A phase II, open label study to investigate the efficacy and safety of domatinostat in combination with avelumab in patients with advanced unresectable/metastatic Merkel Cell Carcinoma progressing on anti-PD(L)1 antibody therapy - the MERKLIN 2 study

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Objectives:Primary Objective: to investigate the anti-tumor efficacy of domatinostat in combination with avelumab in advanced unresectable/metastatic MCC patients progressing on anti-PD-(L)1 antibody monotherapy.Secondary Objectives: to investigate…

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

Summary

ID

NL-OMON49071

Source
ToetsingOnline

Brief title
MERKLIN 2

Condition

- Skin neoplasms malignant and unspecified

Synonym
Merkel Cell Carcinoma (MCC)

Research involving
Human

Sponsors and support

Primary sponsor: 4SC AG
Source(s) of monetary or material Support: Industry: 4SC a Munich/Germany-based Biopharmaceutical Company

Intervention

Keyword: Avelumab, Domatinostat, Merkel Cell Carcinoma (MCC)

Outcome measures

Primary outcome

Primary Objective: to investigate the anti-tumor efficacy of domatinostat in

combination with avelumab in advanced unresectable/metastatic MCC patients

progressing on anti-PD-(L)1 antibody monotherapy.

Secondary outcome

Secondary Objectives: to investigate safety, tolerability, pharmacokinetics,

avelumab anti-drug antibodies (ADA) and health-related quality of life (HrQoL).

Exploratory Objective: to investigate tumor tissue for molecular

characteristics correlating with clinical parameters/clinical outcome.

Study description

Background summary

Study Design:

Phase II, multi-centre, single arm, open-labeled with two cohorts according to previous anti-PD-(L)1 antibody monotherapy:

Cohort 1: progressing on avelumab (anti-PD-L1 antibody).

Cohort 2: progressing on any anti-PD-1 antibody

Study objective

Objectives:
Primary Objective: to investigate the anti-tumor efficacy of domatinostat in combination with avelumab in advanced unresectable/metastatic MCC patients progressing on anti-PD-(L)1 antibody monotherapy.
Secondary Objectives: to investigate safety, tolerability, pharmacokinetics, avelumab anti-drug antibodies (ADA) and health-related quality of life (HrQoL).
Exploratory Objective: to investigate tumor tissue for molecular characteristics correlating with clinical parameters/clinical outcome.

STUDY RATIONALE
Unmet Medical Need
Treatment with avelumab or pembrolizumab could achieve response rates of ~33% in chemotherapy-pretreated and between 40% and 60% in chemotherapy-naïve advanced MCC patients [Nghiem, 2019; Kaufman, 2016; D*Angelo, 2018; EPAR Bavencio]. Nonetheless and irrespective of treatment line, a significant number of patients are either refractory to anti-PD-(L)1 antibody monotherapy or experience a relapse of the disease after a period of initial response but still on anti-PD-(L)1 antibody therapy. For these patients no further, approved treatment options exist; they carry a poor prognosis with a short remaining life expectancy of a few months. In clinical practice most of these patients will receive individualized chemotherapy or no further cancer-directed treatment but best supportive care.
Patients with recurrent MCC, i.e. patients with treatment response and consecutive anti-PD-(L)1 antibody therapy cessation for more than 3 months will not be allowed to enter this study due to uncertainties inasmuch those patients will respond to re-initiation of anti-PD-(L)1 antibody monotherapy again.

Overcoming Tumor Escape Mechanisms

Recent research has shown that the immunological escape of the tumor from the host*s immune response plays an important role for anti-PD-(L)1-antibody therapy resistance. Hereby, the following mechanisms should be highlighted in the context of MCC:

• MHC-I down regulation:

Tumor-associated antigens must be presented in the context of MHC-I molecules to be recognized immunologically by CD8 T cells. Immunohistochemical evaluations have shown a markedly down regulated expression of MHC-I in conjunction with reduced corresponding mRNA content in MCC tumor tissue proving that endogenous T-cell recognition of MCC tumors antigens is significantly disrupted, not to say completely impaired [Vandeven, 2016].

• T Cell Response:

A robust intra-tumoral MCC infiltration with CD8 lymphocytes is associated with a striking 100% survival in a study of N=146 patients [Iyer, 2011]. Furthermore, additional studies have also indicated that MCC tumor infiltrating lymphocytes, including CD3, CD8 T cells, are associated with improved overall and disease-specific survival. Importantly, while robust CD8 responses have been associated with improved outcome in MCC, only 4 to 18% of MCC patients present with significant CD8+ lymphocytes infiltration suggesting that most MCC block intra-tumoral CD8 infiltration as a means of evading immune detection [Andea, 2008; Paulson, 2014].

