PLEASE NOTE: *This trial has been registered retrospectively.*

Trial Description

Title

Neoadjuvant Radiotherapy (N-RT) for Intracerebal Metastases of Solid Tumors

Trial Acronym

NEPO_MUC

URL of the trial

[---]*

Brief Summary in Lay Language

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Brief Summary in Scientific Language

Brain metastases are a frequent cause of oncological morbidity and mortality that affect up to 25% of cancer patients (Gavrilovic und Posner 2005, Barnholtz-Sloan et al. 2012). Thereby, neurosurgical resection, radiosurgery (RS), and whole-brain radiotherapy (WBRT) are the main treatment modalities. Surgical resection is an effective treatment aiming to relieve symptoms associated with mass effect and may even increase overall survival (Patchell et al .1990, Siu et al. 2011). Several studies have shown that the combination of microsurgical resection followed by WBRT lead to lower local and distant recurrence rates (Vecht et al. 1993, Patchell et al. 1998). However, WBRT is also strongly associated with neurocognitive decline (Chang et al. 2009). Therefore, postoperative radiosurgery to the tumor bed is now considered to be the treatment of choice.
A recent study published by Asher and colleagues evaluated the role of neoadjuvant RS in patients with brain metastases (Asher et al. 2014). This concept is characterized by a number of potential benefits compared to postoperative radiosurgery treatment: Mostly, RT of the intact brain metastases and surrounding normal tissue leads to a higher probability of exact target volume definition for RT with subsequent higher safety of effective treatment of all tumor cells and lower toxicity of surrounding healthy tissue. Thereby, the rate of postoperative complications such as wound healing disorders and cerebrospinal fluid leaks is reduced. Also, the much-needed systemic chemotherapy can be initiated more rapidly because there is no 10 to 14 days delay, to ensure adequate wound healing, between surgery and radiosurgery. Due to the explorative character of their study, Asher et al. were rather conservative considering their dose prescription. They were well below the dose thresholds that were established by the dose Radiation Therapy Oncology Group (RTOG) Trial 90-05 (Shaw et al. 2000) and it has to be kept in mind that those dose thresholds were set up for patients who had already received prior radiotherapy with a minimum dose of 30 Gy. This trials aims to escalate the dose up to the dose thresholds (respective to

the tumor size) recommended by the German expert group on stereotactic radiation oncology (Kocher et al. 2014). Given the improved efficacy of systemic cancer therapies, long lasting local control becomes of growing importance. Since local stereotactic radiotherapy aims to prolong the time interval until the application of WBRT, locally efficient doses have to be applied.

Organizational Data

- DRKS-ID: **DRKS00016613**
- Date of Registration in DRKS: **2019/01/29**
- Date of Registration in Partner Registry or other Primary Registry: **[---]***
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **199/18 s , Ethik-Kommission der Fakultät für Medizin der Technischen Universität München**

Secondary IDs

Health condition or Problem studied

- ICD10: **C79.3 - Secondary malignant neoplasm of brain and cerebral meninges**

Interventions/Observational Groups

- Arm 1: <style fontName='DejaVu Sans' isBold='true'>Patients with a brain metastasis, for whom inclusion criteria are fulfilled and the indication for resection is given, are divided into 4 groups according to the size of the metastasis.
  There are 3 dose levels per size group. If 3 patients are treated with the same dose without dose limiting toxicity (DLT), the next patients in this size group will be irradiated with the higher dose. If a DLT occurs at one dose level, three more patients (i. e. 6) must be treated with this dose. At the highest dose level, at least 6 patients must be treated without DLT. Then the maximum tolerated dose/MTD would be reached.

