A Two-cohort, Phase 2 Study of FL-101 as Neoadjuvant Therapy in Patients with Surgically Resectable Non-Small Cell Lung Cancer

Published: 07-07-2021
Last updated: 05-04-2024

Primary Objective:To evaluate the safety and tolerability of FL-101 as monotherapy and in combination with nivolumabTimepoint of evaluation of primary objective: From first dose to 3 months after surgerySecondary Efficacy Objectives1. Cohort 1: To...

Ethical review	Not approved
Status	Will not start
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON50938

Source
ToetsingOnline

Brief title
Phase 2 Study of FL-101 in NSCLC

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Non-Small Cell Lung Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Flame Biosciences

Source(s) of monetary or material Support: Flame Biosciences;Inc.

Intervention

Keyword: Efficacy, Monoclononal Antibody, Non-Small Cell Lung Cancer, Safety

Outcome measures

Primary outcome

1. Incidence and severity of AEs and SAEs graded according to NCI CTCAE v5.0

2. Incidence of immune-related toxicities

3. Incidence of events that inhibit or delay surgery beyond the preplanned surgical date

4. Changes from baseline in clinical safety laboratory values, ECGs, and vital signs

Secondary outcome

Secondary Efficacy parameters

1. Pathological response (% residual tumor) as assessed by independent pathology review.

2. Major pathologic response (MPR), defined as *10% viable tumor at time of surgery.

3. Complete pathologic response (CPR), defined as the absence of residual invasive cancer in resected lung specimens and lymph nodes following completion of neoadjuvant therapy at time of surgery

4. ORR defined by RECIST v1.1 in computed tomography scans.

5. MRD measurement by ctDNA

Secondary Pharmacologic (PK/PD) parameters

1. Estimates of the following FL-101 PK parameters: Cmax, Cmin, AUC0-t,

AUC0-inf, CL, Vz, t*

2. Change from baseline in serum hsCRP, IL-6, and neutrophil / lymphocyte ratio.

3. Change from baseline in plasma IL-1* levels

Secondary Safety Parameters

1. Prevalence and incidence of anti-FL-101 antibodies.

Study description

Background summary

Advances in both targeted and immunotherapies for NSCLC have led to meaningful reductions in incidence-based mortality (Howlader 2020). Nevertheless, an estimated 230,000 new cases of NSCLC are still diagnosed in the US, with some 135,000 deaths annually (Siegel 2020).

In response to local inflammation, IL-1* orchestrates a cascade of myeloid responses and signals bone marrow derived myeloid cells to accumulate at the site of local inflammation supporting both tumorgenesis and then local and systemic immunosuppression. Emerging data suggest that this inflammatory cascade may result in refractoriness to checkpoint inhibitor (nivolumab) therapies. Evidence from preclinical and clinical studies shows that this local and systemic inflammatory response can be identified in NSCLC patients and that inhibiting it protects from tumor development, progression, and metastasis, and very likely improves responsiveness to nivolumab therapies.

There is a significant unmet medical need in patients undergoing resection with curative intent, with 5-year survival of 77% for Stage IA3, dropping to 60% for patients with Stage IIA and 53% for patients with Stage IIIA. The perioperative addition of conventional cytotoxic chemotherapy, either in the preoperative or postoperative period, yields an approximate 5% increase in 5-year overall survival (OS) rates (Bunn 2019).

Recent neoadjuvant studies of single agent CPIs in NSCLC demonstrate that major pathologic responses (major pathologic response *10% viable tumor remaining) occur in approximately 20% of patients after 2 or 3 cycles. Several ongoing Phase 3 NSCLC trials are assessing combinations of preoperative nivolumab plus

chemotherapy followed by single agent nivolumab in the postoperative setting. By contrast to data for conventional cytotoxic chemotherapy (Bunn 2019), immunotherapy may be more effective if applied in the preoperative setting (Gajewski 2018).

