STUDY PROTOCOL

Tissue registry in melanoma (TRIM)

Sponsor	Klinik für Dermatologie Universitätsklinikum Essen Hufelandstraße 55 45147 Essen
Principle Investigator	Prof. Dr. med. Dirk Schadendorf Klinik für Dermatologie Universitätsklinikum Essen Hufelandstraße 55 45147 Essen Germany Email: dirk.schadendorf@uk-essen.de

Protocol number:	CA209-578
Protocol version and date	1.1, 07-Mar-2016

This study will be conducted in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki and other applicable regulatory requirements.

SYNOPSIS

Title of study:	Tissue registry in melanoma (TRIM)
Protocol number:	CA209-578
Sponsor	Klinik für Dermatologie Universitätsklinikum Essen Hufelandstraße 55 45147 Essen
Principal investigator	Prof. Dr. med. Dirk Schadendorf Klinik für Dermatologie Universitätsklinikum Essen Hufelandstraße 55 45147 Essen Germany Phone: +49-201-723-42 0 Fax: + 49-201-723-5935 Email: dirk.schadendorf@uk-essen.de
Protocol Writing Committee:	Prof. Dr. med. Dirk Schadendorf Klinik für Dermatologie Universitätsklinikum Essen Hufelandstraße 55, 45147 Essen, Germany Phone: +49-201-723-42 0 Fax: + 49-201-723-5935 Email: dirk.schadendorf@uk-essen.de Prof. Dr. med. Selma Ugurel Klinik für Dermatologie Universitätsklinikum Essen Hufelandstraße 55, 45147 Essen, Germany Phone: +49-201-723-85364 Email: selma.ugurel@uk-essen.de
Study Duration:	5 years

Study Objective: To identify and validate molecular and clinical novel biomarkers of therapy outcome in metastatic melanoma.

Clinical and molecular parameters of melanoma patients and their tumors will be collected in an online-based registry (ADOREG), and thereafter correlated with the outcome of subsequent systemic therapies in terms of progression-free survival, overall survival, and treatment response. Systemic therapies will include all types of currently used regimens (kinase inhibitors, immune checkpoint inhibitors, chemotherapy).

Study Rationale The current therapeutic options for patients with metastatic melanoma are numerous and include cytotoxic chemotherapy, kinase inhibitors, and immune checkpoint blockers. Clinical efficacy and utility of kinase inhibitors is driven by biomarker-based patient selection, e.g. via mutations in genes like BRAF or NRAS. These patients highly benefit from small molecule kinase inhibitors, which have proven highly clinically effective and superior when compared to standard chemotherapy. Recently, monoclonal antibodies targeting immune regulatory receptor-ligand systems, the so-called immune checkpoint inhibitors, have arised as a promising new treatment modality. Antibodies against PD-1 and CTLA-4 are approved in metastatic melanoma, but molecular or clinical biomarkers predicting the outcome of this therapy strategy are rare and not systematically validated.

So far, expression of PD-L1 by tumor cells or infiltrating immune cells has been shown to correlate with response and survival. However, detection methods and cut-off points are not yet standardized. Importantly, the optimal time point and site of tissue sampling for molecular diagnostics used for patient selection for immune checkpoint blocker therapy is still unclear. Archival tumor samples, especially samples from primary tumors, may not reflect the actual state of the dynamically regulated tumor-host interaction which is targeted by these therapeutic antibodies. Another hypothesis associates high “mutational load” of the tumor with the likelihood of the presentation of neo-epitopes to trigger tumor-specific immune responses.

