A Randomized Phase 3 Study of Sitravatinib in Combination with Nivolumab Versus Docetaxel in Patients with Advanced Non-Squamous Non-Small Cell Lung Cancer with Disease Progression On or After Platinum-Based Chemotherapy and Checkpoint Inhibitor Therapy (SAPPHIRE)

Published: 16-06-2020
Last updated: 10-01-2025

This study has been transitioned to CTIS with ID 2024-516598-60-00 check the CTIS register for the current data. Primary Objective: To compare Overall Survival (OS) in patients with non-squamous NSCLC who have experienced disease progression on or...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON54407

Source
ToetsingOnline

Brief title
SAPPHIRE

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Non-Squamous Non-Small Cell Lung Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Mirati Therapeutics, Inc.
Source(s) of monetary or material Support: Mirati Therapeutics (the sponsor)

Intervention

Keyword: Lung Cancer, Phase 3, Sitravatinib

Outcome measures

Primary outcome

Overall Survival (OS)

Secondary outcome

• Safety characterized by type, incidence, severity, timing, seriousness and

relationship to study treatment of adverse events, laboratory abnormalities,

and number of patients discontinuing study treatment due to an adverse event.

• Secondary efficacy endpoints:

* - Objective Response Rate (ORR) as defined by Response Evaluation Criteria in

Solid Tumors version 1.1 (RECIST 1.1).

* - Duration of Response (DOR);

* - Clinical Benefit Rate (CBR);

* - Progression-Free Survival (PFS); and

* - 1-Year Survival Rate.

• Blood plasma concentrations of MGCD516.

• Patient reported outcome (PROs):

* - Lung Cancer Symptom Scale (LCSS); and

* - European Quality of Life Five Dimensions Questionnaire (EQ-5D-5L).

Study description

Background summary

Combining an immunotherapeutic Programmed Cell Death 1 checkpoint inhibitor with an agent that has both immune modulatory and antitumor properties could enhance the antitumor efficacy observed with either agent alone.
The use of tyrosine kinase inhibitors (TKIs) to treat cancer is well established based on robust clinical efficacy achieved with well-tolerated inhibitors directed toward oncogenic tyrosine kinases. In addition, selected TKIs have been shown to modulate the immunogenic status of tumors, improve tumor perfusion by reducing intratumoral pressure and modulate subsets of immune cells, thereby increasing the frequency and function of effector immune elements while decreasing the number and function of immune suppressor cells. Taken together, these effects on the tumor microenvironment (TME) may lead to improved efficacy when TKIs are combined with checkpoint inhibitors. The TAM (Tyro3, Axl and MERTK) receptor tyrosine kinases (RTKs) are expressed by select innate immune cell subpopulations including macrophages and dendritic cells. The TAM receptors cooperate to create and maintain an immunosuppressive TME. MERTK suppresses the M1 macrophage pro-inflammatory cytokine response involving IL-12, IL-6 and TNF and enhances M2 macrophage anti-inflammatory cytokine production involving IL-10, IL-4, TGFβ and hepatocyte growth factor (HGF). In addition, M2 macrophages express checkpoint ligands such as PD-L1, PD-L2, B7-H1 and B7-H2 that further inhibit T effector cell function. Given that anti-tumor host defense is usually mediated by cytotoxic T lymphocytes whose activation and stimulation is supported by Th1 type cytokines, the inhibition of Axl and MERTK are predicted to enhance an anti-tumor immune response. Furthermore, both Axl and MERTK are expressed by natural killer (NK) cells and negatively regulate NK cell activity in the TME as part of a feedback regulatory mechanism resulting in decreased NK cell anti-tumor activity and enhanced tumor progression and metastasis. Given the immunosuppressive function of TAM RTKs in the TME, inhibition of Axl and MERTK may complement PD-1/PD-L1 checkpoint inhibition to unleash the host anti-cancer immune response.

The MET (Mesenchymal-Epithelial Transition) RTK is implicated in modification of tumor immune responses based on its role in mediating an immunosuppressive TME as well as its role in regulating antigen presenting cell (APC) function.

