# A phase I/II study of safety and efficacy of ribociclib (LEE011) in combination with trametinib (TMT212) in patients with metastatic or advanced solid tumors

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PRIMARY- Phase Ib: To define the maximum tolerated dose (MTD) and/or the recommended Phase 2 regimen (RP2R) of ribociclib and trametinib in patients with solid tumors- Phase II: To assess overall response rate (ORR) with the combination of...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Gastrointestinal neoplasms malignant and unspecified |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON47396

**Source**
ToetsingOnline

**Brief title**
Ribociclib (LEE011) and trametinib (TMT212) in solid tumors

### Condition

- Gastrointestinal neoplasms malignant and unspecified

**Synonym**
colorectal carcinoma, pancreatic carcinoma

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Novartis

**Source(s) of monetary or material Support:** Farmaceutische industrie

## Intervention

**Keyword:** Colorectal, Pancreas, ribociclib (LEE011), trametinib (TMT212)

## Outcome measures

### Primary outcome

Maximum Tolerate Dose (MTD), Recommended Phase 2 Regimen (RP2R), Overall

Response Rate

### Secondary outcome

Safety and tolerability, Pharmacokinetics (PK), Duration of Response (DOR),

Disease Control Rate (DCR), Time to overall Response (TTR), Overall Survival

(OS), Progression Free Survival (PFS), Clinical Benefit Rate (CBR).

# Study description

### Background summary

The RAS/RAF/MEK/ERK or the MAPK (mitogen-activated protein kinase) pathway is a critical proliferation pathway for many human cancers. Additionally, cellular proliferation, growth, and division following DNA damage are tightly controlled by the cell-cycle regulatory machinery that includes CDKs which helps the cell cycle to progress.
Very few signaling inhibitor monotherapies show clinical benefit in RAS-mutant cancers and, therefore, approaches that combine molecular target inhibition are most likely to offer an effective approach for RAS-mutant cancers. One likely approach is to simultaneously inhibit MEK and CDK4/6. Based on the different mechanisms of action of MEK and CDK4/6 inhibitors, our hypothesis is that the combined inhibition will have a synergistic effect in inhibiting cancer cell growth.
Ribociclib (LEE011) is an orally available inhibitor of CDK4 and CDK6, thereby inhibiting Rb protein phosphorylation. Inhibition of Rb phosphorylation prevents CDK-mediated G1-S phase transition, thereby arresting the cell cycle in the G1 phase, suppressing DNA synthesis and inhibiting cancer cell growth.
Ribociclib in combination with endocrine therapy is currently being investigated in three Phase III studies in patients with metastatic breast

cancer.
Trametinib (TMT212) is a reversible, highly selective allosteric inhibitor of MEK1 and MEK2 activation and kinase activity. In multiple Phase III studies, trametinib demonstrated anti-cancer activities as a monotherapy and in combination with a BRAF inhibitor in BRAF V600-mutant metastatic melanoma. Preclinical and preliminary clinical trial data indicate that combined inhibition of CDK4/6 and MEK resulted in synergistic tumor growth inhibition.

Abbreviations
ALK (anaplastic lymphoma kinase)
CDK (cyclin-dependent kinasen)
EGFR (epidermal growth factor receptor)
ERK (extracellular signal-regulated kinase)
MEK (mitogen-activated extracellular signal-regulated kinase)
RAS (v-ras oncogene homolog GTPase)

**Study objective**

PRIMARY
- Phase Ib: To define the maximum tolerated dose (MTD) and/or the recommended Phase 2 regimen (RP2R) of ribociclib and trametinib in patients with solid tumors
- Phase II: To assess overall response rate (ORR) with the combination of ribociclib and trametinib in patients with advanced or metastatic pancreatic adenocarcinoma who have failed at least one prior systemic treatment (Arm 1) and advanced or metastatic KRAS-mutant CRC who have failed at least two prior lines of treatment (Arm 2)

