STUDY TYPE	Prospektive Randomisierte Phase II – Studie
PRINCIPAL INVESTIGATOR	PD Dr. med W. Eberhardt
TRIAL OFFICE	WTZ- Essen, Ruhrlandklinik Essen, Strahlenklinik
SPONSOR	Universitätsklinikum Essen
Study Title	Prospective Phase-II Trial of induction chemotherapy and chemoradiotherapy plus/minus the PDL1 antibody durvalumab followed by surgery or definitive chemoradiation boost and consolidation durvalumab in resectable stage III NSCLC.
	Protocol Name: ESPADURVA EudraCT Number: 2019-000058-77 Clinical Phase: Randomized Phase-II Study Start: Planned Q4 2019
Investigational Product(s) and Reference Therapy:	Durvalumab will be supplied in glass vials containing 500 mg of liquid solution at a concentration of 50 mg/mL for intravenous (IV) administration
Reference treatment: ESPATUE-protocol:	Induction chemotherapy with cisplatin (100 mg/m2) (either given in two days x 50 mg/m2 or three days x 33 mg/m2) and paclitaxel 175 mg/m2 per cycle given every 21 days for three cycles followed by concurrentchemoradiotherapy based on cisplatin (50 mg/m2 d 2 + d 9) and vinorelbine (20 mg/m2 d 2 + d 9) and radiotherapy (45 Gy HFA-RTx) followed by definitive local treatment (surgery or definitive chemoradiation boost (20 Gy, CF-RTx) plus consolidation durvalumab treatment every four weeks for eight months Research Hypothesis Multimodality strategies have been included into several of our phase-II and also randomized phase-III studies [Eberhardt et al 1998, Eberhardt et al 2013, Eberhardt et al 2015b; Goeckenjan et al 2010]. We have currently developed a surrogate endpoint pCR at the time of surgery after induction therapy in this predefined setting [Pöttgen et al 2013, Pöttgen et al 2015; Pöttgen et al 2016]. PD-1 antibody treatment with pembrolizumab has recently become a preferred treatment strategy in patients with high expression of PD-L1 immunomarker in tumor cells for the first line therapy of stage IV NSCLC patients [Reck et al 2016]. Platinum-based doublet chemotherapy containing paclitaxel combined with a PD-1 antibody has shown promising safety and effectiveness in a prospective phase I study [Rizvi et al 2016]. Concurrent PD-L1 immune checkpoint blockade and thoracic radiotherapy has been found save in a prospective trial [Levy et al 2016]. Concurrent PD-1 blockade and radiotherapy is more effective than sequential application of both modalities according preclinical data [Dovedi et al 2014; Gong et al 2017]. Durvalumab (PD-L1) is currently investigated alone or in combination with conventional platinumbased chemotherapy in stage IV NSCLC. Durvalumab has been investigated as a consolidation therapy after concurrent chemoradiotherapy for irresectable stage III NSCLC with a significant increase in PFS already openly reported [Pacific-trial: Antonia et al 2017]. The aim of this study is to investigate the

	introduction of durvalumab immunotherapy within our induction chemotherapy and concurrent chemoradiotherapy protocol in patients with resectable stage III NSCLC with positive and high PD-L1 expression in the tumor and evaluate feasibility and Progression-Free Survival of this approach and investigate the rate of pathological complete responses in resected specimen as an important surrogate endpoint of efficacy.
Objectives:	To compare a complex induction multimodality protocol (ESPATUE) + concurrent immunotherapy with PD-L1 antibody durvalumab given every three weeks to the same induction multimodality protocol without durvalumab immunotherapy induction followed by definitive local treatment (surgery for those considered resectable or chemoradiation boost for those not considered to be R0-resectable) followed by consolidation durvalumab treatment in both arms.
Primary Objective:	The primary objective is to assess the efficacy of a multimodality treatment in resectable stage III nonsmall-cell lung cancer patients including a complex induction chemoimmunotherapy followed by a radiochemoimmunotherapy and definitive surgical resection or radiochemotherapy-boost and immunotherapy consolidation for 32 weeks versus the same multimodality treatment protocol without immunotherapy in the induction and radiochemotherapy as measured by two-year progression-free survival. The primary objective will be measured by the primary endpoint which is the progression-free survival rate (PFS) at 2 years. Reason for this choice / advantage: To determine the PFS-rate at two years only one follow-up visit with exact imaging will be necessary. To exactly determine the median progression-free survival several follow-up visits within a short time-schedule and with several imaging investigations included would be necessary. Disadvantage: Two-year minimal follow-up will be necessary. Arm A: induction therapy with three cycles cisplatin and paclitaxel combined with concurrent durvalumab (1200 mg flat dose qd 21 x 3) and a concurrent chemoradiotherapy of cisplatin and vinorelbin and combined with durvalumab (1200 mg flat dose qd 21 x 2) together with 45 Gy hyperfractionated radiotherapy (2 x 1.5 Gy pro die) followed by surgery if possible and then sequential consolidation durvalumab (1500 mg flat dose qd 28 x 9). Arm B: ESPATUE induction therapy with three cycles cisplatin and paclitaxel and a concurrent chemoradiotherapy of cisplatin and vinorelbin together with 45 Gy hyperfractionated radiotherapy (2 x 1.5 Gy pro die) followed by surgery without concurrent durvalumab and then sequential durvalumab consolidation therapy (1500 mg flat dose qd 28 x 9) [see also: Eberhardt et al 2015b]. The PFS rate at 2 years from both arms combined will be compared with a predefined bench mark result and results from both arms will be compared with each other.