MET is expressed by immature CD14-positive monocytes and can induce an immunosuppressive phenotype when its ligand, HGF, is secreted by tumor stroma and mesenchymal stem cells (MSCs). Depletion of CD14-positive monocytes or neutralization of HGF secretion by MSCs reverses the suppression of T effector proliferation and triggers a shift back toward a Th1 activated T cell phenotype. MSCs are also implicated in expansion of immunosuppressive myeloid-derived suppressor cells (MDSCs), which are also dependent on the secretion of HGF. APCs (i.e., dendritic cells) also express MET and the activation of MET by HGF results in suppression of APC function including both antigen presenting capacity and antigen-dependent T cell responses. Therefore, inhibition of MET may enhance the antitumor response by restoring APC function and reducing or eliminating MDSCs within the TME.

Inhibition of the VEGF receptor family and KIT may further enhance antitumor immunoreactivity by depletion of immunosuppressive cellular subsets from the TME including T regulatory cells (Tregs) and MDSCs. Tregs express VEGFR2 and the inhibition of VEGFR2 utilizing a specific VEGFR2 antibody antagonist or VEGFA neutralizing antibody (but not a VEGFR1 antagonist) inhibited Treg cell proliferation in vitro and in tumor-bearing mice and patient peripheral blood. MDSCs notably express both KIT and VEGFR1 and the inhibition of these RTKs using pharmacologic or genetic approaches resulted in the inhibition of MDSC viability in vitro and depletion of this cell population in mouse tumor models.

Sitravatinib is a spectrum-selective RTK inhibitor that inhibits several closely related RTKs including the TAM family (Tyro3/Axl/MERTK), VEGFR2, KIT, and MET. Based on the role of these receptors in key immune cell types, sitravatinib and checkpoint inhibitor therapy (CIT) are predicted to have complementary effects in triggering a tumor-directed immune response. Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and selectively blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.

Nivolumab has been approved for the treatment of patients with advanced or metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy.

While anti-PD-1/PD-L1 antibodies, including nivolumab, produce durable responses in some patients with NSCLC and other cancers, the majority of patients do not respond to single agent CIT or eventually progress. The mechanism of action of PD-1 inhibitors has been an area of intense research and multiple factors have emerged that correlate with resistance, including both factors intrinsic to tumor cells as well as an immunosuppressive tumor microenvironment.

Combining an immunotherapeutic PD-1/PD-L1 checkpoint inhibitor with an agent that has both immune modulatory and antitumor properties could enhance the

antitumor efficacy observed with either agent alone.
Docetaxel is approved as a single-agent chemotherapy option for the treatment of patients with advanced NSCLC previously treated with platinum-based chemotherapy. Median overall survival reported in randomized clinical trials using docetaxel in the second-line treatment setting has varied between approximately 5.7 and 9.5 months. Median overall survival with docetaxel in the third-line treatment setting, post-CIT, is not expected to be significantly different than in the second-line setting with median overall survival of approximately 6.8 to 9.0 months reported in retrospective analyses.

This study will compare the efficacy of sitravatinib in combination with nivolumab versus docetaxel in patients with advanced non-squamous NSCLC who have previously experienced radiographic disease progression on or after platinum-based chemotherapy and checkpoint inhibitor therapy.

Study objective

This study has been transitioned to CTIS with ID 2024-516598-60-00 check the CTIS register for the current data.

Primary Objective:
To compare Overall Survival (OS) in patients with non-squamous NSCLC who have experienced disease progression on or after platinum-based chemotherapy and CIT, treated with sitravatinib and nivolumab versus docetaxel.

Secondary Objectives:
• To evaluate the safety of sitravatinib in combination with nivolumab in the study population.
• To evaluate the relative tolerability of sitravatinib and nivolumab versus docetaxel.
• To evaluate secondary efficacy endpoints in the study population.
• To evaluate the pharmacokinetics (PK) of sitravatinib (MGCD516) administered in combination with nivolumab.
• To evaluate health-related quality of life and lung cancer-specific symptoms in the study population.

Exploratory Objective:
• To assess correlations between baseline tumor immune biomarkers and gene mutations and treatment-related outcomes.
• To evaluate efficacy endpoints using exploratory disease response criteria.
• To characterize the immunogenicity of nivolumab in combination with sitravatinib.

