A Randomized, Double-Blind Phase 2 Study of Ruxolitinib or Placebo in Combination With Pemetrexed/Cisplatin and Pemetrexed Maintenance for Initial Treatment of Subjects With Nonsquamous Non-Small Cell Lung Cancer That Is Stage IIIB, Stage IV, or Recurrent

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Primary Objectives:• Part 1: To evaluate the safety and tolerability of ruxolitinib in combination with pemetrexed/cisplatin and select a dose for further evaluation• Part 2: To evaluate and compare the overall survival of subjects with nonsquamous...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON41950

Source
ToetsingOnline

Brief title
Not Applicable

Condition

- Other condition

Synonym
lungcancer

Health condition

niet-squamous, niet-kleincellig longcarcinoom

Research involving
Human

Sponsors and support

Primary sponsor: Incyte Corporation
Source(s) of monetary or material Support: Incyte Corporation

Intervention

Keyword: NSCLC, Ruxolitinib

Outcome measures

Primary outcome

Primary Endpoints:

• Part 1: Determination of the dose of ruxolitinib that is safe and tolerable

in combination with pemetrexed/cisplatin.

• Part 2: Overall survival as determined from the date of randomization until

death due to any cause.

Secondary outcome

Secondary Endpoints:

• Progression-free survival as determined from the randomization date until the

earliest date of disease progression, as measured by investigator assessment of

objective radiographic disease assessments per RECIST (v1.1), or death due to

any cause if earlier.

• Objective response rate and duration of response determined by radiographic

disease assessments per RECIST (v1.1).

• Safety and tolerability of the treatment regimens assessed by monitoring the

frequency, duration and severity of AEs; performing physical examinations; and

evaluating change in vital signs and laboratory results.

Study description

Background summary

Overall, the safety profile of ruxolitinib in the PV population treated with ruxolitinib is generally consistent with what was observed in the MF population. Ruxolitinib was generally well tolerated in patients with PV and only a small proportion of patients discontinued ruxolitinib due to AEs (3.6%). Most of the AEs have been managed by dose adjustments. Hematological toxicities were less frequent and less severe in patients with PV as compared to those observed in patients with MF.
No new safety signals emerged from a study in pancreatic cancer in combination with capecitabine.
The AE profile of the compound has been assessed in 198 healthy volunteers, subjects with various degrees of renal (n=32) or hepatic (n=24) impairment, and in patients with RA (n=59) receiving ruxolitinib: AEs were, in general, mild and resolved without interventions.
A thorough QT study was conducted in 50 healthy subjects. There was no indication of a QT/QTc prolonging effect of ruxolitinib in single doses up to a supra-therapeutic dose of 200mg indicating that ruxolitinib has no effect on cardiac repolarization.

Study objective

Primary Objectives:
• Part 1: To evaluate the safety and tolerability of ruxolitinib in combination with pemetrexed/cisplatin and select a dose for further evaluation
• Part 2: To evaluate and compare the overall survival of subjects with nonsquamous non-small cell lung cancer (NSCLC) that is Stage IIIB, Stage IV, or recurrent when treated with ruxolitinib or placebo in combination with pemetrexed/cisplatin and subsequently pemetrexed maintenance
Secondary Objectives:
• To evaluate and compare the efficacy of the 2 treatment arms with respect to progression-free survival (PFS)
• To evaluate and compare the efficacy of the 2 treatment arms with respect to overall tumor response and duration of response

• To evaluate and compare the safety and tolerability of ruxolitinib in combination with pemetrexed/cisplatin versus pemetrexed/cisplatin alone
Exploratory Objectives:
• To evaluate changes in pharmacodynamic (PD) and tumor markers
• To evaluate pharmacokinetics (PK) of ruxolitinib, cisplatin, and pemetrexed alone or in combination
• To evaluate molecular signatures that may be associated with response or resistance to treatment if sufficient numbers of biopsy samples are available
• To evaluate and compare the 2 treatment arms with respect to changes in health-related quality of life (HR-QOL)
• To evaluate and compare the 2 treatment arms with respect to changes in body weight relative to baseline.