Secondary Objective:	The secondary objective is to analyze the toxicity and efficacy of a multimodality treatment in resectable stage III non-small-cell lung cancer patients including a complex induction chemoimmunotherapy followed by a radiochemoimmunotherapy and definitive surgical resection or radiochemotherapy-boost and immunotherapy consolidation for 32 weeks versus the same multimodality treatment protocol without immunotherapy in the induction and radiochemotherapy as measured by response, survival parameters, QoL, compliance and treatment toxicity effects. The secondary objective will be will be achieved by the following secondary endpoints: • To investigate the rate of pathological complete response with the addition of durvalumab to the bimodal induction protocol versus pCR following the same induction protocol without durvalumab (ESPATUE) • To investigate the toxicity of this induction protocol and the following surgical resection in both arms • To compare the results of this combined modality with our sequential phase-II and phase-III trials • To investigate 2-y-overall survival rate in the ITT population • To investigate functional response (PET-CT-scan) to induction therapy prior to thoracotomy • To investigate RECIST response to induction therapy in the whole population and in both arms • Progression free survival time (PFS) • Overall survival (OS) • Histopathologic complete response (pCR) (data from repeat bronchoscopy/EBUS/surgery) • Radiological response (RECIST criteria) • Analysis of the SUVmax response and MTV response on the planning PET-CT in comparison to the pretreatment PET-CT in dependence on immunotherapy • Pulmonary fibrosis or pneumonitis or dyspnoea or other pulmonary adverse events of CTCAE v5.0 grade ≥ 3 within 60 days from start of therapy • Other adverse events as measured by CTCAE v5.0 • Quality of life (EORTC QLQ-C30, QLQ-LC13 and FACT-L) • Estimation number of fully compliant patients
Exploratory Endpoints:	• To define the rate of PD-L1 > or = 50% patients in the group of stage III NSCLC patients (screened population) • To define the R0 (complete resection) rate of the ITT patients following induction therapy • To monitor brain-relapse-free survival in the ITT patients • Brain-relapse-free survival • R0-resection rate • Heart toxicity at the end of therapy and during follow-up using functional and non-invasive assessments • Therapy-associated changes in lung parenchyma on CT-scans during follow-up using a radiomic multiparameter analysis, in dependence on immunotherapy • Analysis of the relation between dose-distribution parameters on treatment related toxicity and effectiveness in dependence on concurrent immunotherapy

