STUDY TYPE	Phase II
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SPONSOR	University Hospital Regensburg, Germany represented by the Chairman of the Board
CONDITION	Non-squamous non-small-cell lung cancer (NSCLC) metastatic to the brain
DESIGN	Prospective, open-label, multi-center
INDICATION	Non-squamous non-small-cell lung cancer (NSCLC) metastatic to the brain, first-line
OBJECTIVE(S)	Combined treatment with nivolumab, ipilimumab and bevacizumab given concomitantly with 2 cycles of induction chemotherapy will provide clinical benefit to subjects with non-squamous NSCLC metastatic to the brain.
INTERVENTION(S)	Nivolumab administered IV over 30 minutes at 360 mg every 3 weeks combined with ipilimumab administered IV over 30 minutes at 1 mg/kg every 6 weeks until progression, unacceptable toxicity, or other reasons specified in the protocol.
OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	Besides PD-L1 predicting response to immune-oncology (IO) therapy is still very challenging. In particular, predictive data of brain metastasized patients of NSCLC are missing. Thus this trial cohort poses a unique opportunity to address this question and shed some light on mechanisms of IO response and resistance. Therefore, we aim to gain a comprehensive insight into this complex clinical and biological situation with a special focus on the following topics.
BACKROUND/RATIONALE	Brain metastases (BM) are a common site of tumor manifestation in a wide range of cancers, but they are particularly prevalent among patients with lung cancer. 40 to 60 percent of patients will develop brain metastases during their course of disease. With improved control of extracranial disease by systemic therapy, enabling the emergence of otherwise not clinically manifested metastasis, the proportion of NSCLC patients experiencing BMs will even increase. There are five mechanical/immunological barriers protecting NSCLC brain metastases from a sufficient immune/treatment response: - The limited anatomical volume causing edema - The immunological barrier at the BBB - The immune-(privileged) suppressive status of the brain parenchyma - The glial pseudo-capsule - The epithelial barrier at the MMPI Now, to achieve a long-lasting treatment response all five barriers have to be taken into account in the treatment of NSCLC brain metastases. Thus, we suggest a regimen of continuous double checkpoint blockade to enhance the leukocyte trafficking and achieve a long-lasting immune attack against the NSCLC brain metastasis. Further, we would add two cycles of chemotherapy to break down the epithelial barrier of the NSCLC at the MMPI. Finally, we would use anti-VEGF-a treatment to omit steroids, reduce intracranial pressure and perform an angio-immunogenic switch of the resident microglia and immune-suppressive TAM.
KEY EXCLUSION CRITERIA	**Target Disease Exceptions**

	1. History of known leptomeningeal involvement (lumbar puncture not required). 2. History of whole brain irradiation 3. History of intracranial hemorrhage 4. Spinal cord compression not definitively treated with surgery and/or radiation, or previously treated spinal cord compression that has been clinically stable for less than 2 weeks prior to first dose of study drug 5. Subjects with oligometastatic disease according to IASLC eligible for a definitive local therapy in curative intent 6. Subjects with oncogenic driver mutations which are sensitive to available targeted inhibitor therapy (i.e. EGFR mutation, ALK or ROS1 translocation, BRAF V600 mutation, NTRK fusion). Subjects with unknown or indeterminate EGFR or ALK status are excluded. 7. Uncontrolled pleural effusion, pericardial effusion, or ascites (patients with pleural drainage system like PleurX catheter and controlled situation are eligible) 8. Uncontrolled tumor-related pain: Patients requiring pain medication must be on a stable regimen at study entry. Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) may be treated by radiotherapy **General Medical Exclusions** 9. Autoimmune disease: subjects with a documented history of inflammatory bowel disease, including ulcerative colitis and Crohn's disease are excluded from study treatment as are subjects with a history of symptomatic disease (eg, rheumatoid arthritis, systemic progressive sclerosis [scleroderma], Systemic Lupus Erythematosus, autoimmune vasculitis [eg, Granulomatosis with polyangiitis, (Wegener's)], and sarcoidosis including interferon-induced sarcoidosis. Subjects with motor neuropathy considered of autoimmune origin (eg, Guillain-Barre Syndrome and Myasthenia Gravis) are excluded from study treatment. a. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. b. Patients with controlled Type I diabetes mellitus on a stable dose of insulin regimen are eligible for this study. 10. Subjects with major medical, neurologic or psychiatric condition who are judged as unable to fully comply with study therapy or assessments should not be enrolled. 11. Any concurrent malignancy other than non-melanoma skin cancer or carcinoma in situ of the cervix. For any prior invasive malignancy, at least 5 years must have elapsed since curative therapy and patients must have no residual sequelae of prior therapy. 12. Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial

	infarction within 3 months prior to start of study treatment, unstable arrhythmias, or unstable angina. *a.* Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction < 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate. *13.* Major surgical procedure other than for diagnosis or treatment of symptomatic brain metastasis within 28 days prior to randomization or anticipation of need for a major surgical procedure during the course of the study *14.* Prior allogeneic bone marrow transplantation or solid organ transplant *15.* Active or latent tuberculosis *16.* Symptomatic interstitial lung disease *17.* Positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection. *18.* Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) even if fully immunocompetent on ART—due to the unknown effects of HIV on the immune response to combined nivolumab plus ipilimumab or the unique toxicity spectrum of these drugs in patients with HIV. **Exclusion Criteria related to Medications** *19.* Any approved anti-cancer therapy, including chemotherapy, or hormonal therapy within 3 weeks prior to initiation of study treatment; the following exceptions are allowed: Hormone-replacement therapy or oral contraceptives *20.* Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 28 days prior to start of study treatment *21.* Simultaneous treatment with another investigational agent or simultaneous anticancer treatment outside this trial *22.* Administration of a live, attenuated vaccine within 4 weeks before randomization or anticipation that such a live attenuated vaccine will be required during the study *23.* History of allergy to study drug components **Exclusions related to bevacizumab** *24.* Inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg) (anti-hypertensive therapy to achieve these parameters is allowable) *25.* Prior history of hypertensive encephalopathy

	26. Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to start of study treatment *27.* History of hemoptysis (≥ one-half teaspoon of bright red blood per episode) within 1 month prior to start of study treatment *28.* Evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic anticoagulation) *29.* Current or recent (within 10 days of start of study treatment) use of aspirin (> 325 mg/day) or treatment with dipyramidole, ticlopidine, clopidogrel, and clostazol *30.* Current use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic purposes that has not been stable for > 2 weeks prior to study start - The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard of the enrolling institution) and the patient has been on a stable dose of anticoagulants for at least 2 weeks prior to start of study treatment - Prophylactic anticoagulation for the patency of venous access devices is allowed, provided the activity of the agent results in an INR < 1.5 × ULN and aPTT is within normal limits within 14 days prior to start of study treatment. - Prophylactic use of low-molecular-weight heparin (i.e., enoxaparin 40 mg/day) is permitted. *31.* Core biopsy or other minor surgical procedure, excluding placement of a vascular/pleural access device, within 7 days prior to the first dose of bevacizumab *32.* History of abdominal or tracheosphageal fistula or gastrointestinal perforation within 6 months prior to start of study treatment *33.* Clinical signs of gastrointestinal obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding *34.* Evidence of abdominal free air not explained by paracentesis or recent surgical procedure *35.* Serious, non-healing wound, active ulcer, or untreated bone fracture *36.* Proteinuria, as demonstrated by urine dipstick or > 1.0 g of protein in a 24-hour urine collection (All patients with ≥ 2+ protein on dipstick urinalysis at baseline must undergo a 24-hour urine collection and must demonstrate ≤ 1 g of protein in 24 hours.)
KEY INCLUSION CRITERIA	**Signed Written Informed Consent** *1.* Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care

	2. Subjects must be willing and able to comply with protocoll **Target Population** 3. Males and Females, ages ≥ 18 years of age 4. ECOG performance status of 0, 1 and 2 (patients with a decline in performance status due to neurologic symptoms of brain metastasis are eligible for the study up to ECOG 3) 5. Life expectancy ≥ 12 weeks 6. Histologically or cytologically documented metastatic non-squamous NSCLC stage IVB (IASLC) [1] 7. Measurable disease, as defined by RANO-BM (intracranial) and RECIST v1.1 (extracranial) 8. at least one measurable brain metastasis (tumor diameter: 0.5 to 3 cm) which has not been previously irradiated and is not judged to require immediate local intervention (radiation/surgery) 9. Known PD-L1 tumor status 10. no prior cytotoxic/systemic (chemo)therapy regimens for metastatic disease (in this context neo-/adjuvant therapy including immunotherapy is not counted as line of therapy) 11. The last dose of prior (neo-/adjuvant) systemic anti-cancer therapy or immunotherapy must have been administered ≥ 21 days prior to first dose of study treatment. 12. The last dose of treatment with any investigational agent or participation in a clinical trial with therapeutic intent must have ended ≥ 28 days prior to first dose of study treatment. 13. Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to first study treatment: a. ANC ≥ 1500 cells/µL (without granulocyte colony-stimulating factor support within 2 weeks of test) b. WBC counts > 2000/µL c. Lymphocyte count ≥ 500/µL d. Platelet count ≥ 100,000/µL (transfusion within 2 weeks of test) e. Hemoglobin ≥ 9.0 g/dL. Patients may be transfused or receive erythropoietic treatment to meet this criterion. 14. Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance ≥ 50 mL/min (using the Cockcroft Gault formula) 15. Adequate liver function: AST or ALT ≤ 3 × ULN; Serum bilirubin ≤ 1.5 × ULN. With the following exceptions: a. Subjects with Gilbert Syndrome who must have a total bilirubin level < 3.0 mg/dL