Study design

This is a Phase 2 study in subjects with nonsquamous NSCLC that is Stage IIIB, Stage IV, or recurrent. The study consists of 2 parts. Part 1 is an open label safety run-in phase designed to assess the safety and tolerability of the combination of ruxolitinib plus pemetrexed/cisplatin and to select an appropriate dose of ruxolitinib in this patient population. Part 2 is planned to be a randomized, double-blind Phase 2 study with 2 treatment arms: ruxolitinib plus pemetrexed/cisplatin versus placebo plus pemetrexed/cisplatin. Maintenance therapy with ruxolitinib or placebo in combination with pemetrexed, based on the original treatment assignment, will be allowed for subjects eligible for maintenance therapy. In Part 1, if a dose of ruxolitinib with concomitant granulocyte colony-stimulating factor (GCSF) is selected for Part 2, then Part 2 will be conducted as a randomized, unblinded, open-label study.
Part 1: Safety Run-in Phase. The safety run-in portion will test up to 2 doses of ruxolitinib (15 mg twice daily (BID) and 10 mg BID) in combination with a single standard dose on Day 1 of pemetrexed/cisplatin (500 mg/m2 pemetrexed administered as an intravenous infusion over 10 minutes/75 mg/m2 cisplatin infused over 2 hours beginning 30 ± 5 minutes after the end of the pemetrexed infusion) for a 21-day assessment period (1 cycle designated Treatment Cycle 1 or TCycle 1). Initially, 9 subjects will be enrolled in Cohort 1 and will receive 15 mg ruxolitinib BID. At the end of 21 days, subjects who took at least 34 doses of ruxolitinib during the 21-day cycle (ie, took BID doses for 17 of the 21 days) OR experienced a dose-limiting toxicity (DLT) will be included in the evaluation cohort. Additional subjects will be enrolled to achieve a minimum of 9 subjects in the evaluation cohort if there are discontinuations or dose interruptions that result in a subject being nonevaluable.

After evaluation, the following actions will occur, involving up to 4 successive cohorts:
Cohort 1 (9 Subjects) : 15 mg ruxolitinib BID plus pemetrexed/cisplatin (single intravenous infusion doses on Day 1).

- DLTs observed : < 3 Action taken : Begin randomized portion of study using 15 mg ruxolitinib BID.
- DLTs observed : >= 3 Action taken : Enroll Cohort 2.

Cohort 2 (9 Subjects) :10 mg BID ruxolitinib plus pemetrexed/cisplatin (single intravenous infusion doses on Day 1).
- DLTs observed : < 3 Action taken : Begin randomized portion of study using 10 mg ruxolitinib BID.
- DLTs observed : >= 3 Action taken : If at least 1 DLT was based on neutropenia, enroll Cohort 3. If DLTs are not neutropenia-related, terminate study.

Cohort 3 (9 Subjects) :10 mg ruxolitinib BID plus pemetrexed/cisplatin (single intravenous infusion doses on Day 1) plus GCSF.
- DLTs observed : < 3 Action taken : Enroll Cohort 4.
- DLTs observed : >= 3 Action taken : Terminate the study.

Cohort 4 (9 Subjects) : 15 mg BID ruxolitinib plus pemetrexed/cisplatin (single intravenous infusion doses on Day 1) plus GCSF.
- DLTs observed : < 3 Action taken : Begin randomized portion of study using 15 mg ruxolitinib BID and prophylactic GCSF support.
- DLTs observed : >= 3 Action taken : Begin randomized portion of study using 10 mg ruxolitinib BID and prophylactic GCSF support.
The maximum tolerated dose (MTD) is the highest dose level tested that is considered tolerated on the basis of fewer than 3 DLTs in a cohort of 9 subjects.

If the MTD is exceeded in Cohort 1 or 2 and >= 1 DLT was neutropenia (see hematologic DLTs below), a third cohort using 10 mg ruxolitinib BID and pemetrexed/cisplatin with prophylactic GCSF will be enrolled. In this case, GCSF will be given as pegfilgrastim or as filgrastim, if the investigative site uses the latter as their standard for GCSF. Evaluation of the 10 mg ruxolitinib BID combination with pemetrexed/cisplatin and prophylactic GCSF support will follow the same decision scheme; the study will be terminated if 10 mg ruxolitinib BID cannot be tolerated in combination with pemetrexed/cisplatin and GCSF prophylactic support as evidenced by an incidence rate of >= 33% DLTs in the 21-day evaluation period. If 10 mg ruxolitinib BID with GCSF prophylactic support is adequately tolerated, a fourth cohort to explore the safety and tolerability of 15 mg ruxolitinib BID with GCSF prophylactic support will be enrolled. Part 2 of the study will proceed with either 15 mg or 10 mg ruxolitinib BID, with prophylactic GCSF support, based on Part 1 of the study.
After the 21-day safety evaluation period, safety run-in subjects may receive 3 additional cycles of pemetrexed/cisplatin (Treatment Cycles or TCycles 2, 3, and 4) in combination with ruxolitinib, and subjects with an objective response or stable disease (SD) may receive up to 2 additional cycles (TCycles 5 and 6), as long as adequately tolerated and disease progression has not occurred,

