A phase II, open label, multicenter study to investigate the efficacy and safety of domatinostat in combination with avelumab in patients with treatment-naïve metastatic Merkel Cell Carcinoma - the MERKLIN 1 Study

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Primary Objective: to evaluate clinical efficacy of domatinostat in combination with avelumab in treatment-naïve metastatic or distally recurrent MCC patients as determined by the Objective Response Rate (ORR) according to Response Evaluation...

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

Summary

ID

NL-OMON51269

Source
ToetsingOnline

Brief title
MERKLIN 1

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: 4SC AG;a Munich;Germany based Biopharmaceutical company

Intervention

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

Outcome measures

Primary outcome

Primary Endpoint:

Confirmed Objective Response (OR) according to RECIST v1.1, determined by independent review. Both CR and PR must be confirmed by a second tumor assessment preferably at the regularly scheduled 6-weeks assessment interval, but no sooner than 4 weeks after the initial diagnosis of CR or PR.

Secondary outcome

Secondary Endpoints include:

• Duration of Response (DOR) according to RECIST v1.1 as determined by independent review.

• Durable Response (DR) according to RECIST v1.1, defined as objective response (CR or PR) determined by independent review with duration of at least 6 months.

• Overall Survival (OS) time, defined as the time from the first administration of study treatment until death due to any cause determined by the Investigator.

• Progression Free Survival (PFS) according to RECIST v1.1, defined as the time from first dosing (Day 1) to the date of PD or death from any cause (whichever comes first) as determined by independent review.

• Disease Control (DC) according to RECIST v1.1, defined as the proportion of patients with either an objective response (CR, PR) or stable disease (SD), as determined by independent review.

• RECIST v1.1 responses at 6 and 12 months after start of study treatment as determined by independent review.

• Safety and tolerability of the study treatment determined by number, frequency, duration and severity of AEs using CTCAE v5.0 classification, physical examination, laboratory tests, vital signs and ECGs.

• ORR, DOR, DR, DC and PFS in correlation to biomarker expression.

• Anti-drug-antibodies (ADAs) and pharmacokinetics of study treatments.

• Changes in EQ-5D-5L and FACT-M scores over the treatment period.

Exploratory Endpoints:

• OR, DOR, DR, DC and PFS assessed by Investigator according to RECIST v1.1

• OR, DOR, DR, DC and PFS assessed according to iRECIST as determined by independent review.

• Dynamics of tumor shrinkage in RECIST v1.1 target lesions at each imaging time point.

• Tumor biology correlated to disease response and to study treatment.

Study description

Background summary

Rationale for the Current Trial
Unmet Medical Need

MCC is a very rare and aggressive type of skin cancer. If the tumor cannot be sufficiently controlled by surgery and radiation in the early stages, medical treatment with chemotherapy or immunotherapy is indicated. Here, the PD-(L)1 checkpoint inhibitors avelumab and pembrolizumab have shown very promising results by achieving ORRs up to 50% with approximately 70% of responses to be durable, i.e. longer than 12 months; far more efficacious than any chemotherapy regimen. Nonetheless, still 50% of patients do not adequately respond to anti-PD-(L)1 monotherapy, are either treatment resistant (best response PD) or relapse early after an initial period of response or SD. For those patients no further treatments options are approved. Until today no generally accepted predictive factors for anti-PD(L)1 therapy are established, although tumor PD-L1 expression, treatment naivety, virus status and some other factors may correlate.

Obviously, the anti-PD-L(1) monotherapy reached its limits in mMCC providing sustained clinical benefits for approximately 50% of patients, but without benefit in the other half of the patients. Therefore, a clear unmet medical need remains to identify additional, immune-modulating 1st line combination partners for PD-(L)1 checkpoint inhibitors capable of breaking the tumor*s ability for primary resistance and to prevent development of tumor escape mechanisms leading to secondary resistance. Eventually, a combination partner to anti-PD-L1 inhibitors must increase the numbers of 1st line responders relevantly as well as duration of response beyond the efficacy of anti-PD-(L)1 monotherapy, especially in case of PD-L1 negative tumors, the tumors with the lowest probability of responding to anti-PD-(L)1 monotherapy.

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 to prevent resistance or relapse. 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 by CD8 T cells. Immunohistochemical evaluations have shown a markedly downregulated expression of MHC-I in conjunction with reduced corresponding mRNA content in MCC tumor tissue demonstrating that T cell recognition of MCC tumors antigens is significantly disrupted, not to say completely impaired [Ugurel, 2019; Ritter, 2017; Vandeven, 2016].

