Phase 2 Study testing the COmbination of Vemurafenib With Cobimetinib in BRAF V600 mutated Melanoma Patients to Normalize LDH and Optimize immunotherapY with Nivolumab and Ipilimumab (COWBOY)

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Primary objective: • To compare efficacy of induction vemurafenib + cobimetinib followed by ipilimumab + nivolumab (Arm A) versus upfront ipilimumab + nivolumab treatment (Arm B).Secondary Objectives• To describe duration of response and overall...

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

Summary

ID

NL-OMON46997

Source
ToetsingOnline

Brief title
COWBOY

Condition

- Skin neoplasms malignant and unspecified

Synonym
Melanoma, skin cancer

Research involving

Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Bristol-Myers Squibb

Intervention

Keyword: COWBOY, Immunotherapy, LDH, Melanoma

Outcome measures

Primary outcome

• Compare the best overall response rate (BORR) according to RECIST 1.1 of both

arms at week 18 from start of treatment.

Secondary outcome

• Progression-free survival (PFS) according to RECIST 1.1

• Overall survival (OS)

• Percentage of grade 3/4 toxicities according to CTCv4.03

• Percentage of ongoing response, percentage of patients requiring

re-induction, response percentage upon re-induction

• Changes in tumor-specific T cell responses

Study description

Background summary

The combination of ipilimumab and nivolumab induces relatively high response rates and promising response depth in late stage melanoma. Nevertheless, it takes time for a response to occur, and still there is a significant number of patients who do not befefit from treatment. In contrast to immunotherapy, targeted therapies (BRAF or MEK inhibitors) can induce faster and higher response rates which are often of shorter duration, even when combined.

Patients with elevated levels of serum LDH are less likely to respond to immunotherapy compared to patients with normal LDH levels. This does not mean that such patients do not benefit at all from immunotherapy.
This raises the question, whether response rates upon immunotherapy can be improved by upfront reduction of tumor burden and normalization of LDH. We postulate that induction therapy with combined BRAF+MEK inhibition, and subsequent LDH normalization, can improve response rates to the rates seen in LDH normal patients.

To address this question we have setup a randomized phase 2 trial comparing the response rates upon ipilimumab + nivolumab versus ipilimumab + nivolumab after 6 weeks vemurafenib + cobimetinib induction in patients with elevated serum LDH.

Study objective

Primary objective:
• To compare efficacy of induction vemurafenib + cobimetinib followed by ipilimumab + nivolumab (Arm A) versus upfront ipilimumab + nivolumab treatment (Arm B).

Secondary Objectives
• To describe duration of response and overall survival induced by vemurafenib + cobimetinib followed by the combination of ipilimumab + nivolumab (Arm A) as compared to ipilimumab + nivolumab t (Arm B)
• To describe the rate and quality of toxicity observed in the two study arms
• To describe the rate of ongoing responses upon response-driven flat dose (240mg, q2w) nivolumab maintenance
• To determine the immune-activating capacity of induction therapy with vemurafenib + cobimetinib followed by the combination of ipilimumab + nivolumab.
• To evaluate the changes in systemic immune competence

Study design

This is a two-arm phase 2 study consisting of 200 BRAFV600E/K mutation-positive late-stage melanoma patients with an elevated baseline LDH level (> ULN, < 5xULN) randomized 1:1 (stratified according to LDH) to receive either vemurafenib + cobimetinib directly followed by ipilimumab + nivolumab (Arm A) as compared to standard first line ipilimumab + nivolumab (Arm B). Subsequently, patients in both arms will receive flat dose (240mg, q2w) nivolumab maintenance in a response-driven manner