FL-101 has not yet been administered for patients diagnosed with NSCLC. However, based on the results of the CANTOS study with another IL-1* blocking antibody, canakinumab, patients with NSCLC who receive FL-101 monotherapy or nivolumab plus FL-101 combination therapy are hypothesized to benefit from FL-101 treatment. Nonclinical, clinical, and pharmacodynamic evidence supports a potential clinical benefit for inhibition of IL-1* driven inflammation and suppression of anti-tumor immune responses in NSCLC and other tumor types

Study objective

Primary Objective:
To evaluate the safety and tolerability of FL-101 as monotherapy and in combination with nivolumab

Timepoint of evaluation of primary objective: From first dose to 3 months after surgery

Secondary Efficacy Objectives
1. Cohort 1: To evaluate the activity of FL-101 neoadjuvant monotherapy in patients with Stage IA3 or IB NSCLC
2. Cohort 2: To evaluate the effect of FL-101 in combination with nivolumab compared to nivolumab plus placebo in neoadjuvant therapy in patients with Stage II-IIIA NSCLC
3. To determine major pathologic response (MPR) rate
4. To estimate complete pathologic response (CPR) rate
5. To estimate the objective response rate (ORR) by RECIST 1.1 following neoadjuvant FL-101
6. To describe the time course of minimal residual disease (MRD) response by ctDNA and recurrence in correlation with clinical response

Pharmacologic (PK/PD) Objectives
1. To evaluate the PK of FL-101 in patients with NSCLC
2. To evaluate the effect of FL-101 on PD biomarkers

Safety Objectives
1. To evaluate possible immunogenicity, anti-drug antibodies

Time of evaluation of secondary objectives: At time of surgery

Study design

This is a 2-Cohort, Phase 2, multicenter, parallel-design trial in patients with surgically resectable non-small cell lung cancer.

In cohort 1 patients will be enrolled to receive FL-101 (200 mg) monotherapy administered IV on Day 1 of a 2-week cycle for 3 cycles preoperative.
In cohort 2 patients will be randomized to (1:1) to receive either PD-1 checkpoint inhibitor (Nivolumab) (240 mg) plus FL-101 (200 mg) combination therapy or Nivolumab (240 mg) plus placebo combination therapy on Day 1 of a 2-week cycle for 3 cycles preoperative. The randomization will be stratified based on the histological type of the NSCLC: squamous, adenocarcinoma, or other.

In both cohorts, Screening can occur up to 4 weeks before visit Day 1 of Cycle 1. There will be a total of 3 treatment visits, which will occur at Day 1 of each treatment cycle. One additional cycle of the assigned therapy can be administered if surgery is delayed for reasons other than toxicity of the therapy, such as Covid-19-related logistic delays.
Surgery should be conducted no earlier than 6 weeks after the first dose of study drug but no longer than 8 weeks after the first dose of study drug.
4 weeks after surgery an End of Treatment visit will take place and a follow up visit will be performed 12 weeks after surgery.

Intervention

In Cohort 1 patients will be receive FL-101 (200 mg) monotherapy administered IV on Day 1 of a 2-week cycle for 3 cycles preoperative.
In Cohort 2 patients be allocated to received either Nivolumab (240mg) plus FL-101 (200 mg) or Nivolumab (240 mg) plus placebo combination therapy administered IV on Day 1 of a 2-week cycle for 3 cycles preoperative.

Study burden and risks

FL-101 is an investigational medicinal product and has not yet been approved for any indication, therefore, it is not guaranteed that subjects will experience a clinical benefit from participation in this clinical study.
However, based on the results of the CANTOS study with another IL-1* blocking antibody, canakinumab, patients with NSCLC who receive FL-101 monotherapy or nivolumab plus FL-101 combination therapy are hypothesized to benefit from FL-101 treatment. Nonclinical, clinical and pharmacodynamic evidence supports a potential clinical benefit for inhibition of IL-1* driven inflammation and suppression of anti-tumor immune responses in NSCLC and other tumor types.
In addition, the data from this study may have an indirect benefit in that it will be used to further understand and characterize the safety and potential clinical benefit of FL-101 and may therefore help patients with certain types of cancer by contributing to medical research. The results of this study are expected to provide further insight into the safety, tolerability and efficacy of FL-101 either as monotherapy or in combination with a PD-1 inhibitor in

patients with NSCLC.