followed by maintenance pemetrexed (Maintenance Cycles or MCycles) in combination with ruxolitinib, with study visits each 21 day cycle.
Measurements and procedures will follow those described in Section 4.1.3.2 for the randomized, double-blind phase. Ruxolitinib doses will be determined by the degree of thrombocytopenia and neutropenia observed in the safety run-in cohort and will follow the dose adjustment rules described in the body of the Protocol.
Adverse events (AEs) occurring during the safety run-in portion of the study will be considered to be DLTs if they are not clearly related to the underlying disease, its progression, a comorbidity, or concomitant medication (excluding pemetrexed or cisplatin), or if they are transient (<= 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination. A DLT will be defined as an AE that is new in onset and meets any of the following criteria, using the CTCAE v4.03 toxicity grading scale:
Hematologic toxicities:
• Grade 3 thrombocytopenia with bleeding requiring transfusion of red blood cells
• Grade 4 thrombocytopenia
• Febrile neutropenia (absolute neutrophil count [ANC] < 1.0 × 109/L and fever > 101°F/38.3°C)
• Grade 4 neutropenia that does not recover to <= Grade 2 within 3 days after holding the ruxolitinib dose or requiring myeloid growth factors
NOTE: Ruxolitinib is suspected to cause transient decreases in white blood cells (WBCs) due to margination; therefore, DLT rules require neutropenia to persist after holding ruxolitinib for 3 days. Where the clinical status of the subject allows, investigators are encouraged to wait 24 hours before starting myeloid growth factors to determine if WBC margination is contributing to the degree of neutropenia.
Nonhematologic toxicity:
• Any >= Grade 3 nonhematologic toxicity EXCEPT:
* Nausea, vomiting, and diarrhea adequately controlled with medical therapy within 48 hours
* Changes in cholesterol levels
Grade 3 or 4 laboratory abnormalities should be confirmed within 72 hours.
Part 1 will be conducted at selected clinical study sites (in United States only). Enrollment will be controlled by distribution of enrollment slots to the clinical sites by the sponsor or its designee. The sponsor will conduct approximately weekly safety teleconferences with the investigators participating in Part 1 to review subject status and safety findings to ensure safe, appropriate dosing.
Part 2: Randomized, Double-Blind Phase. Part 2 will be enrolled and conducted provided an MTD can be established for ruxolitinib in combination with cisplatin/pemetrexed in Part 1 of the study. The randomized, double-blind phase of the study will enroll approximately 120 subjects, randomized 1:1 and stratified for a modified Glasgow prognostic score (mGPS) of 1 or 2 into 2 treatment arms:

• Arm 1: Ruxolitinib (at dose selected from safety run-in phase) plus pemetrexed 500 mg/m2 administered as an intravenous infusion over 10 minutes and cisplatin 75 mg/m2 infused over 2 hours beginning 30 ± 5 minutes after the end of the pemetrexed infusion on Day 1 of each 21 day cycle for up to 4 cycles (Treatment Cycles or TCycles 1, 2, 3, and 4), as long as adequately tolerated and disease progression has not occurred. Two additional cycles (TCycles 5 and 6) may be administered in subjects with an objective response or SD, as long as adequately tolerated and disease progression has not occurred. Subjects will then receive maintenance pemetrexed (Maintenance Cycles or MCycles) (if adequately tolerated) with ruxolitinib.
• Arm 2: Matching placebo plus pemetrexed 500 mg/m2 administered as an intravenous infusion over 10 minutes and cisplatin 75 mg/m2 infused over 2 hours beginning 30 ± 5 minutes after the end of the pemetrexed infusion on Day 1 of each 21 day cycle for up to 4 cycles (TCycles 1, 2, 3, and 4), as long as adequately tolerated and disease progression has not occurred. Two additional cycles (MCycles 5 and 6) may be administered in subjects with an objective response or SD, as long as adequately tolerated and disease progression has not occurred. Subjects will then receive maintenance pemetrexed (MCycles) (if adequately tolerated) with matching placebo.
In Part 1, if a dose of ruxolitinib with concomitant GCSF is selected for Part 2, then Part 2 will be conducted as a randomized, unblinded, open label study. In this case, the control group will utilize cisplatin/pemetrexed with no placebo. Maintenance therapy with pemetrexed and study drug will not include prophylactic GCSF if the induction therapy with pemetrexed/cisplatin requires primary or secondary GCSF prophylaxis.

