharmaceutical

Type of intervention: Specify type

N/A

Trial scope

Therapy

Trial scope: Specify scope

N/A

Study design: Allocation

N/A: Single arm study

Study design: Masking

N/A

Study design: Control

Uncontrolled

Study phase

2

Study design: Purpose

Treatment

Study design: Specify purpose

N/A

Study design: Assignment

Single

Study design: Specify assignment

N/A

IMP has market authorization

Yes, Lebanon and Worldwide

IMP has market authorization: Specify

Lebanon and Worldwide

Name of IMP

Avelumab

Year of authorization

2017

Month of authorization

3

Type of IMP

Immunological

Pharmaceutical class

Immunotherapy:
COMPOUND 2055269 is a fully human antibody directed against programmed death ligand-1 (PD-L1) blocking antibody that results in the restoration of anti-tumor immune responses.

Therapeutic indication

The standard treatment for locally advanced rectal adenocarcinoma involves radiation to the rectum followed by chemotherapy then surgery.
In this clinical trial, we will be adding COMPOUND 2055269 to the chemotherapy treatment for 6 doses for all patients before surgery.
Reasoning: COMPOUND 2055269 10 mg/kg once every 2 weeks has demonstrated meaningful clinical activity across various treatment settings and tumor types, including melanoma and lung cancer.

Therapeutic benefit

There is no guarantee that patients will receive any direct benefits from this study.
Information from this study may help doctors learn more about COMPOUND 2055269 and the treatment of locally advanced rectal cancer.
This information may benefit other patients with cancer of the rectal cancer.
In this trial, we hope many participants will attain pathologic complete response (pCR) by the end of treatment.

Study model

N/A

Study model: Explain model

N/A

Study model: Specify model

N/A

Time perspective

N/A

Time perspective: Explain time perspective

N/A

Time perspective: Specify perspective

N/A

Target follow-up duration

Target follow-up duration: Unit

Number of groups/cohorts

Biospecimen retention

Samples with DNA**

Biospecimen description

1. Slides or Tissue Blocks prepared from the Baseline Biopsy from the rectal mass (taken during diagnostic colonoscopy)
2. Slides or Tissue Blocks prepared from the Biopsy taken from the rectal mass during sigmoidoscopy at Day 10
3. Slides or Tissue Blocks encompassing the entire tumor bed prepared from the gross specimen from the total mesorectal excision procedure.

Target sample size

44

Actual enrollment target size

Date of first enrollment: Type

Actual

Date of first enrollment: Date

20/07/2018

Date of study closure: Type
Actual

Date of study closure: Date
20/10/2023

Recruitment status
Recruiting

Recruitment status: Specify

Date of completion

IPD sharing statement plan
No

IPD sharing statement description
Not Applicable

Additional data URL

Admin comments

Trial status
Approved

Secondary Identifying Numbers

No Numbers

Sources of Monetary or Material Support

No Sources

Secondary Sponsors

No Sponsors

Contact for Public/Scientific Queries

Contact type	Contact full name	Address	Country	Telephone	Email	Affiliation
Public	Ali Shamseddine	Department of Internal Medicine Division of Hematology/Oncology American University of Beirut Medical Center Beirut P.O. Box 11-0236, Lebanon	Lebanon	Phone: +961 1 350 000 (Ext.: 5390)	Email: as04@aub.edu.lb	American University of Beirut Medical Center
Scientific	Ali Shamseddine	Department of Internal Medicine Division of Hematology/Oncology American University of Beirut Medical Center Beirut P.O. Box 11-0236, Lebanon	Lebanon	Phone: +961 1 350 000 (Ext.: 5390)	Email: as04@aub.edu.lb	American University of Beirut Medical Center

Centers/Hospitals Involved in the Study

Center/Hospital name	Name of principles investigator	Principles investigator speciality	Ethical approval
American University of Beirut Medical Center	Ali Shamseddine, MD, FRCP	Oncologist	Approved
Hotel Dieu de France	Joseph Kattan, MD	Oncologist	Approved
King Hussein Cancer Center	Rim Turfa, MD	Oncologist	Approved

Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
American University of Beirut Medical Center	04/06/2018	Fuad Ziyadeh (Chairperson of the IRB at AUBMC)	fz05@aub.edu.lb	Phone:01350000 Ext: 5353

Countries of Recruitment

Name
Lebanon
Jordan

Health Conditions or Problems Studied

Condition	Code	Keyword
Locally Advanced Rectal Cancer	Malignant neoplasm of rectum (C20)	Locally Advanced Rectal Cancer

