AIO-TRK/YMO-0419: Nivolumab with chemotherapy in pleural mesothelioma after surgery (NICITA)

AIO-Studie

Studiennummer/-Code:	AIO-TRK/YMO-0419		
Status:	in Rekrutierungsphase		
Rekrutierungszeit:	von: Q1-2020	bis: Q4-2022 (24 Monate)	
Anzahl Zentren:	geplant: 14	aktuell initiiert: 14	aktiv rekrutierend: 13
Weitere Zentren:	Nicht mehr möglich		
Anzahl Patienten:	geplant: 92	aktuell eingeschlossen: 60	
Letzte Aktualisierung	22.03.2022		

STUDY TYPE	Investigator- intiated trial (IIT)
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SPONSOR	Sponsor representative: Prof. Dr. S.-E. Al-Batran Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main Germany Project Manager of Sponsor: Dr. Johanna Riedel (Riedel.johanna@ikf-khnw.de) // Christina Kopp (kopp.christina@ikf-khnw.de)
CONDITION	Patients with malignant pleural mesothelioma (MPM) in tumor stages I-III, who have previously undergone cytoreductive surgery by extended pleurectomy/decortication with or without hyperthermic intrathoracic chemoperfusion (eP/D ± HITOC)
DESIGN	Open-label, randomized, multicenter phase II trial
INDICATION	Malignant pleural mesothelioma (MPM) in tumor stages I-III
OBJECTIVE(S)	The primary objective is to determine if addition of nivolumab to adjuvant chemotherapy and subsequent administration of nivolumab mono-agent as maintenance therapy will improve TNT in stage I to stage III MPM patients that were previously subject to extended P/D ± HITOC.
INTERVENTION(S)	Arm A: Four cycles (q4w) of platinum-based adjuvant* chemotherapy i.v. • carboplatin AUC5 or cisplatin 75 mg/m^2

	• pemetrexed 500 mg/m^2 Arm B: Four cycles (q4w) of a combination of platinum-based adjuvant* chemotherapy and immunotherapy i.v. • carboplatin AUC5 or cisplatin 75 mg/m^2 • pemetrexed 500 mg/m^2 • nivolumab 480 mg flat-dose followed by up to 12 cycles maintenance immunotherapy • nivolumab 480 mg flat-dose i.v. (q4w) In both arms, treatment will be discontinued upon the Investigator´s decision that patient will not have further benefit from treatment continuation, unacceptable toxicity or patients' request. Active treatment within the experimental arm of the study is limited to 16 months (4 months adjuvant combination therapy + 12 months maintenance immunotherapy).
OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	In the context of this trial, tissue and blood samples are collected at indicated time points. These biomaterials will be analyzed in a translational research program. The program will aim to elucidate the effects of immune checkpoint inhibition in pleural mesothelioma patients and to explore potential biomarkers for immunotherapy in this disease. To this end, both blood and tissue samples will be collected during the trial for future analysis with regard to the following aspects: • Characterization of immunological status • Characterization of immunological tumor environment • Exploring the role of genomic features that are associated with MPM
BACKROUND/RATIONALE	Malignant pleural mesothelioma (MPM) is a locally invasive and highly aggressive cancer, and only 10% of the MPM patients live beyond five years. Due to the complex nature of this disease, the low patient number and a lack of randomized controlled trials in this entity, there is no approved standard therapy for the treatment of early-stage malignant pleural mesothelioma. Based on retrospective analysis and gained experience in the treatment of MPM, few treatment recommendations have been established, but research on adequate and effective mesothelioma treatment options is still ongoing and urgently needed. Considering the evolving landscape of mesothelioma treatment, it has to be noted that i.) the standard of locoregional treatment is extended pleurectomy/decortication (eP/D) and in specialized centers, if feasible, this is combined with HITOC, ii.) adjuvant chemotherapy might establish a tumor microenvironment with increased tumor immunogenicity, and iii.) inhibition of the immune checkpoint with the PD-1 antibody nivolumab shows promising results in advanced treatment lines. Thus, in the light of these recent developments, the combination of upfront locoregional therapy with adjuvant treatment composed of pemetrexed/platinum-based chemotherapy and additional nivolumab administration and with ongoing nivolumab maintenance after the end of chemotherapy is expected to have a beneficial effect due to synergistic mechanisms.
KEY EXCLUSION CRITERIA	1. Metastatic disease. 2. Patients for which surgery was scheduled as a cytoreductive surgery with curative intent but was then defined as palliative P/D by the operating surgeon. 3. Previous drug therapy against MPM. 4. A continuous post-operative hospitalization > 6 weeks due to surgery-related complications. 5. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways. 6. Inadequate hematological, renal and hepatic functions including the following: a. WBC < 2,000/µL b. Neutrophils < 1,500/µL

	c. Platelets < 100 x 103/µL d. Hemoglobin <9.0 g/dL e. Serum creatinine >1.5 x ULN unless creatinine clearance ≥ 45 mL/min (measured or calculated using the Cockroft-Gault formula). For application of cisplatin, creatinine clearance must be ≥ 60 mL/min. (measured or calculated using the Cockroft-Gault formula). f. AST/ALT >3.0 x ULN g. Total bilirubin >1.5 x ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level < 3.0 mg/dL) 7. Prior organ allograft or allogeneic bone marrow transplantation. 8. Concurrent or prior malignancy requiring or anticipated to require concurrent intervention. 9. Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity. 10. Malignancies other than disease under study within 5 years prior to inclusion, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS > 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent). 11. Any serious or uncontrolled medical disorder or active infection that, in the opinion of the Investigator, may increase the risk associated with study participation, study drug administration, or would impair the ability of the subject to receive study drug. 12. Psychiatric disorders or altered mental status precluding understanding of the informed consent process and/or compliance with the study protocol. 13. Pregnant or breast-feeding women. 14. Positive testing for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV RNA) indicating acute or chronic infection. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA. 15. Immunocompromised patients, e.g. patients who are known to be serologically positive for human immunodeficiency virus (HIV). 16. Subjects with active, known, or suspected autoimmune disease. Subjects with Type I diabetes mellitus, residual hypothyroidismdue to autoimmune thyroiditis only requiring hormone replacement, or skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll. For any cases of uncertainty, it is recommended that the medical monitor be consulted prior to signing informed consent. 17. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease. 18. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment. 19. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG. 20. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].
KEY INCLUSION CRITERIA	1. Fully-informed written consent 2. Males and females ≥ 18 years of age