SECONDARY
Phase Ib and II:
* To evaluate the safety and tolerability of ribociclib in combination with trametinib
* To characterize the pharmacokinetics (PK) of ribociclib (and metabolite LEQ803) and trametinib

Phase Ib:
* To assess the preliminary anti-tumor activity of ribociclib in combination with trametinib
Phase II:
* To evaluate duration of response (DOR), disease control rate (DCR), time to response (TTR), overall survival (OS), progression-free survival (PFS) and clinical benefit rate (CBR) of ribociclib in combination with trametinib

**Study design**

This is a phase 1b / II study.

The Phase Ib is an open label, dose escalation portion of the study to establish a MTD/RP2R of ribociclib in combination with trametinib by evaluating the incidence of DLTs in the first cycle of treatment. In the first cohort, trametinib was dosed once daily on Days 1-28 of a 28-day cycle and ribociclib was dosed once daily on Days 1-21 of a 28-day cycle followed by a 7-day break.

Updated study design based on the review of the safety data from the first cohort, alternate dosing schedules will be explored for both ribociclib and trametinib during the Phase Ib part of the study. Alternate dosing schedules are:
* Schedule 1: Trametinib administered once daily on Days 1 to 14, and ribociclib administered once daily on days 8 to 21 of a 21-day cycle
* Schedule 2: Trametinib administered once daily on Days 1 to 14, and ribociclib administered once daily on days 1 to 14 of a 21-day cycle.
* When the MTD is reached for Schedule 1, that dose will be tested using Schedule 2.

Once the RP2R of ribociclib and trametinib in the Phase Ib part of the study is determined, enrollment will commence into the Phase II portion of the trial. The Phase II portion of the study will evaluate the clinical efficacy and safety of the combination of ribociclib and trametinib in patients with advanced or metastatic pancreatic carcinoma or KRAS-mutant CRC.

**Intervention**

Ribociclib (LEE011) + Trametinib (TMT212)
Both studydrugs oral intake. Schedule 21 days

Dose ribociclib: 200 mg, 300 mg, 400 mg, 500 mg or 600 mg once daily. If 200mg ribociclib is not tolerated dose reduction to 150mg is allowed.
Several schedules (combination with trametinib) will be investigated.

2 weeks intake and one week off
1st week no intake followed by 2 weeks intake

Dose trametinib : 1.5mg or 2mg once daily: Several schedules (combination with ribociclib) will be investigated.
2 weeks intake and one week off

**Study burden and risks**

Risk:
Adverse effects of the combination of ribociclib and trametinib (unknown yet).
Risks associated with procedures as CT-scan, MUGA and Bone-scan (radiation), tumor biopsy (bleeding, pain), blooddraw (pain, bleeding).

Burden: Cycles of 4 weeks. Cycle 1: 8 visits, cycle 2-3: 2 visits per cycle, cycle 4 and above: 1 visit per cycle. Duration 1-4 h (1-2 visits of over 8 h).
Physical examination: once per cycle. Pulse and BP every visit.
Blood tests (mostly 10-55 ml/occasion): cycle 1: 4 times, cycle 2-3: 2 times, cycle 4 and above: 1 time per cycle. Fasting if lipids are assessed.
ECG: once per cycle.
Echocardiogram/MUGA every 2nd cycle.
Eye examinations: twice.
CT-/MRI scan: every 6-8 weeks for 1.5 year, thereafter every 12 weeks.
Diary for entry of tablet/capsule intake.
3 tumor biopsies.