	• Analysis of the effect of the breathing control strategy on precision of radiotherapy • Positron emission tomography (PET) response of the primary tumor and lymph nodes using the tracer 18F-fluoro-deoxyglucose as a prognostic marker • Assessment of Tumor Progression Patterns The study contains optional sampling for the Biobank (tumor tissue, plasma, serum). Translational research is important to make advances in understanding tumor biology and immunology with the aim to identify the group of patients most likely to benefit from therapy. Exploratory endpoints of this translational research program with the samples from the Biobank may include, but are not limited to the following ones: • Analysis of the prognostic value of tumor biomarkers from the pretreatment tumor biopsy or the resection specimen on treatment outcome • Changes of Lymphocyte subsets in peripheral blood during induction therapy • To investigate soluble HLA-G and HLA-E and soluble PD-1 and PD-L1 in plasma prior start of treatment as a prognostic/predictive marker as well as at the time after chemoradiation • Presence, phenotype and clonality of tumor infiltrating lymphocytes in NSCLC lesions prior to and after therapy (FFPE tissue, fresh frozen tissue, native biopsy material) • Tumor infiltrating lymphocytes in the surgical specimen after induction therapy compared with the pre-treatment biopsy • Expression of immune modulatory molecules in the tumor prior to therapy and after therapy (FFPE tissue, fresh frozen tissue, native biopsy material) • Presence of inflammatory and immune responses in the draining lymph nodes before, under and after therapy (FFPE tissue, fresh frozen tissue, native biopsy material) • Analyses of the activation status of circulating lymphocytes before, during, and after therapy • To investigate lymph node response to the chemoimmuno-induction therapy • To investigate other translational markers in the treated ITT population (both in blood as well as in the tumor and LN) • T-cell repertoire in mediastinal lymph nodes and in the primary tumor at the time of diagnosis and at thoracotomy • Tumor mutational burden (TMB) measured by an adequate, validated and accepted laboratory assay (at the time of study start)
Study Design:	• All patients will undergo initial staging investigations (see Schedule of Study Assessments) as well as diagnostic work-up for functional and medical resectability (based on cardio pulmonary risk evaluation and interdisciplinary tumor board) • Resectable patients will then be offered randomization into induction protocol plus concurrent immunotherapy with durvalumab (1200 mg flat dose given every three weeks) (Arm A) versus induction protocol without immunotherapy (Arm B)

	• All patients will be offered three cycles of induction chemotherapy consisting of cisplatin and paclitaxel (standard ESPATUE-doses) • All patients without proven disease progression during induction will be taken to concurrent neoadjuvant radiochemotherapy (cc-HFA-RTx 45 Gy bid + cisplatin/vinorelbine) • Following induction CTx + CTx/RTx restaging between days 16 and 21 (after start of RTx) will include thorax CT-scan (including angiographic bolus-tracking) • Patients evaluated to be unresectable or who refuse to be operated on following induction treatment will receive a standard conformal radiotherapy boost; boost RTx should be started immediately after the last fraction of the first 45 Gy radiation series and is recommended to be given without any break • Patients evaluated to be resectable following the induction CTx + CTx/RTx will be taken to thoracotomy and will be completely resected the primary tumor combined with a standard mediastinal lymph node dissection • The decision of resectability/unresectability will be documented within a multidisciplinary conference (tumor board) and will be a written and rationally founded consented document; also patients decision different from this proposed strategy will be documented in detail • All patients in both treatment arms will be offered durvalumab consolidation therapy with 1500 mg durvalumab given as flat dose iv infusion over one hour every four weeks (9 times for a total of 32 weeks)
Number of Centers:	approximately 4 study sites in Germany
Number of Patients:	Inclusion of 90 patients with resectable NSCLC stages IIIA (N2) and selected resectable stages IIIB with the aim to have 84 patients with a complete follow-up in arms A and B (2:1 randomization)
Study Population:	Resectable NSCLC stages IIIA(N2) and selected IIIB non-small-cell lung cancer patients
Inclusion Criteria:	1. Body weight >30 kg 2. Age ≥ 18 years and < 75 years 3. Male or female patients. Female (as well as male) patients have to take care of effective measures of anticonception 4. Histologically proven non-small cell lung cancer 5. Selected patients with non-small cell lung cancer stages IIIA and IIIB: • IIIA: one or more lymph node levels involved at EBUS/mediastinoscopy • IIIA: bulky N2-disease histologically proven at EBUS/cervical mediastinoscopy/parasternal mediastinotomy, not diffuse mediastinal involvement • selected IIIB: N3-disease with contralateral mediastinal nodes involved at EBUS/mediastinoscopy • potentially resectable T4-disease: o involvement of the pulmonary artery (angiogr.-CT/MRI/TEE), o involvement of the carina (histologically proven), o involvement of the left atrium (angiogr.-CT/MRI/TEE),