The aim of the present study is to identify and validate molecular and clinical biomarkers of therapy outcome in metastatic melanoma. Clinical and molecular parameters of melanoma patients and their tumors will be collected in an online-based registry (ADOREG), and thereafter correlated with the outcome of subsequent systemic therapies in terms of progression-free survival, overall survival, and treatment

	response. Systemic therapies will include all types of currently used regimens (kinase inhibitors, immune checkpoint inhibitors, chemotherapy). FFPE tissue samples will comprise different time points (primary tumors versus metastases) as well as organs (lymph node versus organ metastases) to identify potential differences in the predictive value of these materials. The anticipated results from these analyses are of essential importance for future patient selection for individualized therapy strategies.
Study Population:	1,000 subjects with metastatic melanoma stage III or IV from centers of the German Dermatologic Cooperative Oncology Group (DeCOG) (*Arbeitsgemeinschaft Dermatologische Onkologie* (ADO)).
Study Design:	Up to 1,000 patients will be enrolled across multiple DeCOG centers of which more than 40 have signed up for our nation-wide melanoma registry ADOREG (status: Dec 2015). After a patient has given his informed consent, surplus FFPE tissue from already taken tumor excisions or biopsies will be sent to the central laboratory for molecular diagnostics (30 gene panel sequencing, anti-PD-L1 immunohistochemistry) at the Univ Hospital Essen. The patient's baseline data will be entered into a corresponding online database hosted by the ADO (ADOREG). ADOREG has already received a positive vote from the EC (vote #14-5921-BO). All patient data will be pseudonymised at the trial site. Unique patient numbers will be used for identification. Results from molecular analyses will also be entered into the ADOREG database and hereby made accessible to the principal investigators at the participating centers. Patient follow-up information on therapy response, progression-free and overall survival will be entered into the ADOREG system every 3 months. Molecular as well as clinical baseline data will be correlated with therapy response and survival in order to identify predictors of therapy outcome.
Main Inclusion/ Exclusion Criteria	Inclusion Criteria 1. Patients with histologically confirmed metastatic melanoma stage III or IV. 2. Clinically eligible for systemic cancer therapy (cytotoxic agents, immune checkpoint inhibitors, targeted agents). 3. Tumor tissue biopsy already existing (metastasis tissue as recent as possible, but older tissue material or primary tumor tissue also possible). 4. Patient has given written informed consent for the current study as well as for his data to be entered into

	the ADOREG online database system. 5. Patient is ≥18 years old. Exclusion Criteria Patients cannot be included in TRIM if one of the inclusion criteria is not met.
Study endpoints:	Correlation of molecular and clinical biomarkers with outcomes of patients with metastatic melanoma in terms of progression-free survival, overall survival, and treatment response. Systemic therapies will include all types of currently used regimens (kinase inhibitors, immune checkpoint inhibitors, chemotherapy).
Statistical Methods	Exploratory and descriptive analyses of biomarkers are planned, using univariate and multivariate Kaplan-Meier-survival analyses.

SIGNATURE PAGE

Declaration of the Investigator

I have read the attached protocol entitled

"Tissue registry in melanoma (TRIM)", Version 1.0

and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice and all applicable national regulations as well as the requirements of the appropriate Institutional Review Board/Independent Ethics Committee and any other institutional requirements.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the coordinating investigator.

_____ _____

Signature Date

_____

Investigator

CONTACT LIST

Sponsor	Klinik für Dermatologie Universitätsklinikum Essen Hufelandstraße 55 45147 Essen Germany
Principal Investigator	Prof. Dr. med. Dirk Schadendorf Klinik für Dermatologie Universitätsklinikum Essen Hufelandstraße 55 45147 Essen Germany Phone: +49-201-723-42 0 Fax: + 49-201-723-5935 Email: dirk.schadendorf@uk-essen.de
Data acquisition, plausibility and analysis	Prof. Dr. Selma Ugurel Universitätsklinikum Essen Hufelandstraße 55 47147 Essen Germany Phone: +49-201-723-4714 E-Mail: Selma.ugurel@uk-essen.de
Central laboratory	Klinik für Dermatologie Forschungslabor Universitätsklinikum Essen Hufelandstraße 55 45147 Essen Germany Contact person: Antje Sucker Phone: +49-201-723-2406 Fax: +49-201-723-5171 E-Mail: haut-mol-path@uk-essen.de

