A pilot study of Nivolumab with stereotactic ablative radiation therapy after induction chemotherapy in cholangiocarcinoma.

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Main Information

Primary registry identifying number
LBCTR2020124689

Protocol number
CA209-7DJ/BIO-2019-0447

MOH registration number

Study registered at the country of origin
Yes

Study registered at the country of origin: Specify

Type of registration
Prospective

Type of registration: Justify
N/A

Date of registration in national regulatory agency
16/12/2020

Primary sponsor
American University of Beirut

Primary sponsor: Country of origin
lebanon

Date of registration in primary registry
21/03/2021

Date of registration in national regulatory agency
16/12/2020

Public title
A pilot study of Nivolumab with stereotactic ablative radiation therapy after induction chemotherapy in cholangiocarcinoma.

Acronym
N/A

Scientific title
A pilot study of Nivolumab with stereotactic ablative radiation therapy after induction chemotherapy in cholangiocarcinoma.

Acronym
N/A

Brief summary of the study: English

This is a phase II open-label, single-arm, multicenter pilot study investigating the efficacy and safety of Nivolumab treatment followed by SBRT radiation treatment, then monthly Nivolumab in patients with non-resectable locally-advanced, metastatic or recurrent intra-hepatic or extra-hepatic cholangiocarcinoma.
Primary Study Objectives:
-evaluate the progression free survival (PFS) at 8 months and the disease control rate in patients with non-resectable locally-advanced or metastatic or recurrent intra-hepatic or extra-hepatic cholangiocarcinoma following Nivolumab/SBRT treatment.
Secondary Study objectives:
-Evaluate the overall survival (OS) rate in patients with advanced intra-hepatic or extra-hepatic cholangiocarcinoma following Nivolumab/SBRT treatment.
- evaluate the two-year survival in patients with advanced intra-hepatic or extra-hepatic cholangiocarcinoma following Nivolumab/SBRT treatment.
-Evaluate tumor response rates at the primary and secondary sites using RECIST1.1 criteria as well as the duration of response at un-irradiated tumor sites in patients with Stage IV disease.
-evaluate the following biomarkers: CD3+, CD4+, and CD8+ T cell infiltration, and changes in PDL-1 expression following 1 cycle Nivolumab and SBRT.
-assess the safety and tolerability of Nivolumab/SBRT according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAEv5).
-Assess the quality of life of the patients through completed FACT-G questionnaires.

Methodology:
Eligible patients with radiological partial response rate or stable disease following 4 cycles of Cisplatin/ Gemcitzbine will be enrolled. Those patients will receive Nivolumab intravenously every 4 weeks until disease progression or until they experience unacceptable drug related serious adverse event (SAE).
Patients' disease status will be evaluated by CT chest, abdomen and pelvis (RECIST 1.1) criteria after each 4 cycles of Nivolumab.
Enrolled patients will be followed until death. Neither reference therapy, nor placebo nor control group will be added to the trial.
Neither randomization nor blinding will be used in this trial.
Approximately, 40 patients will be accrued from 4 sites over a period of 1 year.

Risks/benefits
Potential risks of this study: Small risk of radiation therapy and immune-related adverse events associated with Nivolumab (typically occurring in less than 10% of patients and mild/reversible however more significant immune-related adverse events are possible).
Potential benefits: Improvement in response rate and chance of cure and potential benefit to future patients with locally advanced and metastatic cholangiocarcinoma patients.