Characteristics

- Study Type: **Interventional**
- Study Type Non-Interventional: **[---]***

Study Type: **Interventional**

Study Type Non-Interventional: **[---]***

- Allocation: **Single arm study**
- Blinding: **[---]***
- Who is blinded: **[---]***
- Control: **Uncontrolled/Single arm**
- Purpose: **Treatment**
- Assignment: **Single (group)**
- Phase: **I**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **[---]***

Primary Outcome

Primary endpoint is to find the MTD for which no dose limiting toxicities (DLT) occur will be evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (2017) continuously during the study until first follow up (4-6 weeks after surgery) for each cohort and dose level. A DLT is defined as central nerve system necrosis (≥G3) or cerebrospinal fluid leakage (≥G4) or wound infection ((≥G4) or wound dehiscence (≥G4) or postoperative hemorrhage (≥G4) or cognitive disturbance (≥G4) or cerebral edema (≥G4) or headache (≥G4) or seizure (≥G4).

Secondary Outcome

Secondary endpoints are the following:

•Central nerve system necrosis according CTCAE Grade 1-3
•Cerebrospinal fluid leakage according CTCAE Grade 1-3
•Wound infection CTCAE Grade 1-3
•Wound dehiscence CTCAE Grade 1-3
•Cerebral edema according CTCAE Grade 1-3
•Local control rates
•Overall survival and progression free survival at 12 months follow up
•Time interval between treatment initiation and start of systemic chemotherapy.
•Health-related quality of life using the EuroQol questioner.
•Assessment of neurocognitive function applying Minimal Mental State Examination (MMSE) testing.
•Late toxicity according CTCAE Grad 1-5
•Immunological Parameters (such as PD-L1 expression on the resection specimen)

Countries of recruitment

- DE **Germany**

Locations of Recruitment

- Medical Center **Abteilung für Radioonkologie und Strahlentherapie - Klinikum rechts der Isar der TU München, 81675 München**

Recruitment

- Planned/Actual: **Actual**
- (Anticipated or Actual) Date of First Enrollment: **2018/10/11**
- Target Sample Size: **48**
- Monocenter/Multicenter trial: **Monocenter trial**
- National/International: **National**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **18 Years**
- Maximum Age: **no maximum age**

Additional Inclusion Criteria

Patients meeting all of the following criteria will be considered for admission to the trial:
•Patients with 1-4 intracerebral metastases on contrast-enhanced MRI from solid tumors with known histology confirmed
•One brain metastasis is ≥ 3cm in size or
-Persisting neurologic symptoms or symptomatic epilepsy from brain metastases despite treatment with steroids.
-Tumor location close to eloquent brain areas therefore neurological symptoms can be expected without longtime steroidal medication.
-Patient is deciding to undergo surgical intervention, if resection and radiation therapy are equal treatment options or if the patient declines radiation therapy.
•Age ≥ 18 years of age
•Karnofsky Performance Score ≥ 70, ECOG ≤ 1
•For women with childbearing potential adequate contraception
•Ability of subject to understand character and individual consequences of the clinical trial
•Written informed consent (must be available before enrolment in the trial)

Exclusion criteria

Patients presenting with any of the following criteria will not be included in the trial:
•Patients with unknown primary (CUP)
•Tumor diameter of any single lesion exceeding 4 cm
•Tumors causing severe neurological deficits or with mass effect requiring immediate surgical intervention
•Previous radiotherapy to the brain

•Known tumor of small cell histology, germ cell histology or lymphoma
•Refusal of the patients to take part in the study
•Patients who have not yet recovered from acute toxicities of prior therapies
•Clinically active kidney-liver or cardiac disease
•Known carcinoma < 5 years ago (excluding carcinoma in situ of the cervix, basal cell carcinoma, squamous cell carcinoma of the skin) requiring immediate treatment interfering with study therapy

Addresses

■ **Primary Sponsor**

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Sources of Monetary or Material Support

- **Institutional budget, no external funding (budget of sponsor/PI)**

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Status

- Recruitment Status: **Recruiting ongoing**
- Study Closing (LPLV): **[---]***

Trial Publications, Results and other documents

** This entry means the parameter is not applicable or has not been set.*

**** This entry means that data is not displayed due to insufficient data privacy clearing.*