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| Study Protocol No | AIO-TRK-0221 / EUDRACT 2017-003780-35 |
| Protocol | Version 6.0 |
| Protocol date | 24.Nov 2021 |
| Study title | Randomized phase II, open-label efficacy and safety study of second-line durvalumab plus tremelimumab versus platinum-based chemotherapy alone in patients with NSCLC and first-line checkpoint-inhibitor therapy followed by 2 cycles of platinum-based chemotherapy (Re-Check) |
| Principal Investigator /Study Chair | PD Dr. Niels Reinmuth, Asklepios Fachkliniken München-Gauting |
| Design | Two armed, randomized, multicenter, open-label phase II study |
| Clinical Phase | II |
| Objectives | The objectives of this therapeutic phase II trial are efficacy and safety of the experimental intervention, as well as quality of life and exploratory biomarker analysis. |
| Endpoints | Primary endpoint<br>The primary endpoint is progression-free survival 1 (PFS1) using Investigator assessments according to RECIST 1.1. PFS1 is defined as the time from randomization to disease progression and will be primarily used for the formal hypothesis test.<br>Secondary endpoints<br>Progression-free survival after initiation of second-line therapy (PFS2)<br>Overall survival after initiation of second-line therapy (OS)<br>Objective response rate (ORR) - best overall response during second-line treatment<br>Subgroup analysis: Objective response rate (best overall response) after randomization<br>Duration of response (DoR)<br>Time to first subsequent treatment (TFST)<br>Tolerability and adverse events<br>Quality of life<br>Biomarkers |
| Patient number | 230 registered, 196 randomized |
| Number of centers | 25 |
| Duration | First Patient In (FPI): Q1-2/2022<br>Last Patient In (LPI): after approx. 24 months<br>Last Patient Last treatment (LPLT): after approx. 37 months<br>End of follow-up period after LPI: after approx. 49 months<br>Study report: after approx. 61 months<br>Publication after approx. 61 months |
| Description | This is an open label, randomized, Phase II multicenter study designed to evaluate the safety and efficacy of two different second-line strategies: After failure of first line mono-immunotherapy with checkpoint inhibitors |

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| | (anti-PD-1/PD-L1), and subsequent 2 cycles of standard of care platinum-based chemotherapy, 2 treatment arms will be compared:<br><br>Arm A (Experimental Arm): After randomization, patients will receive a combination regimen featuring a single, priming dose of tremelimumab together with conventional durvalumab dosing. Durvalumab maintenance therapy will subsequently be continued as study treatment for up to 12 cycles.<br><br>Arm B: After randomization, patients will continue to receive another 2-4 cycles of platinum-based chemotherapy.<br><br>Afterwards, patients will end treatment or receive maintenance pemetrexed therapy as per marketing authorization (depending on histology, maximum of 13 cycles) at the discretion of the investigator.<br><br>After written informed consent has been obtained, and eligibility has been established, the study site will enter demographic and baseline characteristics in the documentation forms. Patients without progression after two cycles of chemotherapy (induction treatment phase) will be randomized at a 1:1 ratio into one of 2 treatment arms (combination treatment phase).<br><br>PD-L1 expression status will be evaluated based on available data. The type of test assay will be documented.<br><br>To better focus on patients with expected good clinical benefit from immunomodulating agents, only patients with checkpoint-inhibitor treatment as first-line monotherapy and a progression-free survival of at least 12 weeks will enter the study (at least two re-assessments after initiation of first-line treatment). Consequently, patients with disease progression as best response of first-line therapy cannot enter this study. Directly re-challenging patients with anti-PD-L1 and anti-CTLA agents after disease progression on checkpoint-inhibitor monotherapy will be avoided by the previous application of two cycles of platinum-based chemotherapy as induction treatment, which may also enhance the antigen release from tumor cells and may further support the subsequent immunotherapy. |
| Study Treatments | Induction treatment:<br><br>2 cyles of Q3W second-line plantium-based chemotherapy according to standard of care: Cisplatin or carboplatin in combination with pemetrexed, paclitaxel, nab-paclitaxel, vinorelbine or gemcitabine<br><br>Combination treatment:<br><br>Study arm A (experimental arm):<br><br>Durvalumab 1500 mg fixed dose plus tremelimumab 300 mg fixed bolus dose<br><br>Study arm B (control arm):<br><br>Continuation of second-line chemotherapy with 2-4 further cycles (Q3W) platinum-based combination therapy. |

