AIO-YMO/TRK-0319: Thoracic Radiotherapy plus Durvalumab in Elderly and/or frail NSCLC stage III patients unfit for chemotherapy- Employing optimized (hypofractionated) radiotherapy to foster durvalumab efficacy (TRADEhypo)

AIO-Studie		
Studiennummer/-Code:	AIO-YMO/TRK-0319 - TRADEhypo	
Status:	in Rekrutierung	
Rekrutierungszeitraum:	2020 – 2022	
Weitere Zentren:	nicht mehr möglich	
Zentren:	geplant: 21	initiiert: 20
Patienten:	geplant: 57	aktuell eingeschlossen: 27
Letzte Aktualisierung	22.03.2022	

STUDY TYPE	Investigator- initiated 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)
DESIGN	Randomized, open-label, multicenter, phase II trial with safety stop-and-go lead-in phase
INDICATION	Locally advanced, unresectable NSCLC (stage III) not eligible for sequential chemo-/radiotherapy
OBJECTIVE(S)	Primary objective: To evaluate the safety and tolerability of either conventionally fractionated (CON-group) or hypofractionated (HYPO-group) thoracic radiotherapy in combination with durvalumab. Primary efficacy objective: To investigate the efficacies of either mode of fractionation of radiotherapy in combination with durvalumab with respect to the response rates in patients with unresectable stage III NSCLC, who are not suitable for chemotherapy. Secondary objectives: To determine further parameters for efficacy, safety, and quality of life in both treatment arms. Exploratory objectives: Analyses of concomitant “Vulnerability assessment” (G8 screening questionnaire); Biomarker exploration.

INTERVENTION(S)	Durvalumab
OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	Radiation-induced tumor-specific immune effects can explain events of tumor regression upon radiation treatment both within and beyond the irradiated fields and the immune system can be further stimulated by administration of a PD-L1 blocking antibody such as durvalumab. The translational research planned to be conducted on these samples (tumor tissue, blood and stool) aims to elucidate the immune-related mechanisms behind these observations.
BACKROUND/RATIONALE	Based on the PACIFIC study, sequential treatment with durvalumab after chemoradiotherapy has become the new standard treatment for locally advanced, unresectable NSCLC. However, an estimated proportion of more than 20% of patients with this diagnosis is not subjected to such a combined modality treatment due to age and/or comorbidities and receives radiotherapy only. Now, when combining durvalumab therapy with radiotherapy, the immune-promoting characteristics of radiotherapy are expected to boost the efficacy of the checkpoint inhibitor, thereby improving response in these otherwise potentially undertreated patients. Moreover, in the case of early concomitant application, combination of local radiotherapy with systemic immunotherapy is hypothesized to particularly increase efficacy on the control of distant micrometastases. In addition, hypofractionated treatment considerably increases convenience and practicability for the patient due to the shorter duration time of radiotherapy. However, safety of concurrent application of radiotherapy, in particular in a hypofractionated scheme, and checkpoint inhibitors is a concern as both therapy modalities by themselves can cause severe pneumonitis. Therefore, a prospective clinical trial is warranted that investigates the feasibility of hypofractionated radiotherapy in combination with PD-1/PD-L1 blockade and evaluates the efficacy of this treatment. The trial aims to i) determine the safety and tolerability of the combination of immunological and radiological treatment in the first-line setting for stage III NSCLC patients only prone to radiotherapy, ii) increase the efficacy of radiotherapy by utilizing its immune-sensitizing effect when combining it with durvalumab, and iii) to collect tumor tissue as well as blood and stool samples to be able to explore the immunological mechanisms responsible for checkpoint inhibitor efficacy and immune-promoting effects of radiotherapy, gain insight into the tumor-host biology, and identify novel biomarkers. <u>Hypothesis:</u> It is hypothesized that TRT combined with concurrent durvalumab administration in patients with unresectable stage III NSCLC, who are not amenable to sequential radio-/chemotherapy 1. is safe and feasible, 2. will improve treatment efficacy by a synergistic effect of checkpoint inhibition and the photon-induction of immunostimulatory pathways, 3. will have an effect on the immunological characteristics of the tumor, the microenvironment, and the systemic immune response, such as upregulation of PD-L1 or secretion of stimulatory cytokines and recruitment and priming of immunocompetent cells, which might then mediate the “abscopal effect” beyond the irradiated targets.
KEY EXCLUSION CRITERIA	1. Prior immunotherapy or use of other investigational agents, including prior treatment with an anti-Programmed Death receptor-1 (PD-1), anti-Programmed Death-1 ligand-1 (PD-L1), anti-PD-L2, or anti-cytotoxic T-lymphocyte associated antigen-4 (anti-CTLA-4) antibody, therapeutic cancer vaccines. 2. History or current radiology suggestive of interstitial lung disease. 3. Any concurrent chemotherapy, investigational product (IMP), biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer related conditions (eg, hormone replacement therapy) is acceptable.