• CD8 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, triggers tumor infiltration of CD8 T cells, and Th1 CD4 cells, and increases IFN-γ expression within the tumors resulting in an enhanced immunogenicity and susceptibility 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 [Bretz, 2019]. 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 [Bretz 2019]. Ultimately, the hypothesis for the MERKLIN 1 study is to facilitate synergistic effects of domatinostat in combination with avelumab in treatment-naïve patients to effectively address known escape mechanisms in MCC and initiate a more effective immune response to achieve a higher rate of responses, increase durability and depth of response and prevent development of secondary resistance.

Combination with Avelumab
Avelumab was selected as the combination partner in MERKLIN 1 for the following reasons:
• Worldwide approval status of avelumab in mMCC based on the largest study ever conducted in mMCC and recruitment of patients in the major regions including USA, Europe and Australia.
• To allow the best possible comparison of the MERKLIN 1 data (combination therapy of domatinostat and avelumab) with the results of the avelumab monotherapy registration trial JAVELIN Merkel 200.
• To facilitate sample size calculation and estimation of effects size for the primary endpoint of MERKLIN 1 by referencing to a single, published reference (i.e. JAVELIN Merkel 200 Part B) to better control sources for statistical uncertainties and bias in that rare indication where the number of patients is very limited and clinical trials are very difficult to conduct.
• The combined treatment of domatinostat and avelumab seems to be safe and well-tolerated based on the first data derived from the EMERGE study.
In MERKLIN 1 all patients will receive domatinostat in combination with avelumab which means that all patients will receive the approved standard of care. Domatinostat will be the investigational add-on therapy. The hypothesis

is that domatinostat in combination with avelumab synergistically enhances response rates and prolongs duration of response compared to avelumab monotherapy, taking the potential predictive value of tumor PD-L1 expression into account. The analysis and interpretation of the clinical efficacy in MERKLIN 1 will take the JAVELIN Merkel 200 trial Part B data as the historical reference.

Conclusion
Domatinostat is expected to have considerable clinical potential as epigenetic modifier in mMCC synergizing with the anti-PD-L1 antibody avelumab therapy. This Phase II study is designed to investigate efficacy and safety of domatinostat in combination with avelumab in treatment-naïve mMCC patients to increase the number of responders, depths of responses and to prolong the duration of response taking the potential predictive value of tumor PD-L1 expression into account.

Study objective

Primary Objective: to evaluate clinical efficacy of domatinostat in combination with avelumab in treatment-naïve metastatic or distally recurrent MCC patients as determined by the Objective Response Rate (ORR) according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1) by independent review.

Secondary Objectives:
Evaluation of additional parameters for the clinical efficacy of avelumab in combination with domatinostat, correlation of clinical data to biomarker expression, safety profile of the study treatment, Anti-Drug Antibodies (ADAs) to avelumab and pharmacokinetics (PK) of avelumab and domatinostat, Health-related Quality of Life (HrQoL)

Exploratory Objectives:
• Tumor response assessed by Investigator according to RECIST v1.1
• Tumor response assessed according to iRECIST
• Tumor biology correlated to disease response and to study treatment

Study design

Phase 2, international, multi-center, single arm, open-labeled, therapeutic

Intervention

The study treatment will comprise of 2 components:
1. Domatinostat tablets 200 mg, p.o. intake twice daily (BID)
2. Avelumab intravenous (i.v.) infusion 800 mg every 2 weeks (Q2W)

All patients will receive the study treatment in an open-labeled manner.

Study burden and risks

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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. Signed written informed consent.
2. Age > 18 years at signature of Informed Consent Form (ICF).
3. Histologically proven MCC.
• Confirmation of the diagnosis by immune-histochemistry as per standard at the

institution, including (but not limited to) CK20 and TTF-1.
• Patients must have metastatic or distally recurrent disease; M1 status must be confirmed at entry.
• Patients must not have received any prior systemic treatment for metastatic MCC. Prior treatment in the adjuvant setting (no clinically detectable disease; no metastatic disease) will be allowed, if the end of the treatment occurred at least 6 months prior to study entry, i.e. signing ICF.
[Note: Not applicable for patients entering re-treatment (Section 4.4.1.1); in case the patient is eligible for re-treatment as defined in this protocol, the most recent treatment before re-treatment must be MERKLIN 1 study drug and no other anti-tumor treatment is allowed since end of previous MERKLIN 1 treatment]
4. Fresh biopsy or archival tumor tissue (not older than 6 months) from an unirradiated lesion.
[Note: No systemic anti-cancer treatment should have been given since archival tumor tissue has been collected]
5. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 1 at study entry.
6. Estimated life expectancy of more than 12 weeks.
7. Disease must be measurable with at least one unidimensional measurable lesion by RECIST v1.1 (including skin lesions).
[Baseline imaging will be performed within 18 days prior to planned start of the study treatment, if no RECIST v1.1 evaluable imaging was done within 4 weeks prior to the planned start of the study treatment.]
8. Adequate hematological and organ function defined by the following parameters:
Adequate hematological function defined by
• White blood cell count (WBC) > 3000/µl
• Absolute Neutrophil Count (ANC) > 1500/µl
• Lymphocyte count > 500/µl
• Hemoglobin (Hb) > 9 g/dl (or > 5.6 mmol/L), may have been transfused
• Platelet count > 100.000/µl
Adequate hepatic function defined by
• Serum total bilirubin < 1.5 x ULN
• ALT and/or AST < 1.5 x ULN
Adequate renal function defined by
• eGFR > 60 ml/min (as per Cockcroft-Gault formula)
9. Highly effective contraception for both male and female subjects if the risk of conception exists. Female patients of childbearing potential must have a negative urine or serum pregnancy test before receiving the first dose of study medication and must comply with contraception methods as requested by the study protocol.