LIST OF ABBREVIATIONS

ADO	Arbeitsgemeinschaft Dermatologische Onkologie *(Dermatologic Cooperative Oncology Group/DeCOG)*
ADOREG	Skin tumor registry of the *Arbeitsgemeinschaft Dermatologische Onkologie*
CRF	Case report form
cKIT	Tyrosine-protein kinase Kit
DNA	Deoxyribonuleic acid
EC	Ethics Committee
eCRF	Electronic case report form
FFPE	Formalin-fixed paraffin embedded
GCP	Good Clinical practice
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
NRAS	NRAS
PD-L1	Programmed death-ligand 1
PTEN	Phosphatase and tensin homolog
WBE	Westdeutsche Biobank Essen (*West German biobank Essen*)

TABLE OF CONTENTS

1. INTRODUCTION

1.1 Background

The current therapeutic options for patients with metastatic melanoma are numerous and include cytotoxic chemotherapy, kinase inhibitors, and immune checkpoint blockers [1]. Clinical efficacy and utility of kinase inhibitors is driven by biomarker-based patient selection, e.g. via mutations in genes like BRAF or NRAS [2;3]. These patients highly benefit from small molecule kinase inhibitors, which have proven highly clinically effective and superior when compared to standard chemotherapy. Recently, monoclonal antibodies targeting immune regulatory receptor-ligand systems, the so-called immune checkpoint inhibitors, have arisen as a promising new treatment modality [4;5]. Antibodies against PD-1 and CTLA-4 are approved in metastatic melanoma, but molecular or clinical biomarkers predicting the outcome of this therapy strategy are rare and not systematically validated.

So far, expression of PD-L1 by tumor cells or infiltrating immune cells has been shown to correlate with response and survival [6]. However, detection methods and cut-off points are not yet standardized. Importantly, the optimal time point and site of tissue sampling for molecular diagnostics used for patient selection for immune checkpoint blocker therapy is still unclear [7]. Archival tumor samples, especially samples from primary tumors, may not reflect the actual state of the dynamically regulated tumor-host interaction which is targeted by these therapeutic antibodies. Another hypothesis associates high “mutational load” of the tumor with the likelihood of the presentation of neo-epitopes to trigger tumor-specific immune responses.

The aim of the present study is to identify and validate molecular and clinical biomarkers of therapy outcome in metastatic melanoma. Clinical and molecular parameters of melanoma patients and their tumors will be collected in an online-based registry (ADOREG), and thereafter correlated with the outcome of subsequent systemic therapies in terms of progression-free survival, overall survival, and treatment response. Systemic therapies will include all types of currently used regimens (kinase inhibitors, immune checkpoint inhibitors, chemotherapy). FFPE tissue samples will comprise different time points (primary tumors versus metastases) as well as organs (lymph node versus organ metastases) to identify potential differences in the predictive value of these materials. The anticipated results from these analyses are of essential importance for future patient selection for individualized therapy strategies.

1.2 Risk-Benefit Assessment

No risk exists for the patients since formalin-fixed paraffin embedded (FFPE) tumor samples already taken prior to enrollment for other reasons will be used. Therefore, the patient will not be subjected to any surgical sampling procedure.

Each patient can potentially benefit from the fact that molecular analysis results are provided to the investigator. The investigator can provide the patient with the results and is allowed to use the results to optimize the patient’s therapy. However, this is not an

objective of the study, and the investigator and the patient can decide whether or not the analysis results should be used for therapy optimization.

2. STUDY OBJECTIVES

To identify and validate molecular and clinical novel biomarkers of therapy outcome in metastatic melanoma.

Clinical and molecular parameters of melanoma patients and their tumors will be collected in an online-based registry (ADOREG), and thereafter correlated with the outcome of subsequent systemic therapies in terms of progression-free survival, overall survival, and treatment response. Systemic therapies will include all types of currently used regimens (kinase inhibitors, immune checkpoint inhibitors, chemotherapy).

3. INVESTIGATIONAL PLAN

3.1 Overall Design

In this study in patients with metastatic melanoma stage III or IV, only surplus FFPE tissue from tumor biopsies already taken before enrollment will be used. Approximately 1,000 patients will be enrolled at multiple centers, in particular at centers which are part of the *Arbeitsgemeinschaft Dermatologische Onkologie* (ADO). After a patient has given his informed consent, the tissue specimen will be sent to the central laboratory at the University Hospital Essen where nucleic acid analyses (30 gene panel sequencing) and protein analysis (anti-PD-L1 immunohistochemistry) will be performed.