Intervention

Patients will be randomized 1:1 to receive either 6 weeks vemurafenib 960 mg bid 28 day + cobimetinib 60 mg QD 21-day on, 7-day off (21/7) schedule,

directly followed by 4 courses of ipilimumab 3mg/kg q3wk + nivolumab 1mg/kg q3wk (Arm A) or first line standard 4 courses of ipilimumab 3mg/kg q3wk + nivolumab 1mg/kg q3wk (Arm B).
Subsequently, patients in both arms will receive nivolumab maintenance flat dose (240mg, q2w) in a response-driven manner according to their response at week 18

Study burden and risks

Combined ipilimumab and nivolumab therapy and the combination of vemurafenib and cobimetinib have both been tested as safe and effective treatment options in melanoma patients, and are approved therapies for late stage melanoma. The combined administration of ipilimumab + nivolumab has a higher level of anti-melanoma activity than monotherapy with either nivolumab or ipilimumab, but is also associated with increased toxicity. A burden for the patients that is not different to the current standard combination treatment. An additional burden however could in theory evolve, if the pre-treatment with vemurafenib + cobimetinib increases the toxicity of subsequent ipilimumab + nivolumab. Currently there is no indication for this, as we have already performed a pilot study with induction vemurafenib followed by ipilimumab without increased toxicity.

Another additional burden for patients participating in this trial (as compared to combination therapy with BRAFi + MEKi or ipilimumab + nivolumab outside the study) are the optional additional tumor biopsies that will be taken only from easy accessible lesions (lymph node or subcutaneous lesions, which are encouraged), and more blood drawing

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

In order to participate in this study, a subject must meet all of the following criteria:;• Adults 18 years and older ;• World Health Organization (WHO) Performance Status 0-2;• Histologically or cytologically confirmed Stage IV, or unresectable stage III, BRAF V600E/K mutated melanoma;• Measurable disease according to RECIST 1.1;• Signed and dated informed consent form;• No prior immunotherapy targeting CTLA-4, PD-1 or PD-L1;• No prior BRAFi and/ or MEKi therapy;• No immunosuppressive medications;• Screening laboratory values must meet the following criteria and should be obtained within 10 days prior to randomization:;o WBC >= 2.0x109/L, Neutrophils >= 1.0x109/L, Platelets >= 100 x109/L, Hemoglobin >= 5.0mmol/L;o Creatinine <= 2x ULN;o AST, ALT <= 2.5 x ULN (<=5 x ULN for patients with liver metastases);o Bilirubin <=2 X ULN;o LDH > ULN, < 5x ULN;• No symptomatic brain metastases (asysmptomatic brain metastases, accidentally found during screening can be included) ;• No leptomeningeal metastases;• No active autoimmune disease requiring systemic treatment in the past 3 months or a documented history of autoimmune disease, or history of syndrome that required systemic steroids, at daily dose of >=10mg prednisone or equivalent, or immunosuppressive medications. (Subjects with vitiligo or resolved childhood asthma/atopy are excluded from this rule (and will not be excluded from this study). Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen*s syndrome will not be excluded from the study.);• No evidence of interstitial lung disease or active, non-infectious pneumonitis;• No active infection requiring therapy;• No known additional malignancy that is progressing or requires active treatment;• Women of childbearing potential (WOCBP) must use appropriate method(s) of contraception. WOCBP should use an adequate method to avoid pregnancy for 23 weeks (30 days + the time required for nivolumab to undergo five half-lives) after the last dose of study medication;• WOBCP must have a negative serum or urine pregnancy test within 96 hours prior to the start of study treatment and must not be breast feeding;• Men must agree to the use of male contraception during the study treatment period and for at least 31 weeks after the last dose of study drug.;• Currently not participating in a study of an

investigational agent or using an investigational device within 4 weeks of the first dose of treatment.;• No underlying medical conditions that, in the Investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or adverse events

Exclusion criteria

Not applicable

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-02-2017
Enrollment:	200
Type:	Actual

Ethics review

Approved WMO Date:	12-01-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-06-2017

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-08-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-10-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-03-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-04-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-07-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-08-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
ClinicalTrials.gov	NCT02968303
CCMO	NL58446.091.16