Intervention

Study Schedule/Procedures:
Safety Run-in Phase: Subjects will have regularly scheduled study visits at screening and baseline (Day 1). Blood samples will be drawn at each visit to monitor hematologic and serum chemistry parameters. Subjects will also have brief study visits at Day 8 and Day 15, primarily for hematology assessments. The prestudy radiographic measurement for tumor size will be performed at the screening visit. After 21 days, safety run-in subjects may receive up to 3 additional cycles of pemetrexed/cisplatin (TCycles 2, 3, and 4) in combination with ruxolitinib, and subjects with an objective response or SD may receive up to 2 additional cycles (TCycles 5 and 6), as long as adequately tolerated and disease progression has not occurred, followed by maintenance pemetrexed (MCycles) in combination with ruxolitinib at the same cohort-specific dose or as adjusted based on the dose reduction rules described in the body of the Protocol. Subjects will have a regularly scheduled study visit at the clinical site on Day 1 (± 3 days) of each cycle and a brief study visit, primarily to perform hematology assessment, on Day 10 (± 4 days) of each cycle.
Randomized, Double-Blind Phase: Subjects will have a regularly scheduled study visit at the clinical site at screening, baseline (Day 1), and every 3 weeks (± 3 days) where blood samples will be collected and assessments conducted. All

laboratory assessments will be performed using a central laboratory except for hematology.
Subjects will also have brief study visits at the study clinic laboratory (or as described in the Laboratory Manual) on Day 10 of each cycle (± 4 days), primarily to provide blood samples for hematology. Additional monitoring of hematology or serum chemistry parameters may be performed at the investigator's discretion.
Radiographic tumor assessments (typically computed tomography scan) will be conducted every 6 weeks until disease progression. The prestudy radiographic measurement for tumor size will be conducted during the 28 day screening period. Subjects discontinued from study treatment who have not progressed will still be assessed every 6 weeks until disease progression, beginning new anticancer therapy, or death.
After discontinuation of study treatment for disease progression, laboratory and nonradiographic assessments will cease and follow-up will occur every 6 weeks for subsequent anticancer therapies and survival. After the final primary analysis is performed, follow-up for anticancer treatments and survival will be reduced to every 12 weeks.
Premedication/Concomitant Medication Treatments: All subjects will be instructed to take a low dose folic acid preparation or multivitamin with folic acid on a daily basis. At least 5 daily doses of folic acid must be taken during the 7 day period preceding the first dose of pemetrexed/cisplatin, and dosing will continue during the full course of pemetrexed-containing therapy and for 4 weeks after the last dose of pemetrexed. Subjects must also receive 1 intramuscular injection of vitamin B12 during the week preceding the first dose of pemetrexed/cisplatin and every 3 cycles during pemetrexed-containing therapy. Subjects will be instructed to take antiemetic medications during cycles where pemetrexed/cisplatin or pemetrexed are used. Subjects must be pretreated with 4 mg dexamethasone BID (or equivalent) the day before, the day of, and the day after each infusion with pemetrexed/cisplatin or pemetrexed. Note that alternatives to BID dexamethasone are described in the body of the Protocol. If required based on the results from the safety run-in phase, GCSF will be administered as a single subcutaneous injection of 6 mg pegfilgrastim (Neulasta® or its equivalent) on Day 2 of each 21-day cycle, or as filgrastim (Neupogen® or its equivalent) if the investigative site uses the latter as their standard for GCSF.