The patient's baseline data will be entered into a corresponding online database hosted by the ADO (ADOREG) by the treating physician. ADOREG has already received a positive vote from the EC (vote #14-5921-BO). All patient data will be pseudonymised automatically at the trial site. Unique patient numbers will be used for identification.

Results from molecular analyses will also be entered into the ADOREG database and hereby made accessible to the principal investigators at the participating centers. Patient follow-up information on therapy response, progression-free and overall survival will also be entered into the ADOREG system every 3 months by the treating physician. Molecular as well as clinical baseline data will be correlated with therapy response and survival in order to identify predictors of therapy outcome. The results of these analyses will be centrally evaluated at the Department of Dermatology at the University Hospital Essen. The planned study duration is 5 years with 4 years recruitment and 1 year of additional follow up.

3.2 Endpoints

Correlation of molecular and clinical biomarkers with outcomes of patients with metastatic melanoma in terms of progression-free survival, overall survival, and treatment response. Systemic therapies will include all types of currently used regimens (kinase inhibitors, immune checkpoint inhibitors, chemotherapy).

Key endpoints are:

Treatment Response
Overall Survival (OS)
Progression Free Survival (PFS)

4. STUDY POPULATION

4.1 Inclusion Criteria

1. Patients with histologically confirmed metastatic melanoma stage III or IV.

2. Clinically eligible for systemic cancer therapy (cytotoxic agents, immune checkpoint inhibitors, targeted agents).

3. Tumor tissue biopsy already existing (metastasis tissue as recent as possible, but older tissue material or primary tumor tissue also possible).

4. Patient has given written informed consent for the current study as well as for his data to be entered into the ADOREG online database system.

5. Patient is ≥18 years old.

4.2 Exclusion criteria

Patients cannot be included in TRIM if one of the inclusion criteria is not met.

4.3 Withdrawal criteria

Patients are free to withdraw from participation in the study at any time.

5. STUDY SCHEDULE

5.1 Screening and enrolment

Potentially eligible patients will be identified among the patients at the study centers. In an on-site visit, the investigator will inform the patient about the study and potential risks and benefits for the patient. The patient will be provided with the specific patient information

sheet for both, TRIM study participation as well as data entry into the ADOREG system. The investigator will clarify any questions the patient may have regarding study participation. The patient will be given sufficient time to thoroughly consider participation in the study. If the patient decides to participate, the investigator will obtain the patient's written informed consent on the Informed Consent Form (ICF) and sign the ICF himself, in order to document the information process. The patient will keep a copy of the signed ICF, and the original will be filed by the investigator. An individual patient number will be assigned, which will be used to identify the patient's FFPE tumor sample and all patient data entered into the ADOREG system.

5.2 Molecular Diagnostics

After a patient will have given his informed consent, the tissue specimen will be sent by the participating center to the central laboratory at Essen where nucleic acid analyses (30 gene panel sequencing) and protein analysis (anti-PD-L1 immunhistochemistry) will be performed. Before shipping, the center staff will pseudonymize the samples using the individual patient numbers assigned to each patient via ADOREG system.

30 gene panel sequencing comprises:

- NRAS
- cKIT
- PTEN
- KRAS
- KIT
- NF1
- HRAS
- RAC1
- TERT Prom.
- TERT
- CDKN2A
- CDK4
- PTEN
- TP53
- MAP2K1
- MAP2K2
- PIK3R1
- PIK3CA
- MITF
- ARID2
- ARID1A
- SMARCA4
- EZH2
- IDH1
- CTNNB1
- FBXW7

- WT1
- GNAQ
- GNA11
- BAP1
- SF3B1

Anti-PD-L1 immunohistochemistry analyses includes:

- Percentage of tumor cells
- Percentage of PD-L1 positive cells
- PD-L1 staining intensity
- Amount of tumor-infiltrating immune cells

5.3 Data Capture

The investigator or designated staff at study centers will enter the patient's demographic data, data on tumor characteristics, and previous anti-tumoral treatment extracted from the patient's file into the online ADOREG database (Baseline data capture).