	o involvement of the vena cava (angiogr.-CT/MRI/TEE), o involvement of ipsilateral intrapulmonary satellite nodules, o mediastinal involvement (not diffuse) 6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 7. Resectable disease at the time of inclusion 8. Fulfillment of adequate criteria for functional and medical resectability as described in the ERS/ESTS guidelines [Brunelli et al 2009] and acceptable general clinical condition for multimodality treatment (interdisciplinary committee) 9. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent and any locally required authorization (e.g, European Union [EU] Data Privacy Directive in the EU) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations 10. Must have a life expectancy of > 12 weeks 11. Adequate normal organ and marrow function as defined below: o Haemoglobin ≥ 9.0 g/dL o Absolute neutrophil count (ANC) > 1.5 x 109/L (> 1500 per mm3) o Platelet count ≥ 100 x 109/L (≥ 100.000 per mm3) o Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN) This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician. o AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal Clinical Study Protocol Drug Substance Durvalumab Study Name ESPADURVA Version 2.3, Date 09-June-2020 Page 8 of 157 o Measured creatinine clearance (CL) > 40 mL/min or Calculated creatinine CL > 40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24- hour urine collection for determination of creatinine clearance: Males: Creatinine CL (mL/min) = Weight (kg) x (140 – Age) 72 x serum creatinine (mg/dL) Females: Creatinine CL (mL/min) = Weight (kg) x (140 – Age) x 0.85 72 x serum creatinine (mg/dL) 12. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female premenopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply: o Women < 50 years of age would be considered post-menopausal if they have been

	amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy) o Women ≥ 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy) 13. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up 14. Stable cardiac function (no Myocardial infarction (MI) within 6 months, no heart failure NYHA III-IV)
Exclusion Criteria:	Patients should not enter the study if any of the following exclusion criteria are fulfilled: 1. resectable IIB or selected IIIA (T3N0; T3N1) 2. unresectable disease pre-treatment 3. mixed histology with areas of small cell carcinoma (neuroendocrine markers) 4. clinically symptomatic vena cava superior syndrome 5. diffuse mediastinal involvement 6. patients with T3N3 and T4N3 tumors (IIIC IASLC/UICC 8) 7. invasion of the thoracic aorta (T4 – aorta) 8. invasion of the heart (except left atrium – T4 – heart) 9. invasion of the esophagus (T4 – esophagus) 10. invasion of spine (T4 – spine) 11. (full blown) Pancoast-syndrome in tumors of the superior sulcus (T3-4 Nx) 12. malignant (positive) pericardial effusion (M1a – pericardial effusion) 13. malignant (positive) pleural effusion (M1a – pleural effusion) 14. involvement of the contralateral hilar nodes (if any data available) 15. endobronchial tumor extension to the contralateral main stem bronchus 16. ipsi- or contralateral supraclavicular nodes (N3 – supraclavicular nodes) 17. lung or heart function not allowing at the time of inclusion the intended surgical procedure 18. previous administration of chemotherapy and/or radiotherapy 19. previous immunotherapy 20. insufficient patients compliance (e.g. symptomatic psychiatric disorder) 21. loss of weight > 10 % in the last six months 22. missing written informed consent or definitive refusal for participation 23. Participation in another clinical study with an investigational product during the last 12 months 24. Concurrent enrolment in another clinical study, unless it is an observational (noninterventional) clinical study or during the follow-up period of an interventional study 25. Must not have required the use of additional immunosuppression other than corticosteroids for

	the management of an AE, not have experienced recurrence of an AE if re-challenged, and not currently require maintenance doses of > 10 mg prednisone or equivalent per day 26. History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest CT scan 27. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable 28. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable 29. History of allogenic organ transplantation 30. History of a stem cell transplantation 31. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.]). The following are exceptions to this criterion: – Patients with vitiligo or alopecia – Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement – Any chronic skin condition that does not require systemic therapy – Patients without active disease in the last 5 years may be included but only after consultation with the study physician – Patients with celiac disease controlled by diet alone 32. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent 33. History of another primary malignancy except for – Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence – Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease – Adequately treated carcinoma in situ without evidence of disease 34. History of active primary immunodeficiency 35. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice),

	hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C, or human immunodeficiency virus (positive HIV-1 or HIV-2 antibodies). 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 36. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion: – Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection) – Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent – Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication) 37. Current or prior use of immunostimulatory agents within 14 days before the first dose of durvalumab 38. Receipt of live attenuated vaccine within 90 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 90 days after the last dose of IP 39. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy 40. Known allergy or hypersensitivity to durvalumab or any excipient
Investigational Product(s), Dose and Mode of Administration:	Patients in the durvalumab induction treatment group will receive 1200 mg durvalumab via IV infusion Q3W given prior to induction chemotherapy application in cycles one, two and three on day 1 of these cycles as well as at the start of concurrent chemoradiotherapy (day 2 of Block 2). Patients not resected but instead given definitive chemoradiation boost may receive durvalumab as given above for one more cycle concurrently to the boost radiotherapy. In the consolidation durvalumab phase (Block 4) are all patients in both arms planned to be given a consolidation durvalumab treatment of 1500 mg given via IV infusion every four weeks for up to a maximum of 8 months (up to 9 doses/cycles). The last administration of durvalumab is planned 32 weeks after the end of Block 3 or until confirmed disease progression or unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. If a patient's weight falls to ≤ 30 kg in the consolidation phase (Block 4), then the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W after consultation between the Investigator and the country coordinating investigator, until the weight improves to ≥ 30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg Q4W, see also Appendix 1.

Study Assessments and Criteria for Evaluation:	Initial staging investigations should include PET-CT, EBUS-TBNA, mediastinoscopy (if clinically indicated), MRI-brain (CT brain if MRI cannot be performed) before the start of treatment. Further investigations see the Schedule of Study Assessments. A further PET-CT has to be added as current standard pre-radiotherapy-planning investigation in the last week of the third cycle of induction chemotherapy (Block 1).
Safety Assessments:	See Schedule of Study Assessments for details regarding hematology, clinical chemistry, C-reactive protein (CRP), ECG and physical examinations as well as other scheduled investigations during induction chemotherapy and throughout the study.
Efficacy Assessments:	CT scans of thorax/upper abdomen every three months post definitive local treatment. Pharmacodynamic / Pharmacokinetic Assessments (if applicable): Not applicable.
Sample Size Determination, Statistical Methods and Data Analysis:	The primary endpoint is progression-free survival rate at 2 years. It is expected that progression-free survival rate (PFS) at two years is 35% according to historical controls comprising comparable resectable stage III patient cohorts treated with neoadjuvant radiochemotherapy followed by surgery (H0) [Eberhardt et al 2015b; Senan et al 2016; Bradley et al 2015]. H0 can be rejected at one sided alpha =0.025 using an exact binominal test, if 39 or more patients among 84 recruited patients in both randomization arms with durvalumab maintenance or durvalumab during induction and maintenance combined at two years are alive without progression at 2 years. In the case of rejection of H0, the gate is opened for a second comparison in fixed sequence as step 2. Here, PFS data from both treatment arms will be compared by a log rank test.
Toxicity run in Phase:	Neoadjuvant chemotherapy plus radiochemotherapy combined with durvalumab immunotherapy does not increase dose limiting toxicity. This hypothesis is rejected if > 3 patients among the first 7 patients in the durvalumab treatment Arm A have pulmonary fibrosis or pneumonitis or bleeding of CTCAE Version 5.0 grade 3 or at least one patient has a grade ≥ 4 and at least another patient a grade ≥ 3 pulmonary fibrosis or pneumonitis or bleeding within 60 days from start of therapy. After these seven patients are randomised in the durvalumab treatment Arm A the recruitment is halted for 60 days until toxicity evaluation for these patients is completed to observe delayed toxicities in all treated patients. Otherwise, the trial will be stopped. In addition the trial will be stopped at any time during recruitment, if the rate of treatment associated deaths is > 15 % or of grade ≥ 3 pulmonary events is > 40%.
Hypothesis H0:	35% progression-free survival rate (PFS) of a comparable stage III population at two years according to historical controls [Eberhardt et al 2015b; Senan et al 2016; Bradley et al 2015].
Hypothesis H1:	The progression-free survival rate at two years in both arms together exceeds 35%. If H0 was rejected the PFS in both arms will be compared by log rank statistics between both arms. The

	power of the comparison is 80% to detect a HR of < or = 0.5 between arm B and arm A at a significance level of alpha = 0.05.
Participating Centers:	1. Universitätmedizin Essen (Universitätsklinikum und Ruhrlandklinik), 2. Robert-Bosch Krankenhaus Stuttgart, 3. Universitätsmedizin Oldenburg, Pius-Hospital Oldenburg, 4. Universitätsmedizin Freiburg, Universitätsklinikum
Further Centers desired:	yes, two more are in current negotiations
Number of Patients:	90 Pts
Current number of Patients:	22 Pts (29.9.2021)