Study burden and risks

Side Effects from Ruxolitinib
The risks of ruxolitinib may not be fully known, and may vary depending upon the disease you are being treated for. Therefore, you will be informed of the important symptoms or medical events (called *adverse events*) that have occurred frequently in patients who had serious blood conditions called myelofibrosis (MF) and polycythemia vera (PV). You will also be informed of any adverse events that were rare but serious and might have been related to the study drug. During your participation, you will be given any new

information that may affect your willingness to start or continue in the study
You should discuss the risks listed here with your Study Doctor. Many side effects go away shortly after the study drug is stopped, but in rare cases they may be serious, long lasting, and/or permanent, and may even cause death. If you experience any of the described symptoms or have any other problems, you must immediately tell the appropriate study staff member or the Study Doctor. If you feel that these symptoms or side effects are life threatening seek medical assistance immediately.
The following adverse events were reported as common side effects (occurring in at least 1%) or very common (occurring in at least 10%) of patients who were treated with ruxolitinib for MF or for PV.
Very Common (at least 10%)
• Anemia (low red blood cells)
• Thrombocytopenia (low platelets)
• Bruising
• Neutropenia (low white blood cells)
• Raised ALT and AST (blood proteins that may indicate mild liver damage)
• Hypercholesterolemia (increase in cholesterol)
• Hypertriglyceridemia (increase in triglycerides)
• Dizziness
• Headache
• Urinary tract infections
• Weight gain
Common (more than 1% but less than 10%)
• Flatulence (gas)
• Constipation
• Herpes zoster (shingles)
• Hypertension (high blood pressure)
Ruxolitinib may cause low blood cell counts (white blood cells, red blood cells and platelets). If your white blood cell count becomes low while you take the drug, this means you may have an increased chance of getting an infection, including urinary tract infections and viral infections. You will be checked for any signs of infection before starting ruxolitinib and any serious infections should be treated before you start ruxolitinib; your physician will check you carefully for signs of infection while you are being treated. You also may become anemic (low red blood cell count) while you take the study drug, and that may cause you to feel fatigued or short of breath. If your platelet count becomes low while you take the study drug, it may lead to bleeding and/or bruising. In some people taking ruxolitinib, the decreases in blood cell counts have been severe. In most cases, low blood cell counts can be reversed by stopping the study drug temporarily or reducing the dose; you will be checked often for this side effect while on study. If your blood cell counts do not recover quickly, the study drug may be stopped for a longer duration to allow the blood cell counts to recover.
Uncommon (occurring in fewer than 1% of patients)
These events are events that were uncommon, but occurred ruxolitinib treatment and are potentially serious.

• Non-melanoma skin cancers (NMSCs) are skin cancers such as basal cell cancer or squamous cell cancer that usually develop on the sun-exposed areas of skin, and commonly require surgery to remove. NMSCs have been reported in patients with MF or PV who were treated with ruxolitinib. Most of these patients had histories of extended treatment with medications known to increase the risk of NMSC, and had NMSC or pre-cancerous skin lesions before being treated with ruxolitinib. It is not known whether or not ruxolitinib contributed to these cases of NMSC. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.
(The following conditions have occurred in patients with MF who were treated with ruxolitinib)

• Tuberculosis (TB) has occurred in a small number of patients (less than 1%) with MF who received ruxolitinib, but it is not known whether this was due to MF, ruxolitinib, or other factors that are known to increase the risk of tuberculosis (such as diabetes, bronchitis, asthma, smoking, emphysema, or steroid use). Tell you study doctor if you have been treated for TB in the past, or have ever had a positive skin test for TB.
• About one week following interruption or discontinuation of ruxolitinib, some patients with MF experienced a return of symptoms (such as fatigue, bone pain, fever, itching, night sweats, weight loss, or an enlarged spleen). There have been cases of MF patients stopping ruxolitinib during another ongoing illness who became more severely ill, but it was not clear whether stopping ruxolitinib therapy contributed to the patients* conditions worsening.
• A rare disease called progressive multifocal leukoencephalopathy (PML) has been reported during ruxolitinib treatment for MF. PML comes from a viral infection that causes brain damage and can be fatal. It is unknown whether this was due to ruxolitinib treatment since PML has occurred in patients with blood cancers, including MF, who were not treated with ruxolitinib. Tell your study doctor immediately if you have any of the following symptoms or if anyone close to you notices that you have any of these symptoms: confusion or problems thinking, loss of balance or problems walking, clumsiness, difficulty speaking, decreased strength or weakness on one side of your body, blurred and/or loss of vision.
Side Effects from Pemetrexed and Cisplatin When Given Together
The bullet points below provide the frequency and severity of adverse reactions that have been reported in more than 5% of 839 people with NSCLC (165 people) who were randomized to study and received pemetrexed plus cisplatin.
Reaction - Pemetrexed/Cisplatin (all grade toxicities - All adverse reactions = 90 %)
Laboratory:
• Hematologic
o Anemia - 33%
o Neutropenia - 29%
o Leukopenia - 18%
o Thrombocytopenia - 10%
• Renal