Baseline Data Capture:

- Patient ID
- Confirmation of Patient informed consent
- Date of Birth
- Gender
- Ethnicity
- Primary diagnosis of metastatic melanoma (date)
- pT Localization
- pT Type
- pT Tumor tickness
- pT Ulceration
- pT Rate of mitosis
- pT Regression
- infiltration of inflammation cells
- tumor on actinic pre-damaged skin
- SLNB procedure and result
- Primary diagnosis of stage III (date)
- Previous treatment in stage II / III
- Primary diagnosis stage IV (date)
- Previous treatment in stage IV
- BRAF mutation status

- Current stage
- Current weight and height
- Current serum LDH
- Current serum S100
- Current serum CRP
- Current number of leucocytes
- Current number of neutrophils
- Current number of lymphocytes
- Current number of eosinophils
- Current number of basophils
- Current number of monocytes
- Current overall performance state (ECOG)
- Current number of pigmented lesions on left forearm
- Current number of atypical pigmented lesions on whole body
- Current sites of metastasis
- Date of tissue sample
- Origin of tissue sample

Results from molecular analyses will also be entered into the ADOREG database and hereby made accessible to the principal investigators at the participating centers. Patient follow-up information on therapy response, progression-free and overall survival will be entered into the ADOREG system every 3 months (Follow-Up data capture).

Follow-up data capture:

- Patient ID
- Primary systemic therapy after molecular analysis
- Impact of results of molecular analysis on choice of therapy
- Date of therapy start
- Therapy scheme
- Last treatment stage
- Treatment cycles
- Date of end of treatment
- Reason for end of treatment
- Best Response
- Date of best response
- Progress under treatment
- Date of progress
- Localization of progress
- Progress: non-previous brain metastasis
- Progress: previous known brain metastasis
- Second-line therapy and response
- Date of last follow-up
- Date of death

- Comments

Molecular as well as clinical baseline data will be correlated with therapy response and survival in order to identify predictors of therapy outcome.

6. SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of recording SAEs and non-serious AEs.

6.1 Adverse Events

According to the International Conference of Harmonisation (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product,

Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition),

Recurrence of an intermittent medical condition (e.g., headache) not present at baseline,

Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram [ECG], X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study medicine.

6.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

An SAE is any AE that meets any of the following criteria:

- Is fatal (i.e., the AE actually causes or leads to death)
- Is life-threatening (NOTE: The term “life-threatening” refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient’s ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study medicine

- Is a significant medical event in the physician's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE criteria); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the CRF.

SAEs are required to be reported by the physician to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

6.3 Non-Serious Adverse Events

Non-serious AEs will be collected in the registry ADOREG.

6.4 Methods and Timing for Capturing and Assessing Safety Parameters

The physician is responsible for ensuring that all AEs are recorded on the AE eCRF.

6.5 Assessment of Severity of Adverse Events

The AE severity grading scale for the NCI CTCAE will be used for assessing AE severity. The table below will be used for assessing severity for AEs.

Table 1 Adverse Event Severity Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to AE [d]

Note: Based on the NCI CTCAE (v 4.03)

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as an SAE.

[d] Grade 4 and 5 events must be reported as SAEs.

6.6 Reporting of AEs and SAEs

AEs of grade 3 and higher are considered to be SAEs and therefor directly reported within 24 hours to the Sponsor. All reported AEs will be forwarded weekly via line listings.

7. STATISTICAL METHODS AND SAMPLE SIZE

7.1 Statistical analysis

Statistical analysis will be primarily explorative and descriptive. To gain new insights into the novel topic rapidly, interim analyses may be conducted as soon as significant numbers of cases are evaluable.

The gene panel sequencing data and data from PD-L1 immunohistochemistry analyses will be tested for their predictive value on treatment response, progression-free and overall survival of the respective patients in univariate analyses. Moreover, this question will be tested multivariately including known prognostic parameters of metastastic melanoma (serum LDH, performance state classified by the ECOG system, site and number of metastases, disease stage according to AJCC classification, therapy line). Multivariate analyses will be done using the multiple hazards model of Cox.