## Contacts

**Public**
Novartis

Raapopseweg 1
Arnhem 6824 DP
NL
**Scientific**
Novartis

Raapopseweg 1
Arnhem 6824 DP
NL

## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

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

## Inclusion criteria

1.Patient has histologically and/or cytologically confirmed malignancies:
Phase I: advanced or metastatic solid tumors who have failed at least one prior line of systemic antineoplastic therapy without a standard of care treatment option available.
Phase II: Advanced or metastatic pancreatic adenocarcinoma who have failed at least one prior systemic antineoplastic therapies and advanced or metastatic KRAS-mutant CRC who have failed at least two prior systemic antineoplastic therapies without a standard of care treatment option available.
2. Phase II only: measurable disease.
3. ECOG performance status 0 or 1.
4. Adequate bone marrow and organ function (see protocol 5.2 inclusion criterium 7)
5. 12-lead ECG values (mean of triplicate ECGs): QTcF interval at screening <450 msec (using Fridericia*s correction) and resting heart rate 50-90 bpm
For details see protocol section 4.2 pages 46-47

## Exclusion criteria

1. Phase II only:Patient has received prior treatment with a MEK inhibitor or a CDK4/6 inhibitor.
Phase Ib and Phase II:
2. Radiotherapy * 4 weeks or limited field radiation for palliation * 2 weeks prior to Cycle 1 Day 1, and who has not recovered to grade 1 (with the exception of alopecia).
3. Local therapy to liver * 3 months of C1D1, Local therapy includes surgical resection, radiotherapy, and/or embolization/ablation.
4. History of liver disease as follow: Cirrhosis - Autoimmune hepatitis - Active viral hepatitis - Portal hypertension - Drug induced liver steatosis
5. Prior systemic anti-cancer treatment within 28 days prior to Cycle 1 Day 1, or chemotherapy without delayed toxicity within the last 2 weeks preceding the first dose of study treatment with no more than grade 1 treatment related AEs..
6. Warfarin or other Coumadin derived anti-coagulant, for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH), or fondaparinux is allowed.
7. History of deep vein thrombosis or pulmonary embolism within 6 months from screening.
8. CNS involvement unless they meet ALL of the criteria specified in protocol bullet 12.
9. Impairment of GI function or GI disease that may significantly alter the absorption of the study drugs
10. A known history of HIV infection
11. History of interstitial lung disease or pneumonitis.
12. Any other concurrent severe or uncontrolled medical condition
13. Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality. See details in protocol bullet 17.
14. Currently receiving any of the substances listed in protocol bullet 19 and cannot be discontinued 7 days prior to the start of the study medication.

15. Patient is currently receiving or has received systemic corticosteroids * 2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment.
16. History of retinal vein occlusion.
For detailed description of exclusion criteria see protocol section 4.3 pages 65-68

# Study design

## Design

**Study type:** Interventional

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|---|---|
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 04-07-2016 |
| Enrollment: | 12 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Mekinist |
| Generic name: | trametinib |
| Registration: | Yes - NL outside intended use |
| Product type: | Medicine |
| Brand name: | Nvt |
| Generic name: | ribociclib |

# Ethics review

Approved WMO

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|---|---|
| Date: | 25-04-2016 |
| Application type: | First submission |

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|---|---|
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 24-05-2016 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 17-06-2016 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 15-08-2016 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 03-10-2016 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 04-01-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 17-03-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 29-03-2017 |
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| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
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| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 14-06-2017 |
| Application type: | Amendment |

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|---|---|
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 15-06-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 27-09-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 13-10-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 19-10-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 12-12-2017 |
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| Approved WMO Date: | 20-12-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
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| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 15-03-2018 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 19-03-2018 |
| Application type: | Amendment |

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|---|---|
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 16-05-2018 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 28-05-2018 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 09-08-2018 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 20-08-2018 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 24-12-2018 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 07-01-2019 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
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| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 18-02-2019 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 25-03-2019 |
| Application type: | Amendment |

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|---|---|
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 18-04-2019 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 24-05-2019 |
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| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 20-06-2019 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |

# 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 | EUCTR2015-005019-34-NL |
| ClinicalTrials.gov | NCT02703571 |
| CCMO | NL57106.041.16 |