o Creatinine Elevation - 10%
Clinical:
• Constitutional Symptoms
o Fatigue - 43%
• Gastrointestinal
o Nausea - 56%
o Vomiting - 40%
o Anorexia - 27%
o Constipation - 21%
o Stomatitis/Pharyngitis - 14%
o Diarrhea - 12%
o Dyspepsia/heartburn - 5%
• Neurology
o Neuropathy - Sensory - 9%
o Taste disturbance - 8%
• Dermatology/Skin
o Alopecia - 12%
o Rash/Desquamation - 7%
Reaction - Pemetrexed/Cisplatin (grade 3 + 4 toxicities - All adverse reactions = 37 %)
Laboratory:
• Hematologic
o Anemia - 6%
o Neutropenia - 15%
o Leukopenia - 5%
o Thrombocytopenia - 4%
• Renal
o Creatinine Elevation - 1%
Clinical:
• Constitutional Symptoms
o Fatigue - 7%
• Gastrointestinal
o Nausea - 7%
o Vomiting - 6%
o Anorexia - 2%
o Constipation - 1%
o Stomatitis/Pharyngitis - 1%
o Diarrhea - 1%
You should get medical help and call your study doctor or the study staff right away if you experience any of the following:
• Fever of 38°C (100.4°F) for more than 1 hour
• Confusion or hallucinations (sensing things that aren*t real but made up by the mind)
• Difficulty breathing
• A new rash
• Trouble swallowing, drooling or swelling of the face, neck or tongue
• Increased pain

• Headache
• Abdominal pain
• Constipation or uncontrollable diarrhea
• Uncontrolled nausea and or vomiting
• Bleeding
• Swelling in the arms or legs

Side Effects from Pemetrexed When Used for Maintenance Therapy
The bullet points below provide the frequency and severity of adverse reactions reported in more than 5% of the 438 people with NSCLC who received ALIMTA® (pemetrexed) maintenance and the 218 people with NSCLC who received placebo following a platinum-based induction therapy. All people received study drug immediately following 4 cycles of platinum-based treatment for locally advanced or metastatic NSCLC. People in both study arms were fully supplemented with folic acid and vitamin B12.
Reaction - Pemetrexed (all grade toxicities - All adverse reactions = 66 %)
Laboratory:
• Hematologic
o Anemia - 15%
o Neutropenia - 6%
o Leukopenia - 6%
• Hepatic
o Increased ALT - 10%
o Increased AST - 8%
Clinical:
• Constitutional Symptoms
o Fatigue - 25%
• Gastrointestinal
o Nausea - 19%
o Anorexia - 19%
o Vomiting - 9%
o Mucositis/stomatitis - 7%
o Diarrhea - 5%
• Infection - 5%
• Neurology
o Neuropathy - Sensory - 9%
• Dermatology/Skin
o Rash/Desquamation - 10%
Reaction - Pemetrexed (grade 3 - 4 toxicities - All adverse reactions = 16 %
Laboratory:
• Hematologic
o Anemia - 3%
o Neutropenia - 3%
o Leukopenia - 2%
Clinical:
• Constitutional Symptoms
o Fatigue - 5%

• Gastrointestinal
o Nausea - 1%
o Anorexia - 2%
o Mucositis/stomatitis - 1%
o Diarrhea - 1%
• Infection - 2%
• Neurology
o Neuropathy - Sensory - 1%

Reaction - Placebo (all grade toxicities - All adverse reactions = 37 %
Laboratory:
• Hematologic
o Anemia - 6%
o Leukopenia - 1%
• Hepatic
o Increased ALT - 4%
o Increased AST - 4%
Clinical:
• Constitutional Symptoms
o Fatigue - 11%
• Gastrointestinal
o Nausea - 6%
o Anorexia - 5%
o Vomiting - 1%
o Mucositis/stomatitis - 2%
o Diarrhea - 3%
• Infection - 2%
• Neurology
o Neuropathy - Sensory - 4%
• Dermatology/Skin
o Rash/Desquamation - 3%
Reaction - Placebo (grade 3 - 4 toxicities - All adverse reactions = 4 %
Laboratory:
• Hematologic
o Anemia - 1%
o Leukopenia - 1%
Clinical:
• Constitutional Symptoms
o Fatigue - 1%
• Gastrointestinal
o Nausea - 1%
Some people in the study will get placebo instead of ruxolitinib. Placebo is a tablet that looks like ruxolitinib, but has no drug in it. If you take placebo during the study, it is possible that your condition may get worse. Please ask the study doctor or study staff if you have any questions about placebo.