Brief summary of the study: Arabic

دراسة تجريبية من المرحلة الثانية، مفتوحة التسمية، ذات ذراع واحد، متعدّدة المراكز لتقييم فعالية وسلامة نيفولوماب مع العلاج الشعاعي التجسيمي التجزيئي بعد العلاج الكيميائي التعريفي ضد سرطان الأوعية الصفراوية.
تهدف هذه الدراسة السريرية إلى تقييم فعاليّة وسلامة الجمع بين جرعة مرتفعة من العلاج الشعاعي والعلاج المناعي (نيفولوماب) لمعالجة المرض الذي تعاني منه والمعروف بإسم سرطان الأوعية الصفراوية.
سيتم تسجيل المرضى المؤهلين الذين لديهم معدل استجابة جزئية إشعاعية أو مرض مستقر بعد 4 دورات علاجية من Cisplatin / Gemcitabine. سيتلقى هؤلاء المرضى Nivolumab عن طريق الوريد كل 4 أسابيع حتى تطور المرض أو حتى يواجهوا حدثًا ضارًا خطيرًا غير مقبول مرتبط بالعقاقير (SAE).
سيتم تقييم حالة المرض لدى المرضى من خلال معايير تصوير مقطعي محوسب للصدر والبطن والحوض (RECIST 1.1) بعد كل 4 دورات من Nivolumab.
سيتم متابعة المرضى المسجلين حتى الوفاة. لن يتم إضافة العلاج المرجعي أو العلاج الوهمي أو المجموعة الضابطة إلى التجربة.
لن يتم استخدام التعشية أو التعمية في هذه التجربة.
سيتم تجميع 40 تقريبًا من 4 مريضًا واحد على مدار عام واحد مواقع .

المخاطر المحتملة لهذه الدراسة: خطر ضئيل من العلاج الإشعاعي. والأحداث المرتبطة بـ Nivolumab (تحدث عادةً في أقل من 10٪ المرضى وخفيفة / قابلة للعكس ولكن من الممكن حدوث أحداث سلبية ذات صلة بالمناعة أكثر أهمية).
الفوائد المحتملة: تحسين معدل الاستجابة وفرصة الشفاء وإحتمال الفوائد للمرضى المستقبليين المصابين بسرطان القنوات الصفراوية المتقدم.

Health conditions/problem studied: Specify

Locally Advanced, recurrent or metastatic cholangiocarcinoma.

Interventions: Specify

Experimental arm : locally advanced, metastatic or recurrent cholangiocarcinoma
Day 1: Nivolumab treatment
Day 8: radiotherapy 3 to 5 fractions SBRT
Day 20: CT guided Biopsy
Day 28: Nivolumab treatment 480 mg IV drip
Monthly treatment Nivolumab
CT scan chest abdomen and pelvis: after each 4 Doses

Key inclusion and exclusion criteria: Inclusion criteria

Inclusion criteria:
1)Signed and dated informed consent form.
2)Patients aged ≥18 years.
3)Pathologically (histologically or cytologically) and radiologically confirmed diagnosis of non-resectable locally advanced or metastatic or recurrent intrahepatic or extrahepatic CCA within 90 days of registration.
4)Patients who have stable disease or partial response following 4 cycles of cisplatin/gemcitabine.
5)ECOG performance score <3
oAn estimated life expectancy of more than 3 months.
6)Have adequate hematologic and biochemical function by meeting the following:
oTotal bilirubin acceptable level ≤ 1.5 × the institutional upper limit of normal (ULN) range;
oAspartate aminotransferase (AST) and alanine aminotransferase (ALT) acceptable levels up to 5 x ULN range;
oSerum urea and serum creatinine acceptable levels up to 1.5 x ULN range;
oCalculated glomerular filtration rate ≥ 45 mL/min according to the Chronic Kidney Disease Epidemiology Collaboration equation (or local institutional standard method).
7)Negative serum or urine pregnancy test at screening for women of childbearing potential who are sexually active.
8)Highly effective contraception for both males and females of child-bearing potential who are sexually active throughout the study and for at least 5 months and 7 months after the last Nivolumab treatment administration, respectively.
9)Candidate for percutaneous biopsy as per tumor location evidenced by CT scan and interventional radiologist.