Study design

Study 516-005 is an open-label, randomized (1:1), multicenter, Phase 3 clinical

trial evaluating the efficacy and safety of nivolumab in combination with the investigational agent sitravatinib compared to docetaxel in patients with advanced non-squamous NSCLC who have previously experienced radiographic disease progression on or after treatment with CIT either administered in combination with platinum-based chemotherapy or following platinum-based chemotherapy. The primary objective is to compare OS in the two treatment arms. Secondary objectives include evaluation of safety and tolerability, secondary efficacy endpoints, PK of sitravatinib, and patient reported outcomes. Correlative science endpoints include tumor PD-L1 expression, tumor gene mutations, nivolumab ADA and ctDNA. The Schedule of Assessments to be performed in the study is presented in Table 1.

Patient eligibility for study enrollment based on radiographic disease progression on or after treatment with CIT and platinum-based chemotherapy will be evaluated by the Investigator. Data entered into the case report form (CRF) are to include the date of at least one radiographic evaluation prior to the occurrence of disease progression on most recent CIT treatment and the date the radiographic evaluation demonstrating disease progression, as well as specifics about organ systems (e.g., lung, liver, lymph node, bone and/or brain) having tumors that increase in size or are new.

Patient randomization will be stratified based on:
1. Prior treatment regimens in the advanced setting (1 versus 2);
2. ECOG Performance Status at baseline (0 versus 1); and
3. Presence of brain metastasis at baseline (presence versus absence).

Patients randomized to the experimental arm will receive treatment with nivolumab in combination with sitravatinib, delivered in 28-day cycles. Nivolumab will be administered as an infusion over approximately 30 minutes at 240 mg every 2 weeks or 480 mg every 4 weeks, at the discretion of the Investigator. Sitravatinib capsules will be administered orally at 120 mg once daily (QD).
Patients randomized to the comparator arm will receive treatment with docetaxel, delivered in 21-day cycles. Docetaxel will be administered by intravenous infusion at 75 mg/m2 over 1 hour or according to institutional practices, every 3 weeks. Premedication with dexamethasone will be required in accordance with regional standards.

Disease assessments and patient-reported outcomes questionnaires must be performed as scheduled according to the calendar to prevent the introduction of bias based on toxicity into the assessment of efficacy. Disease response and progression per RECIST 1.1 as documented by the Investigator in the CRF will be the basis for patient management and supportive statistical analyses of radiology-based study endpoints.

Central radiology review for disease response and progression will be conducted. Timely and complete disease assessments and transfer of radiographic

documentation to the Central Radiology Laboratory is critical to the integrity of this clinical trial.

Patients will receive study treatment as assigned at randomization until disease progression, unacceptable adverse events, investigator decision, patient refusal or death. Patients experiencing clinical benefit in the judgment of the Investigator may continue study treatment beyond disease progression as defined by RECIST 1.1 if the progression is not rapid, symptomatic, or requiring urgent medical intervention. Patients considering continuation of study treatment beyond RECIST 1.1 defined disease progression must be provided with and sign an informed consent detailing any available therapies and potential clinical benefit that the patient may be foregoing by continuing study treatment. Patients remaining on study treatment beyond RECIST 1.1. defined progression will continue to undergo disease assessments until study treatment is discontinued. Post- treatment disease assessment will continue until objective disease progression and PRO assessments will continue until start of subsequent anti-cancer therapy. No crossover to the alternative treatment assignment is provided in this study.

A sample size of approximately 532 patients is planned for this study; a total of 372 OS events will be required to detect the hypothesized HR. The study will employ a group sequential design with one planned interim analysis and a final analysis for the primary endpoint of OS.

Intervention

Patients will be randomly assigned (like tossing a coin) to either the sitravatinib with nivolumab group or the docetaxel group. They have a 50% chance of receiving sitravatinib combined with nivolumab and a 50% chance of receiving chemotherapy docetaxel. This means 1 out of 2 people will get sitravatinib with nivolumab. The patient and the doctor will know which treatment they are assigned to.

Sitravatinib will be provided as capsules. Nivolumab and docetaxel will be administered by intravenous infusions (infusion of the liquid medication directly into the vein).

See also protocol Table 1 - Schedule of Assessments.

Study burden and risks

Please see Table 1 (Schedule of Assessments) in the protocol, page 20-23; and Table 2 (Schedule of PK Samle Collection for Sitravatinib and Triplicate ECG Assessments) in the protocol, page 24, for a detailed overview of visits, tests and examinations.

