



# 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 unirradiated 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/ Gemcitabine 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، متعددة المراكز لتقييم فعالية وسلامة نيفولوماب مع العلاج الشعاعي التجزيئي بعد العلاج الكيميائي التعريفي ضد سرطان الأوعية الصفراوية.

تهدف هذه الدراسة السريرية إلى تقييم فعالية وسلامة الجمع بين جرعة مرتفعة من العلاج الشعاعي والعلاج المناعي (نيفولوماب) لمعالجة المرض الذي تعاني منه والمعروف باسم سرطان الأوعية الصفراوية.

Cisplatin / دورات علاجية من 4 سيتم تسجيل المرضى المؤهلين الذين لديهم معدل استجابة جزئية إشعاعية أو مرض مستقر بعد أسابيع حتى تطور المرض أو حتى يواجهوا حدثًا ضارًا 4 عن طريق الوريد كل Nivolumab سيتلقى هؤلاء المرضى.

أسابيع حتى تطور المرض أو حتى يواجهوا حدثًا ضارًا 4 عن طريق الوريد كل Nivolumab سيتلقى هؤلاء المرضى. (SAE) خطيرًا غير مقبول مرتبط بالمعاقير دورات 4 بعد كل (RECIST 1.1) سيتم تقييم حالة المرض لدى المرضى من خلال معايير تصوير مقطعي محوسب للصدر والبطن والحوض 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.

. مواقع على مدار عام واحد 4 مريضًا من 40 تقريبًا ، سيتم تجنيد

% من 10 تحدث عادةً في أقل من ( Nivolumab المخاطر المحتملة لهذه الدراسة: خطر ضئيل من العلاج الإشعاعي. والأحداث المرتبطة به (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  $\geq 18$  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  $< 3$ 
  - o An estimated life expectancy of more than 3 months.
- 6) Have adequate hematologic and biochemical function by meeting the following:
  - o Total bilirubin acceptable level  $\leq 1.5 \times$  the institutional upper limit of normal (ULN) range;
  - o Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) acceptable levels up to  $5 \times$  ULN range;
  - o Serum urea and serum creatinine acceptable levels up to  $1.5 \times$  ULN range;
  - o Calculated glomerular filtration rate  $\geq 45$  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  $\geq 3$ ).
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  $\leq 10$  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 ( $\geq$  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 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                   |
|--------------|-------------------|--|---------|-----------|-----------------|-------------------------------|
| Public       | Ali Shamseddine   | American University of Beirut Medical Center<br>P.o.Box : 11-0236 Riad El Solh : 110 72020 | Lebanon | 01350000  | as04@aub.edu.lb | American University of Beirut |
| Scientific   | Ali Shamseddine   | American University of Beirut Medical Center<br>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 Hendlitz              | 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 done after each 4th cycle of Nivolumab 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 4th 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**