These analyses will be done in the whole patient cohort as well as in patient subgroups (e.g. different therapy types, different melanoma subtypes). Also duration of response, type and site of progression, e.g. brain metastases, will be analyzed.

7.2 Sample size

No formal sample size calculation was performed. TRIM will be considered as a registry: a registry is a complete collection of patients for a given time period and for a given set of centers willing to participate. Applying this principle of collecting all available patients in a locally and chronologically defined range makes a formal sample size calculation inapplicable.

Given these conditions, we expect to capture up to 1,000 patients in about 50 clinical centers in Germany.

8. ETHICAL CONSIDERATIONS

8.1 Declaration of Helsinki/Good Clinical Practice

The responsible investigator will ensure that this study is conducted in accordance with the Declaration of Helsinki (last revised in Fortaleza, Brazil, 2013[1]) and the laws and regulations of the country where the study is performed. The protocol has been written and the study will be conducted according to the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice. It is the responsibility of all persons engaged in research on human beings to ensure that the study is performed in accordance with the international Good Clinical Practice standards and according to all local laws and regulations concerning clinical studies.

8.2 Patient Information and Informed Consent

It is the responsibility of the site investigator to obtain written informed consent for study participation as well as participation in the ADOREG database from each patient participating in this study, after adequate explanation of aim, importance, anticipated benefits, and potential hazards and consequences of the study, according to the applicable local laws.

With the declaration of consent the patient agrees that biosamples are processed, stored and analyzed in a pseudonymized way. The informed consent form must be personally signed and dated by the patient and her or his treating physician before any study procedure is performed and must be kept on file by the site investigator.

8.3 Confidentiality

All study findings and documents will be regarded as confidential. The investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating patients must be maintained. Patients will be identified on eCRFs and other documents submitted to the Department of Dermatology, University Hospital Essen, by their patient identification number, not by name. Documents should not be submitted to the Department of Dermatology, University Hospital Essen which identify the patient (e.g., the signed informed consent) must be maintained in confidence by the investigator.

Patient data in the study database and the FFPE tumor samples will be kept for at least 10 years and will then be discarded or transferred into the skin tumor biobank of the Department of Dermatology, University Hospital of Essen.

8.4 Study discontinuation

Patients do not receive study-specific treatment in this study. In case of study discontinuation, no need for therapy adjustment arises. If a patient gives notice of study discontinuation, all patient-related records and residual biomaterials should be deleted and discarded.

9. CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications to the ongoing study must be made via amendment. The coordinating investigator is responsible to obtain positive opinion from the independent ethics committee in accordance with local legal requirements. Approval must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial subjects or when the changes are non-substantial and involve only logistical or administrative aspects of the trial (e.g. change of telephone numbers).

10. STUDY DOCUMENTATION, CRF, AND RECORD KEEPING

10.1 Clinical data

All clinical data will be pseudonymized and entered into the ADOREG system by trained study personnel under strict obedience of data protection regulations. All documents must be archived in a secure place and treated as confidential material. The personnel at the dermatology department who will perform laboratory analyses and data analyses will only have access to pseudonymized data.

10.2 Source Documents and Background Data

If required, source data verification will be conducted using the medical records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audits and/or inspections, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected at all times. According to the standards of the national data protection laws, all data obtained in the course of a clinical study must be treated with discretion in order to guarantee the rights of the patient's privacy.

10.3 Audits and Inspections

This study may be audited by the coordinating investigator, any person authorized by the coordinating investigator or inspected by competent health authorities in order to determine the authenticity of the recorded data and compliance with the study protocol.

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from coordinating investigator/monitors/ auditor/health authority inspectors after appropriate notification needed for source data verification and proper review of the study progress. The verification of the patient data in the ADOREG system must be performed by direct review of source documents. The investigator agrees to comply with the coordinating investigator and competent authority requirements regarding the auditing/inspection of the study.

All material used in clinical studies are subjected to quality control.

10.4 Case Report Form (CRF)

For each patient enrolled, an eCRF in the ADOREG system will be completed by the investigator or an authorized delegate from the study staff. This also applies to records for those patients who fail to complete the study.