The risks associated with the study are described in the informed consent form, chapter 6 (Possible side effects and complications).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study. 1. Histologically or cytologically confirmed non-squamous NSCLC with metastatic (Stage IV) or unresectable, locally advanced (Stage IIIB/IIIC) disease, not amenable to treatment with curative intent including concurrent chemoradiotherapy. 2. Receipt of at least one but not more than two prior treatment regimens in the advanced disease setting to include: * Treatment with a CIT (i.e., anti-PD-1/PD-L1) and a platinum-based chemotherapy, which may have been in combination or in sequence (i.e., platinum-based chemotherapy followed by CIT) o Prior treatment may have included maintenance therapy with a

chemotherapy agent (e.g., pemetrexed) and/or a CIT * Most recent treatment regimen must have included a CIT with radiographic disease progression on or after treatment, for example: o 1 prior treatment regimen: platinum-based chemotherapy in combination with CIT radiographic disease progression, or o 2 prior treatment regimens: platinum-based chemotherapy -> disease progression * CIT -> radiographic disease progression* NOTE: Platinum-based adjuvant, neoadjuvant, or definitive chemoradiation therapy given for locally advanced disease followed by recurrent or metastatic disease within 6 months of completing chemotherapy may be considered treatment in the advanced disease setting. 3. Duration of at least 4 months (120 days) from first dose of most recent CIT to date of radiographic disease progression. 4. Availability of source documents for historical disease evaluations to allow Investigator certification of disease progression on or after most recent CIT. 5. Most recent prior therapy (e.g., chemotherapy, CIT, or radiation therapy) discontinued at minimum of 2 weeks before the date of randomization; palliative radiation therapy to skeletal metastases and stereotactic radiation for brain metastases allowed if discontinued at least 7 days before the date of randomization. 6. Candidacy to receive treatment with docetaxel as the next line of therapy if randomized to the comparator arm. 7. Recovery from adverse effects of prior therapy to baseline or Grade 1 (excluding alopecia). 8. >= 18 years of age. 9. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. 10. Life expectancy of at least 3 months. 11. Adequate bone marrow and organ function demonstrated by: a. Absolute neutrophil count **1,500/mm3 (**1.5 × 109/L). b. Hemoglobin >= 9.0 g/dL not dependent on transfusion support. c. Platelet count >= 100 × 109/L (>= 100,000 per mm3). d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <= 1.5 × ULN with alkaline phosphatase <= 2.5 × ULN. e. Serum bilirubin <= 1.0 x ULN. f. Calculated creatinine clearance >= 40 mL/min, using the Cockcroft-Gault formula. 12. Women of child-bearing potential (WOCBP) or men whose partner is a WOCBP agrees to use contraception while participating in this study, and for a period of 6 months following termination of study treatment. 13. Completed informed consent process, including signing IRB/EC-approved informed consent form. 14. Willing to comply with clinical trial instructions and requirements.

Exclusion criteria

Patients presenting with any of the following will not be included in the study: 1. Discontinuation of prior treatment with CIT more than 90 days prior to the date of randomization. 2. Receipt of systemic cancer therapy since discontinuation of CIT, with the exception of maintenance chemotherapy. 3. Active brain metastases. Patients are eligible if brain metastases are adequately treated and patients are neurologically stable (except for residual signs or symptoms related to the central nervous system (CNS) treatment) for at least 2 weeks prior to randomization without the use of anticonvulsants and without the use of corticosteroids (or are on a stable or decreasing dose of <=10 mg daily prednisone or equivalent). 4. Carcinomatous meningitis. 5. Known history of tumors that test positive for EGFR, ROS1, ALK mutations, or ALK fusions. 6. Prior therapies: a. Immunotherapies not previously specified, including anti-OX40 and anti-CD137; prior anti-CTLA-4 is permitted. b. Cancer therapy having the same mechanism of action as sitravatinib (e.g., tyrosine kinase inhibitor with a similar target profile or bevacizumab). 7. Known toxicity on prior checkpoint inhibitor treatment: a. >= Grade 3 immune-related AE related to checkpoint inhibitor. b.