	4. Prior thoracic radiotherapy within the past 5 years before the first dose of study drug. 5. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion: o Intranasal, inhaled, topical steroids, or local steroid injections (e.g. intra articular injection) o Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent o Steroids as premedication for hypersensitivity reactions (e.g. CT scan premedication) 6. Active or prior documented autoimmune or inflammatory disorders (except inflammatory bowel disease [e.g. ulcerative colitis or Crohn's disease]; including diverticulitis [with the exception of diverticulosis], celiac disease, systemic lupus erythematosus, Sarcoidosis, or Wegener's syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis). The following are exceptions to this criterion: o Patients with vitiligo or alopecia o Patients with hypothyroidism (e.g., following Hashimoto's disease) stable on hormone replacement o Any chronic skin condition that does not require systemic therapy o Patients without active disease in the last 5 years may be included but only after consultation with the study physician. 7. Oxygen-dependent medical condition.
KEY INCLUSION CRITERIA	1. Histologically documented diagnosis of unresectable stage III NSCLC. 2. Fulfills <u>at least one</u> of the following criteria: • Performance status (PS) ≥ 2 (ECOG scale) • ECOG 1 <u>and</u> CCI ≥ 1 • Age ≥ 70 years 3. Non-feasibility of sequential chemo-/radiotherapy 4. FEV1 ≥ 40% (Best/Soll) 5. DLCO or DLCO/VA (Hb-corrected, if available) ≥ 40% (Best/Soll) 6. FVC or VC ≥ 70% (Best/Soll) 7. Adequate organ function.
OUTCOME(S)	<u>Primary endpoint:</u> Toxicity, defined by the occurrence of treatment-related pneumonitis grade ≥ 3 <u>Primary efficacy endpoint:</u> Objective response evaluated at 12 weeks (3 months) after first durvalumab administration according to RECIST 1.1 criteria <u>Secondary endpoints:</u> • Occurrence of treatment-related AEs and SAEs according to CTCAE V5.0 • Abnormal values of laboratory parameters • PFS according to RECIST 1.1 • Duration of Clinical Benefit (Duration of CR, PR, SD) according to RECIST 1.1 • MFS • OS • QoL (FACT-L)

STATISTICAL ANALYSIS	The analysis of the primary efficacy endpoint objective response is based on the ITT population. We assume that we can demonstrate that the ORR in both treatment arms is higher than 0.42, i.e. the null hypotheses for arm HYPO and CON are defined as H_0^{HYPO}: $\pi^{HYPO} \leq 0.42$ and H_0^{CON}: $\pi^{CON} \leq 0.42$, which are tested against the alternatives H_1^{HYPO}: $\pi^{HYPO} > 0.42$ and H_1^{CON}: $\pi^{CON} > 0.42$, respectively, where π^{HYPO} and π^{CON} denotes the actual ORR in arm A and B, respectively. The null hypotheses H_0^{HYPO} and H_0^{CON} will both be assessed at one-sided significance levels of $\alpha=0.10$ each, using an optimal Simon's two-stage design, ensuring a power of $1-\beta=0.8$ for each comparison with the planned sample size of n=40 patients per group. After n=18 patients have been enrolled to the respective treatment arm HYPO or CON, an interim analysis for the respective arm will be conducted. If among 18 patients, the number of patients who have achieved a response is 8 or lower, the respective null hypothesis will be prematurely accepted and the respective treatment arm will be terminated. Otherwise, the trial will continue until n=40 patients have been enrolled to the respective treatment arm. If the number of responders is 20 or less, the null hypothesis will be accepted, otherwise, it will be rejected. All analyses of safety endpoints are based on the Safety Population. A safety interim assessment based on the primary safety endpoint, occurrence of a pneumonitis grade ≥ 3, is conducted after 18 patients have been enrolled to the HYPO-group. If the number of patients with a pneumonitis grade ≥ 3 is 1 or less, regimen assessment will continue with the interim efficacy analysis. If among 18 patients, the number of patients with a pneumonitis grade ≥ 3 is 2 or more, recruiting patients to the HYPO-treatment arm will be stopped.
SAMPLE SIZE	88 Patients (initial); reduced to 57 after HYPO-arm closure
TRIAL DURATION	Duration of recruitment: 20 months starting from FPI Maximum treatment duration per subject: 12 months Individual follow-up: ≥ 3 months after last administration of study drug
TREATMENT, DOSAGE AND ADMINISTRATION	• Durvalumab: fixed dose of 1,500 mg as an IV infusion over 1 hour, on day 1, to be repeated every 4 weeks (Q4W) for a maximum of 12 months • Thoracic radiation therapy (TRT) is started within 72 hours after start of durvalumab treatment. **CON group:** Patients receive conventional fractions of 30 x 2 Gy (60 Gy) within 6 weeks (+9 days) of thoracic radiotherapy in combination with durvalumab treatment. **HYPO group:** Patients receive hypofractionated thoracic radiotherapy consisting of 20 x 2,75 Gy (55 Gy) within 4 weeks (+9 days) in combination with durvalumab treatment. A safety stop-and-go phase will precede full enrollment in the HYPO-group. Toxicity will be evaluated with a 6+6 design that is based on the statistical assumption that ≤1 events in n = 18 patients conforms to a non-toxicity scenario, with "event" being defined as the occurrence of pneumonitis grade ≥ 3.
SAFETY ASSESSMENTS	Safety assessments will include physical examinations, performance status (ECOG), clinical laboratory profile and continuous assessments of adverse events.

	All observed toxicities and side effects will be graded according to NCI CTCAE v5.0 for all patients and the degree of association of each with the procedure assessed and summarized. • Rate of treatment-related Grade 3 and 4 pneumonitis, • treatment related serious adverse events rate, and • frequency of abnormal laboratory parameters will be determined. **Safety Lead-In phase (stop-and-go design):** A safety lead-in phase with stop-and-go design will precede full enrollment into the HYPO-group. Toxicity will be evaluated with a 6+6 design that is based on the statistical assumption that ≤1 events in n=18 patients conforms to a non-toxicity scenario, with “event” being defined as the occurrence of pneumonitis grade ≥ 3.