	b. Subjects with documented liver metastases: AST and/or ALT ≤ 5 × ULN *c.* Subjects with documented liver or bone metastases: alkaline phosphatase ≤ 5 × ULN. **Reproductive Status** *16.* Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test [minimum sensitivity 25 units per litre (IU/L) or equivalent units of human chorionic gonadotropin (HCG)] within 3 days prior to the start of study drug. *17.* Women must not be breastfeeding *18.* WOCBP must agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment plus 5 half-lives of nivolumab (half-life up to 25 days) plus 30 days (duration of ovulatory cycle) for a total of 23 weeks post treatment completion. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus 5 half-lives of nivolumab plus 90 days (duration of sperm turnover) for a total of 31 weeks post treatment completion.
OUTCOME(S)	**Safety** Safety will be monitored throughout the whole study, with a specific focus on the safety-lead-in phase. • Predefined dose limiting toxicities (DLTs) will be counted and dosing will be adjusted according to the recommendations of the DSMB. • Incidence and intensity of adverse events (AEs) and serious adverse events (SAEs) according to Common Terminology Criteria for Adverse Events (CTCAE) version v5.0 **Primary Efficacy Endpoint** Central nervous system (CNS) clinical benefit rate (CBR) 6 months after patient inclusion (pCBR), defined as either • complete response [CR], • partial response [PR] or • stable disease [SD] ≥ 6 months
STATISTICAL ANALYSIS	**Safety** Safety analyses will be performed within the safety population. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All treatment emergent AEs, drug-related AEs, SAEs and drug- related SAEs (will be coded according to MedDRA) and tabulated using worst grade per NCI CTCAE V.5.0 criteria by system organ class and preferred term. Primary efficacy endpoint CBR rate 6 months after study inclusion (pCBR) will be calculated as effect estimate using the intention to treat population. Further, a corresponding exact one-sided 95%-confidence interval (Clopper-Pearson) will be calculated. The null-hypothesis pCBR≤0.35 will be rejected if the lower limit of the one-sided 95%-confidence interval is above 0.35. **Secondary endpoints** Time to event endpoints will be presented graphically by using Kaplan-Meier curves. Time distributions, median time to event and event rates at specific time points with corresponding one-sided 95% confidence intervals will be estimated by means of the KM method. Scores of PROs will be calculated according to the manuals and presented by descriptive statistics (N, mean,

	standard deviation, median, interquartile range, minimum, and maximum) for each visit.
SAMPLE SIZE	Sample size is based on the primary efficacy endpoint. The uninteresting CBR-rate p0 (historical control) was set to 35%. Our desired and expected CBR rate p1 was set to 55%. Alpha was set to 5% (one-sided) and beta to 0.2 (Power 80%). This results in a required sample size of n=37 patients. With a lost-to-follow-up rate of maximal 5% (high burden of patients and closed meshed controls), a total of n=39 patients need to be included.
TRIAL DURATION	Recruitment duration: 2 years and 9 months Treatement: 1 year, all adverse events documented for a minimum of 100 days after the last dose of study medication
PARTICIPATING CENTERS	Uniklinikum Regensburg Universitätsklinikum Augsburg Evangelisches Krankenhaus Hamm Universitätsklinik Mannheim LMU, Klinikum der Universität München Universitätsklinikum Münster Oldenburg, Pius Hospital Klinikum Stuttgart Uniklinikum Gießen Sana Klinikum Offenbach Thoraxklinik Heidelberg