• CD4 T cell polarization:

In several neuroendocrine cancer types, intra-tumoral infiltration of CD4 T cells subtype Th1 is strongly associated with good clinical outcomes, due to induction of IFN-γ secretion which facilitates intra-tumoral priming and expansion of CD8 T cells. Th1 CD4 cells also serve to recruit pro-inflammatory NK and type-I macrophages to the tumor site, hereby orchestrating robust anti-tumor immunity. Several experimental approaches that promote a Th1 CD4 type response have shown first promising results in MCC [Iyer, 2011]. Domatinostat activates the antigen-presenting machinery by increasing MHC I and MHC II expression on tumor cells and triggers tumor infiltration of cytotoxic T-cells, mainly Th1 CD4 cells, resulting in an enhanced immunogenicity of the tumor cells. This primes the tumor and its microenvironment to be more susceptible to treatment with anti-PD-(L)1 antibodies [Hamm, 2018, Song, 2019]. Combining domatinostat with anti-PD-(L)1 antibodies had better effects on tumor growth inhibition in pre-clinical models. These synergistic immune modulating effects of domatinostat plus PD-(L)1 inhibitors favor domatinostat to be a unique therapeutic partner in malignancies where T-cell infiltration in tumors plays a main role.
Avelumab Treatment
The data from the JAVELIN Merkel 200 study have defined anti-PD-(L)1 checkpoint inhibition as the new standard of care for patients with metastatic MCC and avelumab was the first drug approved in 2017. The second drug now approved for advanced unresectable/metastatic MCC is pembrolizumab, an anti-PD-1 inhibitor, cleared by the FDA in January 2019. To take this fact into account, patients with prior anti-PD-1 antibody treatment will be also allowed to enter this study. However, once enrolled into the study, all patients will receive domatinostat in combination with avelumab.
The anti-PD-(L)1 antibody monotherapy must be the last systemic therapy for MCC. One line of chemotherapy prior to anti-PD-(L)1 antibody monotherapy or adjuvant anti-PD-(L)1 antibody monotherapy in case of former R0 resection will be allowed.

Conclusion

In summary, domatinostat is expected to have considerable clinical potential as an epigenetic modifier synergizing with an anti-PD-(L)1 antibody to achieve an anti-tumor immune response in patients progressing on anti-PD-(L)1 monotherapy. This Phase II study is designed to explore efficacy and safety of domatinostat in combination with avelumab in advanced unresectable/metastatic MCC patients progressing on anti-PD-(L)1 antibody therapy with avelumab (cohort 1) or any anti-PD-1 antibody (cohort 2). MCC patients progressing on anti-PD-(L)1 antibody therapy have a poor prognosis and there remains a high unmet medical need to develop effective new treatment alternatives for these patients.

Study design

Phase II, multi-central, single-armed, open label with two cohorts in accordance with previous anti-PD (L) 1 antibody monotherapy:

Intervention

All patients receive the study medication, which consists of the following two components:
• Domatinostat oral intake, 200 mg twice daily (BID)
• Avelumab infusion 800 mg every 2 weeks (Q2W)
All patients receive the study medication in an open-label manner. Temporary interruption of the study medication (or one of the components) is allowed in cases of treatment-related toxicities or intolerances.

Study burden and risks

Domatinostat
The following adverse reactions have been observed in more than 1 patient to date:
• Effects on blood counts such as:
o Anemia (reduced oxygen-transporting capacity of the blood); this may cause shortness of breath, tiredness and fatigue
o Reduced number of white blood cells (these are part of the immune system for the defense against infections, associated with an increased risk of infections)
o Reduced number of platelets (platelets are involved in the control of bleeding, e.g. after injuries or surgery)
• Gastrointestinal symptoms such as flatulence, constipation, nausea, vomiting, diarrhea (which may cause loss of fluid and an imbalance of minerals in the blood), dry mouth
• General symptoms such as fatigue, fever, chills, insomnia, vertigo, paresthesia, reduced appetite or inflammation of mucous membranes, cough, peripheral edema (abnormal accumulation of fluid in certain tissues of the body; e.g. swelling of the legs)
• Skin reactions such as a rash and dry skin

• Changes in laboratory measurements such as liver function tests
• Hypersensitivity reactions / allergic reactions with symptoms such as rash, chills, itching, fever, nausea, vomiting and low blood pressure. (In case of rash due to a suspected hypersensitivity reaction, a skin biopsy may be taken for clarification of cause).