Exclusion criteria

1. Participation in another interventional clinical study within the past 30

days (participation in observational studies is permitted)
[Note: A patient in the survival follow-up phase will be eligible.]
2. Concurrent treatment with a non-permitted drug
3. Prior therapy with any histone deacetylase (HDAC) inhibitor or antibody/drug targeting T cell coregulatory proteins (immune checkpoints) such as anti-programmed death 1 (PD-1), anti-programmed death-ligand 1 (PD-L1) or anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibody.
[Note: Not applicable for patients entering re-treatment (Section 4.4.1.1); in case the patient is eligible for re-treatment as defined in this protocol, the most recent treatment before re-treatment must be MERKLIN 1 study drug and no other anti-tumor treatment is allowed since end of previous MERKLIN 1 treatment]
4. Concurrent anti-cancer treatment (for example, cytoreductive therapy, radiotherapy [except for palliative bone directed radiotherapy, or radiotherapy administered on non-target superficial lesions], immune therapy, or cytokine therapy except for erythropoietin). Radiotherapy administered to superficial lesions is not allowed if such lesions are considered target lesions in the efficacy evaluation or may influence the efficacy evaluation of the study treatment.
5. Major surgery for any reason, except diagnostic biopsy, within 4 weeks and/or if the subject has not fully recovered from surgery.
6. Concurrent systemic therapy with steroids or other immunosuppressive agents (e.g. methotrexate, azathioprine, interferons, mycophenolate, anti-TNF agents and other), or the use of any investigational drug within 28 days before the start of study treatment. Short-term administration of systemic steroids e.g. for allergic reactions or the management of immune-related adverse events [irAE] while on study is allowed. Also, patients requiring hormone replacement with corticosteroids for adrenal insufficiency are eligible if the steroids are administered only for purpose of hormonal replacement and at doses < 10 mg or equivalent prednisone per day.
[Note: Patients receiving bisphosphonate or denosumab are eligible.]
7. 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.
8. Patients with active central nervous system (CNS) metastases are excluded and a brain CT/MRI will be required during screening if not performed within 6 weeks prior to the planned start of the study treatment. Subjects with a history of treated CNS metastases (by surgery or radiation therapy) are not eligible unless they have fully recovered from treatment, demonstrated no progression for at least 2 months, and do not require continued steroid therapy.
9. History of or concurrent malignancies, except the malignancy is clinically insignificant, no systemic treatment is or has been required for the last 6 months, and the patient is clinically stable
10. Prior organ transplantation (including allogeneic stem-cell transplantation).
11. 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.

12. Positive testing for HIV or known AIDS or HBV or HCV infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening is positive).
13. Active or history of any autoimmune disease (except for patients with vitiligo) or immune-diseases that required treatment with systemic immune modulating drugs.
14. 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 and known severe hypersensitivity reactions (Grade >= 3) to monoclonal antibodies.
15. Persisting toxicity related to prior therapy Grade > 1 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0; however, sensory neuropathy Grade < 2 will be acceptable.
16. Pregnancy or lactation period.
17. Known or suspected alcohol or drug abuse.
18. Clinically significant (i.e. active) cardiovascular and/or thromboembolic diseases:
• Cerebral vascular accident or stroke < 6 months prior to enrollment.
• Uncontrolled hypertension
• Congestive heart failure (New York Heart Association (NYHA) Class III or IV)
• Serious cardiac arrhythmia requiring medication (patients with status post pacemaker 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 screening, i.e. signing ICF
19. All other significant diseases (for example, inflammatory bowel disease), which, in the opinion of the Investigator, might impair the patient*s tolerance to the study treatment.
20. Any psychiatric condition that would prohibit the understanding or rendering of informed consent.
21. Legal incapacity or limited legal capacity.
22. Administration of a live vaccine within 28 days prior to study drug administration. Live vaccines are also prohibited during study treatment.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	15-07-2021
Enrollment:	2
Type:	Anticipated

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:	01-04-2021
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	21-09-2021
Application type:	First submission
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	EUCTR2019-003575-19-NL
CCMO	NL76627.031.21