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

90

Key inclusion and exclusion criteria: Exclusion criteria

Exclusion Criteria:
1. Patients who have progression following 4 cycles of cisplatin/ gemcitabine evidenced by CT scan as per RECIST 1.1.
2. Active brain metastases or leptomeningeal metastases.
3. Prior organ transplantation or allogenic stem-cell transplantation.
4. Known prior severe hypersensitivity to IMP or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI-CTCAE v4.03 Grade ≥ 3).
5. Active infection requiring systemic therapy within 28 days before the first dose of study treatment (e.g., urinary tract infection).
6. Known history of testing positive for the human immunodeficiency virus or known acquired immunodeficiency syndrome.
7. Evidence of liver cirrhosis.
8. 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).
9. Active autoimmune diseases that might deteriorate upon receiving an immune-stimulatory agent.
10. Conditions such as vitiligo, psoriasis, diabetes type I, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible.
11. Commonly excluded conditions include: Addison's disease, thyroiditis/ Hashimoto's thyroiditis, systemic lupus erythematosus, Sjogren's syndrome, scleroderma, myasthenia gravis, Goodpasture's syndrome, and Grave's disease
12. Hepatic insufficiency manifesting as clinical jaundice, hepatic encephalopathy, and/or variceal bleed within 60 days prior to study entry.
13. Transmural myocardial infarction within 6 months of enrollment; provided

that anti-platelets cannot be stopped to perform percutaneous biopsy.
14. Congestive heart failure (≥ New York Heart Association Classification Class II) requiring hospitalization within the last 6 months provided that anti-platelets cannot be stopped to perform percutaneous biopsy.
15. Serious cardiac arrhythmia requiring medical treatment provided that anti-platelets cannot be stopped to perform percutaneous biopsy.
16. Recent cerebral vascular accident/stroke within 6 months of enrollment provided that anti-platelets cannot be stopped to perform percutaneous biopsy.
17. End-stage renal disease requiring dialysis.
18. Other severe acute or chronic medical conditions including immune colitis, inflammatory bowel disease, immune pneumonitis, pulmonary fibrosis, or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior.
19. Vaccination within 4 weeks of the first dose of BMS-936558 and while on trial is prohibited except for administration of inactivated vaccines.
20. Treatment with an investigational agent within 28 days before the first dose of study treatment.
21. Prior treatment with any drug or antibody (anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody) targeting T cell costimulation or checkpoint pathways.
22. Patients suspected by the physician that he/she will not be compliant to the protocol conduct.
23. Pregnant women are excluded from this study; breastfeeding should be discontinued.
24. Patients participating in another clinical trial.
25. Patients not willing to sign the consent form.
26. Any psychiatric condition that would prohibit the understanding or rendering of informed consent.
27. Legal incapacity or limited legal capacity patients receiving other oncology specific medication not authorized in the protocol.

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

Single Arm Study

Study design: Masking

Open (masking not used)

Study design: Control

Historical

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

IMP has market authorization: Specify

Name of IMP

Nivolumab

Year of authorization

2015

Month of authorization

12

Type of IMP

Immunological

Pharmaceutical class

Immunotherapy

Therapeutic indication

locally advanced, recurrent, metastatic cholangiocarcinoma

Therapeutic benefit

The combination of Nivolumab and SBRT following chemotherapy will improve outcomes of cholangiocarcinoma patients including progression free survival and and disease control rate.