In patients who were treated with medications from the same drug class as domatinostat (i.e. histone deacetylase inhibitors) certain changes in the ECG have been observed (a so-called prolonged QT interval) which, in rare cases, may lead to severe arrhythmias (irregular heartbeat) up to cardiac arrest. To date, such significant ECG changes have not been observed under treatment with domatinostat. Still, for safety reasons, regular ECG recordings are performed in the course of the study and while on study treatment. You should avoid co-medications known to have the potential to prolong the QT interval and to lead to serious cardiac arrhythmias (irregular heartbeat). Your study doctor will discuss with you the medications you may have to discontinue during the study treatment.

Avelumab

Three types of risks are associated with avelumab: general signs and symptoms, reactions that occur during or following the infusion (so called infusion-related reactions), and immune side effects.
The following general side effects have been observed in >= 10 % of patients among 1738 patients treated with avelumab according to the results from two clinical studies in patients with cancer:

Observed in 10% or more of patients
Tiredness
Nausea (feeling sick to the stomach)
Diarrhea (Frequent loose, watery stools)
Constipation (difficulty passing stools)
Decreased appetite
Infusion-related reaction
Weight decreased
Vomiting
Anemia (low number of red blood cells)
Abdominal pain
Cough
Pyrexia (fever)
Dyspnea (shortness of breath)
Pruritus (itching)*
Edema peripheral (buildup of fluid in the body causing swelling)

Musculoskeletal pain (including back pain, neck pain)
Arthralgia (joint pain)
Dizziness*

Headache*
Hypertension (increase in blood pressure)*
Urinary tract infection*

* side effects included in the table even though occurring in less than 10%, because they are part of the product information

Although avelumab is a fully human protein, the risk cannot be completely excluded that allergic reactions or reactions in the context with the infusions might occur during or after the infusion. Symptoms may include chills or shaking, fever, flushing, back pain, belly pain, shortness of breath or wheezing, decrease in blood pressure, and hives. Infusion-related reactions have already been observed under treatment with avelumab. In general, these reactions are mild to moderate and generally resolve with a slowdown or discontinuation of the infusion and with appropriate drugs, but in less than 1 % of patients severe to life-threatening reactions might occur, which require advanced cardiac life support and could potentially be fatal.
For the prevention of infusion-related adverse effects and possible allergic reactions you will receive a premedication of an antihistamine drug (so-called H1 blocker) and an anti-inflammatory drug (e.g. paracetamol) 30 to 60 minutes before the first infusions of avelumab.
In addition, side effects resulting from an increased activity of the immune system have also been observed. The side effects listed below may be temporary, long term, permanent or result in death. However, most of these side effects are reversible. That means they will stop once the drug is discontinued. The reactions that are more severe require treatment with drugs that decrease the immune system function, also called immunosuppressant drugs (like corticosteroids or more potent drugs).
The following immune-mediated side effects have been observed in patients receiving the study drug and might occur, such as:
Immune side effects observed in 5% to less than 10% of patients
• Abnormal function of the thyroid gland (could include low or high function or inflammation of the thyroid gland): may include rapid heartbeat; increased sweating; extreme tiredness; weight gain or weight loss; hair loss; changes in mood or behavior such as irritability or forgetfulness; feeling cold; constipation; voice gets deeper.
• Inflammation of the skin (rash): may include skin rash, itchy skin, skin redness, skin blisters, or peeling.

Immune side effects observed in 1% to less than 5% of patients
• Inflammation of the large intestine (colitis): may include diarrhea (loose stools) or more frequent bowel movements than usual; blood in stools or dark, tarry, sticky stools; severe stomach area (abdomen) pain or tenderness.
• Inflammation of the lungs (pneumonitis): may include new or worsening cough, shortness of breath, chest pain.
Immune side observed in less than 1% of patients
• Inflammation of the liver (hepatitis): may include yellowing of skin or of