Interventions

Intervention	Description	Keyword
Visit 1- Baseline laboratory tests including free T4, TSH, Hepatitis B virus surface antigen, and Hepatitis C virus antibodies	Visit 1	Visit 1
Visit 1- Tissue blocks or at least 7 slides of the baseline biopsy specimen upon which diagnosis was based	Visit 1	Visit 1
Visit 1- PD-L1 expression on tumor cells and Tumor infiltrating lymphocytes will be assessed by the pathologist at AUBMC. Also, CD4+, CD8+ and CD3+ T cell infiltration will be quantified in mm2 in the most abundant tumor-infiltrating area in both, the stroma and the tumor, of the baseline biopsy. Microsatellite instability, MSI or MMR status, will be evaluated once on either the baseline biopsy or day 10 (D10) biopsy, and the predictive markers to be assessed are: MLH-1, MSH-2, MSH-6, and PMS-2.	Visit 1	Visit 1
Visits 2-6 - Short Course Radiation Therapy will be administered for 5 days from day 1 (D1) to D5 during week 1 (Either 3D conformal or in intensity-modulated radiotherapy (IMRT) treatment planning may be used. The daily dose will be 5 Gy to a total dose of 25 Gy.)	Visits 2-6	Visits 2-6
Visit 7- Sigmoidoscopy will be performed and a biopsy taken	Visit 7	Visit 7
Visit 7- Slides of the corresponding specimen will be provided	Visit 7	Visit 7
Visit 7- PD-L1 expression on tumor cells and TILs will be assessed by the pathologist at AUBMC. Also, CD4+, CD8+ and CD3+ T cell infiltration will be quantified in mm2 in the most abundant tumor-infiltrating area in both, the stroma and the tumor, of the baseline biopsy. Microsatellite instability, MSI or MMR status, will be evaluated once on either the baseline biopsy or day 10 (D10) biopsy, and the predictive markers to be assessed are: MLH-1, MSH-2, MSH-6, and PMS-2.	Visit 7	Visit 7
Visits 8-13- mFOLFOX-6 chemotherapy plus COMPOUND 2055269 will be administered every 2 weeks for 6 cycles.	Visits 8-13	Visits 8-13
Visits 8-13- COMPOUND 2055269 at a dose of 10mg/kg is administered, followed 30 minutes later by mFOLFOX as follows: 85 mg/m2 of oxaliplatin in a 2-hour infusion, 400 mg/m2 of leucovorin over 2 hours, followed by a 48-hour infusion of fluorouracil 2,400 mg/m2.	Visits 8-13	Visits 8-13
Visits 8-13- Hematologic and biochemical laboratory tests are ordered prior to every cycle	Visits 8-13	Visits 8-13
Visit 13- This is the end of treatment visit which includes, in addition to the procedures mentioned above, an assessment of tumor markers (CEA and CA 19-9).	Visit 13	Visit 13
Visit 14- 2 to 3 weeks after last cycle of mFOLFOX-6 plus avelumab, an open, laparoscopic, or robotic TME is performed at the corresponding site. All TME procedures will be video recorded and the corresponding videotapes and images of the resected specimens are to be provided to AUBMC.	Visit 14	Visit 14
Visit 14- An optional pelvic MRI might be ordered prior to surgery to evaluate the patient's disease status.	Visit 14	Visit 14

Visit 14- All specimens are to be processed and graded using the recommendations of the College of American Pathologists PD-L1 expression on tumor cells and TILs will be assessed. CD4+, CD8+ and CD3+ T-cell infiltration will be quantified in mm2 in the most abundant tumor-infiltrating area in both, the stroma and the tumor, of the tumor excision specimen.	Visit 14	Visit 14
Follow-up Visits- Follow-up laboratory tests including tumor markers (CEA, Ca19-9) are to be performed every 3 months for 3 years after the surgical procedure.	Follow-up Visits	Follow-up Visits

Primary Outcomes

Name	Time Points	Measure
The primary efficacy endpoint is the proportion of patients who achieve a pathological complete response, defined as no viable tumor cells on the resected specimen.	The primary efficacy endpoint is the proportion of patients who achieve a pathological complete response, defined as no viable tumor cells on the resected specimen.	The primary efficacy endpoint is the proportion of patients who achieve a pathological complete response, defined as no viable tumor cells on the resected specimen.

Key Secondary Outcomes

Name	Time Points	Measure
The secondary efficacy endpoints are: 1)PFS at 3 years will be estimated with the Kaplan-Meier method and presented with the 95% CI. 2)Evaluation of response by obtaining TRG just after surgery (week 16 or 17 ± 3 days).	The secondary efficacy endpoints are: 1)PFS at 3 years will be estimated with the Kaplan-Meier method and presented with the 95% CI. 2)Evaluation of response by obtaining TRG just after surgery (week 16 or 17 ± 3 days).	The secondary efficacy endpoints are: 1)PFS at 3 years will be estimated with the Kaplan-Meier method and presented with the 95% CI. 2)Evaluation of response by obtaining TRG just after surgery (week 16 or 17 ± 3 days).

Trial Results

Summary results

Study results globally

Date of posting of results summaries

Date of first journal publication of results

Results URL link

Baseline characteristics

Participant flow

Adverse events

Outcome measures

URL to protocol files