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 without DNA

Biospecimen description

tissue samples

Target sample size

40

Actual enrollment target size

Date of first enrollment: Type

Anticipated

Date of first enrollment: Date

15/02/2021

Date of study closure: Type

Anticipated

Date of study closure: Date

15/02/2024

Recruitment status

Pending

Recruitment status: Specify

Date of completion

IPD sharing statement plan

Yes

IPD sharing statement description

Patient data will be kept strictly confidential and patient anonymity will be protected by using number codes and initials.
The Principal Investigator, the CRO and the Health Authorities will not disclose any personal patient information.
Bristol-Myers Squibb will not have access to identified patients' data and samples.
Data processing, from data collection to database lock, will be carried out in accordance with GCP.
The database and data entry screens will be created in software specifically designed for clinical data management in compliance with ICH-GCP requirements.
The study data are the property of the Principal Investigator. The co-Principal Investigator, co-investigators and any of the research team shall obtain written approval from the Principal Investigator prior to the publication/communication of the results of any work carried out during or in relation to the study.
Publication and/or communication of the results of the clinical study is the responsibility of the Principal Investigator. It will be of a cooperative nature involving authors representing the Principal Investigator, the Co-Principal Investigator and Co-Investigators and the scientific committee, if any.

Additional data URL

N/A

Admin comments

Trial status

Approved

Secondary Identifying Numbers

Full name of issuing authority	Secondary identifying number
clinicalTrials.gov	NCT04648319

Sources of Monetary or Material Support

Name
Bristol Myers Squibb

Secondary Sponsors

Name
NA

Contact for Public/Scientific Queries

Contact type	Contact full name	Address	Country	Telephone	Email	Affiliation
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Scientific	Ali Shamseddine	American University of Beirut Medical Center P.o.Box : 11-0236 Riad El Solh : 110 72020	Lebanon	01350000	as04@aub.edu.lb	American University of Beirut

Centers/Hospitals Involved in the Study

Center/Hospital name	Name of principles investigator	Principles investigator speciality	Ethical approval
American University of Beirut Medical Center	Dr. ALi Shamseddine	Professor of medicine/hematology-Oncology	Approved
Institut Jule Bordet	Dr. Alain Hendlizs	Professor of Medicine/GI oncology	Pending
Cliniques universitaires Saint-Luc	Dr. Ivan Borbath	Professor of Medicine/GI oncology	Pending
Centre hospitalier de Luxembourg	Dr. Guy Berchem	Professor of Medicine/medical oncologist	Pending

Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
American University of Beirut Medical Center	22/10/2020	Dr. Ali Shamseddine	as04@aub.edu.lb	961-1-350000 (ext:5390)

Countries of Recruitment

Name
Lebanon
Belgium
Luxembourg

Health Conditions or Problems Studied

Condition	Code	Keyword
cholangiocarcinoma	Malignant neoplasm of other and unspecified parts of biliary tract (C24)	biliary tract

Interventions

Intervention	Description	Keyword
Nivolumab at day 1 and then monthly Nivolumab until progression	day 1 and then monthly Nivolumab until progression	Nivolumab
radiotherapy	30 grays of 3 to 5 fractions of high dose SBRT at day 8	SBRT
CT guided biopsy	at day 22 after first dose of Nivolumab and radiotherapy to assess	will evaluate PD-L1 expression and on tumor cells and infiltrating immune T cells.
CT scan Abdomen and Pelvis	CT scan CAP will be dpne after each 4rth cycle of Novolumab to assess tumor response using RECIST 1.1	Tumor response evaluation

Primary Outcomes

Name	Time Points	Measure
assess the median progression free survival (PFS) and PFS rate and DCR in patients with non-resectable locally-advanced or metastatic or recurrent intrahepatic or extrahepatic CCA following Nivolumab/SBRT treatment	at 8 months from first nivolumab dose	Kaplan-Meier methods

Key Secondary Outcomes

Name	Time Points	Measure
evaluate the overall survival (OS) rate	every 3 months after progression	Kaplan-Meier
Tumor response rates at the primary and secondary sites	after each 4rth cycle of Nivolumab until progression	descriptive RECIST 1.1
duration of response at non-irradiated tumor sites in	: every 4 months from the date of first treatment visit until the date of first documented progression,	descriptive
Evaluate the following biomarkers: CD3+, CD4+, and CD8+ , and changes in PD-L1 expression at baseline and following first cycle of Nivolumab and radiotherapy	at Baseline visit and at Day 22	quantification
Assess the Quality of life	on each visit	FACT -HEP questionnaire

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