the whites of eyes; severe nausea or vomiting; pain on the right side of stomach area (abdomen); drowsiness; dark urine (tea colored); bleeding or bruising more easily than normal; feeling less hungry than usual.
• Inflammation of the kidneys (nephritis): may include urinating less than usual; blood in urine; swelling in ankles; loss of appetite.
• Low function of the adrenal glands (glands on top of the kidneys), which may be due to the reduced function of the pituitary gland (a gland in the head): may include very low blood pressure; extreme tiredness.
• Increase in blood sugar (diabetes): may include urinating more often than usual; feeling more hungry or thirsty than usual, nausea or vomiting, stomach area (abdomen) pain.
• Inflammation of the eyes (uveitis): may include changes in eyesight.
• Inflammation of the muscles (myositis): may include severe or persistent muscle or joint pain; severe muscle weakness.
• Inflammation of the heart (myocarditis): may include chest pain or tightness; tiredness; changes in heartbeat, such as beating fast, or seeming to skip a beat, or pounding sensation; swelling of feet and legs; trouble breathing.
• Inflammation of the nerves (Guillain-Barre syndrome): may include "pins and needles" sensations in arms and legs; weakness in legs that spreads to the upper body and may lead to temporary paralysis.
• Inflammation of the pancreas (pancreatitis): may include pain in upper abdomen, nausea, vomiting, constipation, weight loss, indigestion.
Single cases of immune-mediated pneumonitis, immune mediated hepatitis, immune-mediated pancreatitis and immune-mediated myocarditis with fatal outcome have been observed with avelumab.

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

1. Age >= 18 years (at signature of ICF), mentally and physically able and willing to provide informed consent for study participation.

2. Histologically confirmed Merkel Cell Carcinoma (MCC).

3. ECOG performance status <= 1.

4. MCC in an advanced, unresectable stage III or metastatic stage IV (includes patients who refused surgical resection or are not eligible for such surgical resection) [Note: patients with PD post-R0 surgical resection and adjuvant anti-PD-(L)1 antibody monotherapy of at least 12 weeks will be eligible as long as Inclusion Criterion #6 is fulfilled]

5. RECIST v1.1 evaluable disease.

6. Progressing on previous anti-PD-(L)1 antibody monotherapy within the last 12 weeks before planned first administration of study medication fulfilling at least one of the following criteria:
• Radiology Criteria: - Detection of new lesion(s) or - At least a 20% increase in the sum of diameters; in addition, the sum must also demonstrate an absolute increase of at least 5 mm.
• In case of unresectable locoregional tumor not measurable by scan, assessment with a caliper will be allowed: a single, unirradiated/ untreated lesion must have a diameter of > 10 mm, at least a 20% increase in the diameter and an absolute increase of at least 5 mm.
• Biopsy of new lesion(s) and histological confirmation of PD in case of progression during adjuvant anti-PD-(L)1 treatment.

7. Confirmation of PD not earlier than 4 weeks after initial assessment of PD

on previous anti-PD-(L)1 monotherapy. [Note: Confirmatory scan can be the baseline scan for this study, if evaluable for RECIST v1.1 and can be performed during screening phase]

8. Pretreatment with avelumab monotherapy (cohort 1) or any antiPD-1 antibody monotherapy (cohort 2) fulfilling the following minimum exposure criteria:
• Anti-PD-(L)1 antibody given every 2 weeks Q2W: at least 6 administrations within the last 6 months, last dose within 3 months before planned first administration of study medication.
• Anti-PD-(L)1 antibody given every 3 weeks Q3W: at least 4 administrations within the last 6 months, last dose within 3 months before planned first administration of study medication. • Anti-PD-(L)1 antibody given every 4 weeks Q4W: at least 3 administrations within the last 6 months, last dose within 3 months before planned first administration of study medication.

9. Patients must have been treated with anti-PD-(L)1 antibody therapy as the most recent systemic anti-neoplastic therapy

10. Patients must have been treated with approved doses and schedules of avelumab or anti-PD-1 antibodies. For investigational anti-PD-1 antibodies, patients must have been treated with the recommended phase 2 dose and schedule.

11. Patients with brain or central nervous system metastases will be eligible, if asymptomatic, treated with surgery, whole brain or stereotactic radiotherapy, clinically stable (at least for a period of 2 months prior to signing ICF) and do not require continued steroid therapy. [Note: patients with known leptomeningeal carcinomatosis must be excluded]

12. Locally advanced/unresectable MCC must not be eligible for radiation therapy due to prior cumulative radiation treatment, judgment of radiation oncologist that the tumor is unlikely to respond to therapy or because radiation treatment is contraindicated for other reasons (e.g. tumor location).

13. Female patients of childbearing potential must have a negative urine or serum pregnancy test before receiving the first dose of study medication and they must comply with contraception methods as requested by the study protocol.