11. CONFIDENTIALITY OF TRIAL DOCUMENTS AND PATIENT RECORDS

The investigators and the coordinating investigator must assure that, according to the standards of the data protection law, all data obtained in the course of this clinical study must be treated with discretion in order to guarantee the patient's privacy rights. Patient-related documents must be submitted to the coordinating center and the analytical laboratories in a pseudonymous manner. The investigator must keep a patient identification log showing codes and names. The investigator will maintain documents that will not be provided to coordinating investigator, e.g., patients' written consent forms, in strict confidence.

12. PUBLICATION POLICY

The coordinating investigator is responsible for the timely reporting of study data.

The order of the authors on publications will be determined according to contribution to the biomarker and data analysis, sample provision, sample and data quality, and significant scientific input to the study by the Study Committee.

13.REFERENCES

1 Ugurel S, Rohmel J, Ascierto PA, Flaherty KT, Grob JJ, Hauschild A, Larkin J, Long GV, Lorigan P, McArthur GA, Ribas A, Robert C, Schadendorf D, Garbe C: Survival of patients with advanced metastatic melanoma: The impact of novel therapies. Eur J Cancer 2016;53:125-34. doi: 10.1016/j.ejca.2015.09.013. Epub;%2015 Dec 17.:125-134.

2 McArthur GA, Chapman PB, Robert C, Larkin J, Haanen JB, Dummer R, Ribas A, Hogg D, Hamid O, Ascierto PA, Garbe C, Testori A, Maio M, Lorigan P, Lebbe C, Jouary T, Schadendorf D, O'Day SJ, Kirkwood JM, Eggermont AM, Dreno B, Sosman JA, Flaherty KT, Yin M, Caro I, Cheng S, Trunzer K, Hauschild A: Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol 2014;15:323-332.

3 Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de BF, Larkin J, Garbe C, Jouary T, Hauschild A, Grob JJ, Chiarion S, V, Lebbe C, Mandala M, Millward M, Arance A, Bondarenko I, Haanen JB, Hansson J, Utikal J, Ferraresi V, Kovalenko N, Mohr P, Probachai V, Schadendorf D, Nathan P, Robert C, Ribas A, DeMarini DJ, Irani JG, Casey M, Ouellet D, Martin AM, Le N, Patel K, Flaherty K: Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med 2014;371:1877-1888.

4 Robert C, Thomas L, Bondarenko I, O'Day S, M DJ, Garbe C, Lebbe C, Baurain JF, Testori A, Grob JJ, Davidson N, Richards J, Maio M, Hauschild A, Miller WH, Jr., Gascon P, Lotem M, Harmankaya K, Ibrahim R, Francis S, Chen TT, Humphrey R, Hoos A, Wolchok JD: Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011;364:2517-2526.

5 Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, Hassel JC, Rutkowski P, McNeil C, Kalinka-Warzocha E, Savage KJ, Hernberg MM, Lebbe C, Charles J, Mihalcioiu C, Chiarion-Sileni V, Mauch C, Cognetti F, Arance A, Schmidt H, Schadendorf D, Gogas H, Lundgren-Eriksson L, Horak C, Sharkey B, Waxman IM, Atkinson V, Ascierto PA: Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015;372:320-330.

6 Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, Rutkowski P, Ferrucci PF, Hill A, Wagstaff J, Carlino MS, Haanen JB, Maio M, Marquez-Rodas I, McArthur GA, Ascierto PA, Long GV, Callahan MK, Postow MA, Grossmann K, Sznol M, Dreno B, Bastholt L, Yang A, Rollin LM, Horak C, Hodi FS, Wolchok JD: Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 2015.

7 Carbognin L, Pilotto S, Milella M, Vaccaro V, Brunelli M, Calio A, Cuppone F, Sperduti I, Giannarelli D, Chilosi M, Bronte V, Scarpa A, Bria E, Tortora G: Differential Activity of Nivolumab, Pembrolizumab and MPDL3280A according to the Tumor

Expression of Programmed Death-Ligand-1 (PD-L1): Sensitivity Analysis of Trials in Melanoma, Lung and Genitourinary Cancers. PLoS One 2015;10:e0130142.