Prior to this study FL-101 (formerly LY2189102) has been tested in 4 clinical studies of 220 healthy volunteers and patients with Rheumatroid Arthritis or Type 2 diabetes at doses ranging from a single IV dose of LY2189102(0.05-5.0 mg/kg) to multiple (5 weekly) IV doses of LY2189102 (2.5 mg/kg)

LY2189102 was generally well tolerated at all doses and regimens tested. The most common side effects were headache, nausea, gastroenteritis, rhinitis (runny nose), urinary tract infection, influenza, back pain, cough, upper respiratory infection, rash, skin infection, hypertension, insomnia and injection site or infusion site reactions. Most treatment-emergent adverse events (TEAEs) were considered not related or unlikely related to study drug.

The potential burden and risk of participation in this study are not expected to be different than other comparable clinical research studies.
There are a total of 9 planned visits plus screening.

The number and amount of each blood draw, while more frequent than would be associated with normal clinical care has been planned to keep the total volume of blood drawn as low as possible. The patient will have a few extra visits scheduled for PK and ADA blood testing during the first cycle of treatment (cycle 1). The patient is offered the opportunity to have PK study visit Day 2, Day 4 and Day 8 performed at home or at another convenient alternate location by a home care service to reduce the burden.

Tumor tissue will be collected for the study during the planned surgery. The surgery and tissue resection is performed during normal clinical care to remove the tumor disease.

An ECG will be performed 5 times during the study. Risk associated with this test is minimal, where localized skin irritation from the gel pads is rarely seen.

Subject will require to have a CT-scan 4 times during the study. Possible side effects of CT scans involve the risks of the radiation that is used to obtain the images. If contrast material is used, there is a slight risk of developing an allergic reaction, which may cause symptoms ranging from mild itching or a rash to severe difficulty breathing, shock, or rarely, death. The contrast material may also cause kidney problems, especially if the subject is dehydrated or has poor kidney function. The investigator will ask the subject about any allergies or related conditions before the procedure. If the subject has any of these problems, they may not be allowed to have a CT scan. CT-scan is performed during normal clinical care to assess disease progression in subjects with NSCLC.

A brain-MRI scan will be performed at screening. Some subjects find it

uncomfortable to be confined in a small partially enclosed space and may feel claustrophobic or experience nervousness, sweating or other minor discomfort. As the machine attracts metals, subjects with metal in their bodies will be excluded from the study. There are no other known site effects resulting from exposure to MRI scan.

Contacts

Public
Flame Biosciences

280 Union Square Drive
New Hope 18938
US
Scientific
Flame Biosciences

280 Union Square Drive
New Hope 18938
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Male and female patients *18 years of age.
2. Previously untreated and pathologically confirmed, surgically resectable Stage IA3, IB, II, or IIIA NSCLC of squamous or non-squamous histology. Staging is based on the eighth edition of the AJCC/UICC staging system.
3. *1 radiologically measurable tumor >2 cm in diameter, as defined by RECIST v1.1.

4. Lung function capacity capable of tolerating the proposed lung surgery.
5. Smoking history *10 pack years.
6. High-sensitivity C-reactive protein (hsCRP) level *2 mg/L
7. Adequate organ function as defined by ALL of the following:
* Absolute neutrophil count *1500/µL
* Platelets *100,000/µL
* Hemoglobin *9 g/dL
* Aspartate aminotransferase/alanine aminotransferase *2.5× upper limit of normal (ULN)
* Total serum bilirubin *1.5×ULN*
*Patients with Gilbert*s disease: *3×ULN
* Alkaline phosphatase *2.5×ULN
* International normalized ratio (INR) and activated partial thromboplastin time (aPTT) *1.5×ULN unless the patient is on therapeutic anticoagulation.
* Serum creatinine *1.5×ULN
OR
Creatinine clearance *30 mL/min/1.73 m2 by Cockcroft-Gault estimation. The patient*s estimated CrCl will be calculated by the local laboratory (for eligibility purposes) using screening/baseline height (m), actual weight (kg), and serum creatinine:

Males: CrCl <= (140 * age in years) × weight (kg)
72× serum creatinine (mg/dL)

Females: CrCl <= (140 * age in years) × weight (kg) ×0.85
72× serum creatinine (mg/dL)
8. Available tissue block for analysis from a core needle biopsy (or similar sample).
* Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks (blocks are preferred) or at least 10 unstained slides, with an associated pathology report, for central testing.
* Acceptable samples include core-needle biopsies for deep tumor tissue (minimum of 3 cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.
9. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
10. Men must agree to use contraception or practice abstinence as well as refrain from donating sperm during the treatment period and for at least 180 days after the last dose of study treatment.
11. Women may participate if not pregnant, not breastfeeding, and at least 1 of the following conditions apply:
* Not a woman of childbearing potential (WOCBP)
* WOCBP who agrees to follow contraceptive guidance during the treatment period and for at least 180 days after the last dose of study treatment.