Exclusion criteria

1. History of serious anti-PD-(L)1 therapy-related adverse reactions prohibiting further avelumab treatment:
- Pneumonitis: Grade 3 or 4 or recurrent Grade 2
- Hepatitis: AST or ALT more than 5 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal
- Colitis/diarrhea: Grade 4 or recurrent Grade 3

- Nephritis and renal dysfunction: serum creatinine more than 6 times the upper limit of normal
- Any other immune-mediated adverse reactions which resulted in a life-threatening situation for the patient (excluding endocrinopathies) or infusion-related reactions Grade 3 or 4.

2. More than one line of previous systemic anti-neoplastic therapy other than anti-PD-(L)1 antibody monotherapy.

3. Palliative radiation therapy of single lesions within 2 weeks before planned administration of study medication.

4. Patients currently participating or having participated in a clinical study in which the last administration of the investigational medicinal product was within 2 weeks before consenting to study participation (i.e. signing ICF).

5. Not recovered adequately (<= Grade 1) from toxicities and/or complications from surgical intervention or from previous anticancer therapies (excluding alopecia, fatigue or endocrine dysfunction on replacement therapy) as judged by the investigator.

6. History or current evidence of clinically relevant allergies or hypersensitivity, which includes known or suspected intolerabilities attributed to domatinostat or avelumab or to constituents of the domatinostat tablets or avelumab infusion including known severe hypersensitivity reactions (Grade >= 3) to monoclonal antibodies.

7. Inadequate organ function defined by the following laboratory parameters:
• Absolute Neutrophil Count (ANC) < 1500/µl.
• Hemoglobin (Hb) < 9 g/dl (< Hb 5.6 mmol/L), may have been transfused.
• Platelet count < 100.000/µl.
• Serum creatinine > 1.5 x ULN or eGFR < 60 mL/min (as per Cockroft-Gault formula).
• ALT or AST > 1.5 x ULN.
• Serum total bilirubin > 1.5 x ULN.

8. Any medical condition requiring continuous systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other systemic immunosuppressive medications (e.g. methotrexate, azathioprine, interferons, mycophenolate, anti-TNF agents and other) within 2 weeks before consenting to study participation (i.e. signing ICF) except for the following: intranasal, inhaled, topical, local steroid applications/injection (e.g., intra-articular injection) or single doses of systemic corticosteroids as premedication/prevention for hypersensitivity reactions (e.g., CT scan premedication).

9. Any active gastrointestinal disorder that could interfere with the

absorption of domatinostat characterized by malabsorption or inability to swallow tablets as per judgment of the investigator.

10. Any known or suspected, current or chronic infection, immunodeficiency disorder or autoimmune disease requiring systemic treatment and/or that might deteriorate when receiving an immunostimulatory agent (e.g. chronic lymphocytic leukemia (CLL) or allogeneic stem-cell transplantation).

11. History of other hematologic or primary solid malignancies which received or require any form of active systemic anti-cancer treatment (such as, but not limited to, hormone anti-cancer therapy, immunotherapy or targeted therapy) during the last 12 months before consenting to study participation.

12. Received a live vaccine within 30 days before consenting to study participation.

13. Pregnant or breastfeeding.

14. Conditions requiring systemic anti-arrhythmic therapy known to prolong QT/QTc interval, patients with QTcF interval >480 msec on at least 2 separate and consecutive ECGs at screening or a medical history of long-QT-Syndrome.

15. Clinically significant (i.e. active) cardiovascular and/or thromboembolic diseases:
• Cerebral vascular accident or stroke.
• Uncontrolled hypertension.
• Congestive heart failure (New York Heart Association (NYHA) Class III or IV).
• Serious cardiac arrhythmia requiring medication (patients with status post pace maker and/or defibrillator implantation can be included).
• Symptomatic ischemic or severe valvular heart disease.
• Unstable angina pectoris or a myocardial infarction within 6 months prior to signing ICF. 1

16. Patients with known HIV, acute or chronic active hepatitis B (defined as positive titers for HBsAg, anti-HBc-IgM or DNA) or Hepatitis C (HCV RNA if anti-HCV antibody screening test positive)

17. Significant (current or chronic) diseases or other intercurrent illness, psychiatric illness or social situation that would limit compliance with study requirements or would pose an undue medical hazard, interfere with the conduct of the study or interfere with interpretation of the study results as judged by the investigator.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-10-2021
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	4SC-202
Generic name:	Domatinostat
Product type:	Medicine
Brand name:	Avelumab
Generic name:	Bavencio
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	29-05-2020
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	07-01-2021
Application type:	First submission

Review commission:	METC NedMec
Approved WMO Date:	13-03-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-05-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-01-2023
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
EudraCT	EUCTR2018-004788-30-NL
CCMO	NL72874.031.20