	3. Histologically proven initial diagnosis of malignant pleural mesothelioma of epithelioid subtype (patients can also be included if biphasic histologic subtype has been identified during surgery) 4. Postoperative stage I-III (TNM 8th Edition; pT1-4, pN0-2, cM0). Patients are only included with a completeness of cytoreduction score (CC score) <3 (i.e., residual tumor thickness ≤2.5 cm). 5. Patients must have undergone cytoreductive surgery with curative intent consisting of extended pleurectomy/decortication (eP/D) with or without hyperthermic intrathoracic chemotherapy (HITOC) 6. Surgery conducted ≤12 weeks (≤84 days) before study inclusion and patient recovered from post-surgical complications of P/D or P/D + HITOC 7. Eastern Cooperative Oncology Group (ECOG) performance status 0-2 8. Female patients with reproductive potential must have a negative urine or serum pregnancy test within 7 days prior to start of trial. Women must not be breastfeeding. 9. The patient is willing and able to comply with the protocol for the duration of the study, including hospital visits for treatment and scheduled follow-up visits and examinations. 10. WOCBP must agree to follow instructions for method(s) of contraception for a period of 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo 5 half-lives. The terminal half-lives of nivolumab is approximately 25 days. WOCBP should use an adequate method to avoid pregnancy for approximately 5 months (30 days plus the time required for nivolumab to undergo 5 half-lives) after the last dose of investigational drug. Females must agree to refrain from egg donating (ova, oocytes) during the intervention period and for at least 5 months after last dose of study intervention.
Requirements regarding previous MPM surgery and result of surgery	Cytoreductive surgery should have been performed with the aim of macroscopic complete tumor resection and consisted of extended pleurectomy/decortication (eP/D) or eP/D + hyperthermic intrathoracic chemotherapy (HITOC) as specified in detail: According to the existing ESMO guideline (Baas et al., 2015), extended P/D implies a complete removal of the involved parietal and visceral pleura. If required due to macroscopic tumor infiltration, the diaphragm and pericardium can also be resected in the same procedure but the lung is left in situ: macroscopic complete resection (MCR) is still the goal. HITOC is defined as a 60 minutes intrathoracic lavage at 42°C with cisplatin-based chemotherapeutic agent in the already closed thoracic cavity using four chest tubes and a standardized perfusion system. MCR is reached if residual amounts of tumor are less than 1 cm3, but there are differences among surgeons regarding the definition of MCR. Completeness of resection will be further classified at the end of the operation according to the Completeness of Cytoreduction Score (CC score), defined for quantifying amounts of residual tumor after cytoreductive surgery for stage IV ovarian cancer (Rice D, 2012). The completeness of cytoreduction score (CC score): CC0 No residual tumor nodules CC1 Residual tumor nodules <2.5 mm CC2 Residual tumor nodules ≥2.5 mm or ≤2.5 cm CC3 Residual tumor nodules >2.5 cm Only patients with achievement of a CC-score <3 can be included in the trial. Surgery may have been conducted ≤12 weeks (≤84 days) before first drug administration and patient must have recovered (reduction to grade ≤2 for any local or systemic complication) from post-surgical complications of eP/D or eP/D + HITOC before enrollment into the study.
OUTCOME(S)	<u>Primary efficacy endpoint:</u> • Time-to-next-treatment (TNT) defined as time from randomization until initiation of any additional intervention against MPM due to disease progression (any systemic treatment; any locoregional measures [except for prophylactic radiotherapy

	to prevent procedure-track metastases]; any decision of the Investigator to switch the patient to BSC) Safety endpoints: Safety (according to NCI-CTCAE v 5.0) and tolerability Secondary endpoints: • Progression-free-survival (PFS) [acc. mRECIST for MPM] • Overall survival (OS) • Proportion of patients with Treatment Beyond Progression (TBP), duration of TBP in this population • Quality of life (QoL, based on LCSS-Meso and EQ-5D) Exploratory endpoints: • Biomarker exploration
STATISTICAL ANALYSIS	For the description of the primary endpoint time-to-next-treatment (TNT) a Kaplan-Meier estimator will be used. Moreover, feasibility in terms of toxicity and side effects will be assessed and a descriptive comparison between treatment arms will be conducted. Further analyses will be performed using appropriate descriptive measures and univariate Cox-regressions. 92 patients will be enrolled. With a sample size of n=40 analyzable patients per treatment arm (assuming a 13% drop-out rate), it is possible to adequately describe the tested treatment options.
SAMPLE SIZE	92 patients
TRIAL DURATION	Total study duration: 60 months • Duration of recruitment: 36 months • Maximum treatment duration: 16 months (4 months of chemotherapy in both arms + 12 months maintenance therapy in the experimental arm B) • The follow-up period will end when all study patients have been followed up for at least 8 months after last drug administration (including a safety follow-up period of 100 ± 7 days for all patients which received at least one dose of nivolumab)