Additional Common Side Effects When Ruxolitinib, Pemetrexed/Cisplatin are Used

Together
The side effects of using ruxolitinib/pemetrexed/cisplatin together are unknown. Both ruxolitinib and pemetrexed/cisplatin can cause neutropenia (low white blood cell count, white blood cells help you fight infections so you may be more likely to develop an infection) and thrombocytopenia (low platelet count). Platelets help your blood clot so a low platelet count may put you at risk for bleeding. The study staff will watch your blood work for signs of these two problems and may change the dose of your study drug if needed.
It is possible that taking ruxolitinib, pemetrexed, and cisplatin may change how your regular medications, vaccines, or supplements work. It is very important that you tell the study doctor about any medications, supplements, or vaccines before you take them during the study.
Please tell the study doctor or study staff right away if you have any side effects. Please tell them if you have any other problems with your health or the way you feel during the study, whether or not you think these problems are related to the study drug.
Some side effects are related to required medications and supplements to study procedures or are risks of allergic reaction. For more information see Appendix 2.
Risks of Pregnancy or Fathering a Child
The risks to an unborn human fetus or a nursing child from ruxolitinib are not known. Some drugs cause premature (early) birth or birth defects. Pemetrexed/cisplatin may harm the fetus. Tell your study doctor if you are pregnant, plan to become pregnant, or are breast-feeding. You should not become pregnant or breast-feed while you are in this study. If you become pregnant during this study, contact the study doctor or study staff.
Women who are pregnant or nursing a child may not participate in this study. You must confirm that, to the best of your knowledge, you are not now pregnant, and that you do not intend to become pregnant or you do not intend to father a child during the study. If there is any possibility that you may become pregnant or father a child during the study, the Study Doctor will discuss appropriate birth control measures with you.
Female subjects who are able to have children must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through the follow-up visit. Male subjects must agree to take appropriate precautions to avoid fathering a child (with at least 99% certainty) from screening through the follow-up visit.
If you are female and suspect that you have become pregnant during the study, you must notify the Study Doctor immediately, and you have to stop study drug dosing immediately. You will not be able to continue in the study if you become pregnant. If you become pregnant, the study doctor will medically follow the pregnancy until delivery to monitor you and your child's safety. The study doctor will report the pregnancy and outcome to the Sponsor (Incyte Corporation).
If you father a child during your participation in the study, you must notify the Study Doctor immediately. If your partner becomes pregnant, your Study Doctor will ask to medically follow the pregnancy until delivery in order to

monitor your partner*s and your child*s safety. The study doctor will report the pregnancy to the Sponsor (Incyte Corporation). The Sponsor may request to track your partner*s pregnancy.

Contacts

Public
Incyte Corporation

1801 Augustine Cut-Off
Wilmington DE 19803
US
Scientific
Incyte Corporation

1801 Augustine Cut-Off
Wilmington DE 19803
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

•Men or women aged 18 or older.
•Histologically or cytologically confirmed diagnosis of nonsquamous NSCLC that is Stage IIIB, Stage IV, or recurrent after prior definitive intervention (radiation, surgery, or chemoradiation therapy, with or without adjuvant or neoadjuvant chemotherapy).
*- Subjects who have recurrent NSCLC after prior surgery or radiation therapy are allowed to enter. At least 4 weeks must have elapsed between prior radiation therapy and Cycle 1 Day 1, and all radiation therapy-related toxicities must have resolved.