Female patients will be considered of non-reproductive potential (not a WOCBP) if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause. In women < 45 years of age, a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening

OR

(3) have a congenital or acquired condition that prevents childbearing.

12. Able and willing to comply with protocol-specified requirements and to provide written informed consent.

Exclusion criteria

1. Any prior exposure to chemotherapy, radiotherapy or systemic anti-cancer therapy (e.g., monoclonal antibody therapy) for lung cancer
2. Malignancies other than NSCLC within 2 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death and with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, or ductal carcinoma in situ treated surgically with curative intent) or undergoing active surveillance per standard-of-care management (e.g., chronic lymphocytic leukemia Rai Stage 0, prostate cancer with Gleason score * 6, and prostate specific antigen [PSA] * 10 mg/mL, etc.)
3. Currently participating in, or has participated in, a trial of an investigational agent within 4 weeks prior to the first dose of study treatment or 5 half-lives, whichever is longer without recovery of clinically significant toxicities from that therapy.
4. Any of the following tumor locations/types:
* NSCLC involving the superior sulcus
* Large cell neuro-endocrine cancer
* Sarcomatoid tumor
5. Tumors known to express driver mutations of the EGFR or ALK pathways. Patients whose driver mutation status is unknown may enroll in the study and their tissue will be checked after enrollment. The SAP will describe how the subset of patients who are subsequently found to have one of the 2 drive mutations will be handled.

6. History of non-infectious pneumonitis /interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease that requires steroids.
7. Had allogenic tissue/solid organ transplant.
8. Known severe hypersensitivity (Grade *3) to FL-101, its active substance, or any of its excipients.
9. Known history of human immunodeficiency virus or active Hepatitis B or Hepatitis C infection.
10. Received radiotherapy within 2 weeks of start of study treatment.
11. Symptomatic herpes zoster within the past 30 days, a serious bacterial infection within the past 6 months or have had other recent or ongoing signs of infections.
12. Received a live or attenuated vaccine within 30 days prior to the first dose of study treatment.
13. Clinically unstable disease in any organ system despite current therapy, including, but not limited to ongoing or active infection including tuberculosis, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations.
14. Use of illicit drugs or excess intake of alcohol, based on the judgement of the investigator.
Additional Exclusion Criteria for Patients with Stage II and III Disease
1. Prior treatment with anti-PD-1, anti-CTLA-4, or anti-PD-L1 therapeutic antibody or pathway-targeting agents
2. Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Cycle 1, Day 1
* EXCEPTION: Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled.
* EXCEPTION: The use of inhaled corticosteroids for asthma / COPD and mineralocorticoids (e.g., fludrocortisone) for orthostatic hypotension or adrenocortical insufficiency is allowed.
3. Known severe hypersensitivity (Grade *3) to nivolumab or any of the study chemotherapy agents or to any of their excipients.
4. Active autoimmune disease that has required systemic treatment in past 2 years. History or risk of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener*s granulomatosis, Sjögren*s syndrome, Bell*s palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, uveitis, or glomerulonephritis.
* Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone are eligible.
* Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen are eligible.
* Patients with eczema, psoriasis, lichen simplex chronicus or vitiligo with

dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted if they meet the following conditions:
* Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations.
* Rash must cover <10% of body surface area.
* Disease is well controlled at baseline and only requiring low potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%)
* No acute exacerbations of an underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids)

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	-
Product type:	Medicine
Brand name:	Opdivo

Generic name:	Nivolumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	07-07-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Not approved Date:	13-09-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-10-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2020-005602-26-NL

Register	ID
ClinicalTrials.gov	NCT04758949
CCMO	NL77633.100.21