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| | Maintenance Therapy:<br>Study arm A (experimental arm):<br>Durvalumab 1500 mg fixed dose Q4W up to 12 cycles within the study<br>Study arm B (control arm):<br>Optional continued maintenance therapy with pemetrexed according to marketing authorization will be allowed for a maximum of 13 cycles. |
| IMPs | Experimental IMPs:<br>Durvalumab<br>Tremelimumab<br>Standard-of-Care chemotherapies and comparators:<br>Pemetrexed<br>Paclitaxel<br>nab-Paclitaxel<br>Vinorelbine<br>Gemcitabine<br>Cisplatin<br>Carboplatin |
| Duration of treatment | All patients will be treated within the study until the maximum number of cycles is reached, progressive disease, intolerable toxicity, withdrawal by the patient or decision by the investigator.<br>For subjects in the experimental arm, any follow-up therapy after 12 cycles of on-study durvalumab treatment is at the investigator's discretion |
| Randomisation | 1:1<br>Stratifcation factors: histology (squamous vs. non-squamous) |
| Cross-over | Not allowed |
| Inclusion criteria | Patients must meet all of the following criteria to be eligible for study entry:<br>1. Signed Informed Consent Form<br>2. Age >18 years at time of study entry<br>3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1<br>4. Histologically or cytologically confirmed, stage IV NSCLC (per the Union Internationale contre le Cancer/American Joint Committee on Cancer staging system).<br>5. Indication for standard-of-care second line platinum-based chemotherapy, using cisplatin or carboplatin in combination with pemetrexed, paclitaxel, nab-paclitaxel, vinorelbine or gemcitabine<br>6. Life expectancy of > 12 weeks<br>7. Body weight > 30kg<br>8. First-line mono-immunotherapy with checkpoint inhibitors (anti-PD1/PD-L1) with a best response of stable disease (SD) or better |

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| | 9. Documented tumor PD-L1 expression status of ≥50%. Any existing data can be used.<br>10. First-line progression-free survival of at least 12 weeks after at least two re-assessments after initiation of first-line treatment.<br>11. Patients who have received prior neo-adjuvant, adjuvant chemotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a treatment-free interval of at least 6 months from initiation of first-line immunotherapy since the last adjuvant chemotherapy or chemoradiotherapy cycle.<br>12. Patients with a history of treated asymptomatic CNS metastases are eligible, provided they meet all of the following criteria:<br>- No ongoing requirement for corticosteroids as therapy for CNS disease<br>- No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to enrolment<br>- No evidence of interim progression between the completion of CNS-directed therapy and the screening<br>- Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla or spinal cord)<br>13. No known sensitizing mutation in the EGFR gene or evidence of an ALK fusion oncogene.<br>14. Measurable disease, as defined by RECIST v1.1. Previously irradiated lesions can only be considered as measurable disease if disease progression has been unequivocally documented at that site since radiation.<br>15. Adequate hematologic and end organ function, defined by the following laboratory results obtained within 3 days prior to enrolment:<br>a. ANC 1500 cells/μL without granulocyte colony-stimulating factor support<br>b. Lymphocyte count ≥ 500/μL<br>c. Platelet count ≥ 100,000/μL without transfusion<br>d. Hemoglobin ≥ 9.0 g/dL. Patients may be transfused to meet this criterion. Transfusions are allowed throughout the study.<br>e. 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.<br>f. AST (SGOT)/ALT (SGPT) ≤2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤5x ULN |

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| | g. Measured creatinine clearance (CL) >60 mL/min or calculated creatinine clearance CL>60 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:<br><br>Males:<br><br>Creatinine CL (mL/min) = Weight (kg) x (140 – Age) / 72 x serum creatinine (mg/dL)<br><br>Females:<br><br>Creatinine CL (mL/min) = Weight (kg) x (140 – Age) x 0.85 / 72 x serum creatinine (mg/dL)<br><br>16. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:<br>- Women <50 years of age would be considered post-menopausal if they have been amenorrhoeic 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).<br>- Women ≥50 years of age would be considered post-menopausal if they have been amenorrhoeic 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).<br>17. 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. |
| Exclusion criteria | Patients should not enter the study or be discontinued from the study if any of the following exclusion criteria are fulfilled:<br>1. Use of immunosuppressive medication (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 14 days prior to randomization. The following are exceptions to this criterion:<br>• Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be eligible after discussion with the study chair. |

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| | • The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.<br>• Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)<br>• Systemic corticosteroids at physiologic doses not exceeding 10 mg/day of prednisone or its equivalent<br>• Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).<br>2. Prior treatment with other immune-modulating agents (other than anti-PD-1/PD-L1)<br>3. Treatment with systemic immunostimulatory agents (including but not limited to IFNs, IL-2) within 4 weeks or five half-lives of the drug, whichever is longer, prior to randomization. Prior treatment with cancer vaccines is allowed.<br>4. Involvement in the planning and/or conduct of the study (applies to both sponsor staff and/or staff at the study site)<br>5. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study<br>6. Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 28 days prior to randomization<br>7. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy (including second line platin based chemotherapy) with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria<br>• Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Chair.<br>• Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab may be included only after consultation with the Study Chair.<br>8. Any toxicity that led to permanent discontinuation of prior immunotherapy.<br>9. A ≥ grade 4 immune related AE or an immune related neurologic or ocular AE of any grade while receiving prior immunotherapy.<br>10. Any concurrent chemotherapy, investigational product, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non–cancer-related conditions (e.g., hormone replacement therapy) is acceptable.<br>11. History of allogenic organ transplantation. |