Grade 2 immune-related AE associated with checkpoint inhibitor unless the AE resolved or was well controlled by withholding the checkpoint inhibitor and/or treatment with steroids, with the exception of prior colitis, myocarditis, and pneumonitis, which are exclusionary. c. CNS or ocular AE of any grade related to checkpoint inhibitor. NOTE: Patients with a prior endocrine AE are permitted to enroll if they are stably maintained on appropriate replacement therapy and are asymptomatic. 8. Active or prior documented autoimmune disease: a. Inflammatory bowel disease (e.g., Crohn*s disease, ulcerative colitis). b. History of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD. c. Active or prior documented autoimmune disease within the past 2 years. NOTE: Patients with Type 1 diabetes, vitiligo, Graves* disease, residual hypothyroidism due to an autoimmune condition only requiring hormone replacement, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded. 9. Active or prior immunocompromising conditions: a. Current or prior use of immunosuppressive medication within 28 days before the date of randomization, with the exceptions of topical, ocular, intranasal and inhaled corticosteroids (with minimal systemic absorption) or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid. A brief course (<= 3 days) of systemic corticosteroids >10 mg/day of prednisone (or equivalent corticosteroid) for prophylaxis (e.g., contrast dye allergy) or for treatment of non-immune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted within the 28 days. b. Known acute or chronic human immunodeficiency virus (HIV); i. Sites in Germany and Switzerland only: HIV infection at screening (positive HIV test). c. History of primary immunodeficiency. d. History of allogeneic transplant. 10. History of severe hypersensitivity reaction to any monoclonal antibody or polysorbate 80. 11. Criterion #11 removed, but numbering maintained 12. Use of live vaccines against infectious disease (e.g. varicella) within 28 days of the date of randomization (note: killed vaccinations (e.g. influenza) are allowed at any appropriate time before and during the study). 13. Known acute or chronic hepatitis B or hepatitis C. Patients treated for hepatitis C with no detectable viral load are permitted. Sites in Germany and Switzerland (testing required during screening): positive hepatitis B surface antigen [HBsAg] or positive hepatitis C virus [HCV] antibody; i. patients with past or resolved hepatitis B virus (HBV) infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible only if HBV DNA is negative ii. patients treated for hepatitis C with no detectable viral load (HCV RNA negative) are permitted 14. History of hypersensitivity to study treatment excipient. 15. History of stroke or transient ischemic attack within the previous 6 months. 16. Any of the following cardiac abnormalities: a. Unstable angina pectoris within the past 6 months. b. Symptomatic or uncontrolled atrial fibrillation within the past 6 months. c. Congestive heart failure >= NYHA Class 3 within the past 6 months. d. Prolonged QTc on electrocardiogram >480 milliseconds. e. Left ventricular ejection fraction (LVEF) < 40%. 17. Ongoing need for treatment with concomitant medication known to cause prolonged QTc. Such medication may be discontinued or changed to a different medication prior to enrollment. 18. Uncontrolled arterial hypertension (> 150 mm Hg systolic or > 100 mm Hg diastolic) on multiple observations despite standard of care treatment. 19. Major surgery within 4 weeks of the date of randomization. 20. History of significant hemoptysis or hemorrhage within 4 weeks of the date of randomization. 21. Known or suspected presence of another malignancy that could be mistaken for the malignancy under study during disease assessments. 22. Pregnancy. WOCBP must have a negative serum or urine pregnancy test documented within

the screening period prior to the date of randomization. 23. Breast-feeding or planning to breast-feed during the study or within 30 days following the last dose of docetaxel or sitravatinib and within 5 months following the last dose of nivolumab. 24. Any serious illness, uncontrolled inter-current illness, psychiatric illness, active or uncontrolled infection, or other medical condition or history, including laboratory results, which, in the Investigator*s opinion, interferes with the patient*s capacity to provide informed consent, or would be likely to interfere with the patient*s participation in the study, or with the interpretation of the results.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	15-04-2021
Enrollment:	75
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Opdivo
Generic name:	Nivolumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Sitravatinib
Generic name:	Sitravatinib
Product type:	Medicine
Brand name:	Taxotere

Generic name:	Docetaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	16-06-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	11-12-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	22-03-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-08-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-09-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-11-2021
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	09-12-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-03-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-07-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-07-2023
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	21-12-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-01-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-06-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-06-2024
Application type:	Amendment
Review commission:	METC NedMec

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
EU-CTR	CTIS2024-516598-60-00
EudraCT	EUCTR2019-001043-41-NL
ClinicalTrials.gov	NCT03906071
CCMO	NL73350.031.20