*- Subjects who have received radiation to the spine, pelvis, ribs, or femur should be discussed with the sponsor, as extensive radiation to marrow-forming region may compromise a subject's ability to tolerate myelosuppressive chemotherapy.
*- Subjects must not have received prior chemotherapy for advanced or metastatic disease.
•An mGPS of 1 or 2 as defined below:
Criteria: C-reactive protein > 10 mg/L AND albumin >= 35 g/L Score: 1
Criteria: C-reactive protein > 10 mg/L AND albumin < 35 g/L Score: 2
•Radiographically measurable or evaluable disease.
*- Measurable lesions may be in the field of prior radiation; however, there must be at least a 4 week period between the last radiation treatment and demonstration of interval progression of the lesion compared with the baseline scan documenting disease status for the lesion to be considered measurable.
•Life expectancy of at least 12 weeks.
•Tumor without activating driver mutations for which there is an available therapy (eg, tumor without mutations in EGFR or anaplastic lymphoma kinase).
•ECOG performance status of 0 to 1.
•Adequate renal, hepatic, and bone marrow function demonstrated by protocol-specified laboratory parameters at the screening visit:
- Absolute neutrophil count >= 1.5 × 109/L.
- Platelet count >= 100 × 109/L.
- Hemoglobin >= 85 g/L (transfusion support to maintain this hemoglobin level is acceptable).
- Alanine aminotransferase and aspartate aminotransferase <= 2.5 × upper limit of laboratory normal (ULN) or <= 5 × ULN in the presence of liver metastases.
- Total bilirubin <= 1.5 × ULN; if total bilirubin is > 1.5 × ULN, then direct bilirubin must be <= 1.5 × ULN.
- Creatinine clearance >= 50 mL/min measured or calculated by Cockroft-Gault equation, or glomerular filtration rate >= 50 mL/min/1.73 m2 as calculated using the Modification of Diet in Renal Disease formula.
•Female subjects of childbearing potential (defined as women who have not undergone surgical sterilization with a hysterectomy and/or bilateral oophorectomy, and are not postmenopausal, defined as >=12 months of amenorrhea) must have a negative serum pregnancy test at screening. All female subjects of childbearing potential must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening to follow-up. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subject and their understanding confirmed.
•Male subjects must agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through follow-up. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subject and their understanding confirmed.

Exclusion criteria

•Squamous or mixed histology (eg, adenosquamous) NSCLC
•Previous systemic therapy for advanced or metastatic disease. (Subjects who completed a

platinum-containing regimen as adjuvant, neoadjuvant, or part of a course of chemoradiation therapy within the 6 months before screening are also excluded.)
•Known active (untreated) central nervous system (CNS) metastases. Subjects with CNS metastases who have completed a course of therapy would be eligible for the study provided they are clinically stable for at least 4 weeks before study entry, defined as:
•No evidence of new or enlarging CNS metastasis or new neurological symptoms attributable to CNS metastases.
•Asymptomatic and receiving either no or stable doses of anticonvulsants and/or corticosteroids for the 4 weeks prior to study entry.
•Current or previous other malignancy within 2 years of study entry, except cured basal or squamous cell skin cancer, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in situ of the cervix, or other noninvasive or indolent malignancy without sponsor approval.
•Current uncontrolled cardiac disease such as angina or myocardial infarction, congestive heart failure including New York Heart Association functional classification of 3, or arrhythmia requiring treatment.
•Uncontrolled concomitant medical conditions, including, but not limited to, renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, neurological, cerebral, or psychiatric diseases.
•Known hypersensitivity to any of the active substances or any of their excipients, including ruxolitinib, cisplatin, or pemetrexed.
•Inability to take brief courses of dexamethasone each month.
•Unwillingness or inability to take vitamin B12 and folic acid supplements.
•Chronic or current active infectious disease requiring systemic antibiotics, antifungals, or antivirals.
•Known HIV-positive status.
•Hepatitis B virus (HBV) or hepatitis C virus (HCV) viremia or at risk for HBV reactivation. HBV DNA and testing for HCV RNA must be undetectable. At risk for HBV reactivation is defined as hepatitis B surface antigen positive or anti-hepatitis B core antibody positive.
•Pregnant or breastfeeding women.
•Unwillingness to be transfused with blood components (eg, packed red blood cells, platelets).
•Prior treatment with any JAK inhibitor.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial

Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-12-2015
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ruxolitinib
Generic name:	Ruxolitinib

Ethics review

Approved WMO Date:	22-12-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-06-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-11-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	02-02-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2014-001436-10-NL
ClinicalTrials.gov	NCT02119650
CCMO	NL50341.042.14