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| | 12. 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.<br>13. 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:<br>• Patients with vitiligo or alopecia<br>• Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement<br>• Any chronic skin condition that does not require systemic therapy<br>• Patients without active disease in the last 5 years may be included but only after consultation with the Study Chair<br>• Patients with celiac disease controlled by diet alone<br>14. 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<br>15. History of another primary malignancy except<br>• Malignancy treated with curative intent and with no known active disease ≥3 years prior to study enrolment and of low potential risk for recurrence<br>• Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease<br>• Adequately treated carcinoma in situ without evidence of disease<br>16. History of leptomeningeal carcinomatosis<br>17. History of active primary immunodeficiency<br>18. 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 1/2 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. |

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| | 19. Receipt of live or live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients should also not receive live or live attenuated vaccine for the pertinent time frames during and after treatment defined in the respective study drug's SmPC or IB.<br>20. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.<br>21. 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 a defined timepoint after last dose of treatment (see Section 7.1 for details)<br>22. A marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval >450 ms);<br>A history of additional risk factors for TdP (e.g., heart failure, hypokalemia, family history of Long QT Syndrome). |
| Statistical Methods | Statistical Methods<br><br>Analysis Populations:<br><br>The Full Analysis Set (FAS) includes all enrolled subjects who received at least one dose of study medication. This will be the primary population for evaluating all secondary efficacy endpoints. Subjects will be analyzed according to the randomized treatment; non-randomized subjects will be analysed as separate subgroup.. The primary endpoint will be evaluated from all randomized subjects.<br><br>As a subset of the FAS, the response-evaluable (RE) population includes all subjects in the FAS population who meet key eligibility criteria (including measurable disease at Screening), receive at least one dose of cancer medication, and who either have at least one on-treatment tumor assessment performed that is sufficient to evaluate the endpoint of interest, or withdrew from the study or experienced progression/death at any time on study. The RE population will be used for additional ORR analysis (e.g., sensitivity analysis, signal detection).<br><br>Safety Population: includes all enrolled (SA) subjects who receive at least one dose of study medication. All safety analyses will be based on this population and subjects will be analyzed according to the treatment actually received.<br><br>Primary Efficacy Analyses:<br><br>The treatment difference in PFS will be analyzed using Cox regression stratified for tumor histology (squamous vs. non-squamous); with less than 5% of patients in one stratum, the primary analysis will not be stratified by this factor, and an un-stratified log-rank test will be applied, if applicable.<br><br>Supportive analyses of PFS will be performed using an un-stratified log-rank test and a Cox regression with PD-L1 expression, tumor histology, smoking status and other prognostic factors as covariates. Descriptive statistics, including the median survival time and a 2-sided 95% |

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| | confidence interval for the median, will be computed using the Kaplan-Meier product-limit method.<br><br>Analysis of Key Secondary Endpoints and Other Endpoints:<br><br>The treatment effect on PFS2, OS, TFST and DoR will be evaluated using the methods used in the analysis of the primary endpoint.<br><br>ORR will be compared between the 2 treatment groups by means of a logistic regression model with tumor histology, PD-L1 expression, smoking status and other prognostic factors as covariates. The relative risk ratio estimator will be used, and both a point estimate and a 2-sided 95% confidence interval will be calculated.<br><br>Interim analysis:<br><br>An interim analysis will be performed as soon as 67 PFS events were observed after randomization.<br><br>A non-binding futility threshold for the conditional power of 60% will be applied on the primary endpoint in all randomized subjects. It is also planned to terminate the study early in case of an unexpected large treatment effect, using a Cox-Regression stratified for tumor histology (or un-stratified test with less than 5% of patients in one stratum) with a p-value of 0.1% (two-sided) according to Haybittle-Peto. In case the study is continued, a p-value of 5% (two-sided) will be applied in the final analysis. |
| Sample Size Rationale | In order to detect an improvement of median PFS of 4 months (Control Arm) to 6.5 months (Experimental Arm), corresponding to a hazard ratio of 0.615, 134 PFS events are necessary to provide 80% power for a log-rank test with a significance level of 5% (two-sided). With an enrollment period of 12 months and a minimum follow-up time of 6 months per subject, a total of 186 patients would be necessary for this study to compensate an estimated monthly drop-out rate of 1.5%.<br><br>With the objective to stop the trial in case of futility or superiority, an interim analysis comparing the primary endpoint between groups will be performed as soon as 50% of necessary PFS events (67) after randomization have been observed. In order to compensate for the reduced overall statistical power of this approach, a 5% increased sample size of 196 patients will be randomized into this study. |
| Biomarker Sub-study | Patients can optionally participate in the biomarker sub-study, for which at various timepoints plasma, plasma DNA, serum, RNA and blood cell samples will be collected from blood. |