Durvalumab in frail and elder patients with stage four NSCLC: Study protocol of the randomized phase II DURATION trial

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Study protocol

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Abstract

Background Elderly patients represent a major fraction of non-small cell lung cancer (NSCLC) patients in routine clinical practice, yet are underrepresented in clinical trials. In particular, data regarding efficacy and safety in frail or elderly patients with respect to immunotherapy is lacking. Importantly, immunosenescence in elderly patients might interfere with activities of immune-modulating drugs such as PD-1/PD-L1 inhibitors. Thus, there is an urgent need to assess safety and efficacy of such inhibitors in this group. **Methods/design** In this prospective, open label, treatment stratified, and randomized phase II study, 200 patients with stage IV NSCLC amenable at least to single-agent chemotherapy. Eligible patients must be 70 years or older and/or “frail” (Charlson Comorbidity Index >1), or have a restricted performance score (ECOG >1). Patients are stratified according to modified Cancer and Age Research Group (CARG) Score: “fit” patients are allocated to combination chemotherapy (carboplatin/ nab -paclitaxel), “less fit” patients receive single-agent chemotherapy (gemcitabine or vinorelbine). After allocation to strata, patients are randomized 1:1 to receive either 4 cycles of chemotherapy or 2 cycles of chemotherapy followed by 2 cycles of durvalumab and subsequent maintenance treatment with durvalumab every 4 weeks. The primary endpoint is the rate of treatment related grade III/IV adverse events (CTCAE V4.03). As secondary endpoints, progression-free survival according to RECIST 1.1, response rate, overall survival, descriptive subgroup analyses according to PD-L1 expression, and quality of life are addressed. Geriatric screening assessments and functional tests will be performed to complete the phenotyping of a potential “frail” and “elderly” patient cohort (G8-questionnaire, Timed up & go test, 6MWT). The trial is accompanied by a biomaterial repository (FFPE-tissue, Blood samples) to explore potential biomarkers. **Discussion** The DURATION trial will prospectively investigate the safety and tolerability of anti-PD-L1 treatment with durvalumab after chemotherapy in elderly and frail patients and thereby provide new insights into the effect of PD-L1 blockade and the impact of immunosenescence in this cohort of patients.

Background

Lung cancer is one of the most commonly diagnosed cancer types and the leading cause of cancer death worldwide (1). Lung cancer is predominantly a disease of the elderly with about 50% of patients diagnosed aged 70 years or older (2). Age is an independent prognostic factor affecting survival in this group of patients (3).

Metastatic non-small cell lung cancer (NSCLC) carries a dismal prognosis with a median survival of less than 12 months. Systemic treatment, such as mono-chemotherapy (e.g. vinorelbine or gemcitabine) (4,5) or a dose adapted combination of carboplatin (AUC6) / paclitaxel (90 mg/m²; d1+8+15) (6) is considered to improve outcome in patients who are aged ≥ 70 years, are frail or have a reduced performance score (i.e., ECOG ≥ 2).

The use of geriatric assessment and screening tools is recommended in elderly patients to better adapt intensity of treatment to patient condition and comorbidities (7). As a complex geriatric assessment (comprehensive geriatric assessment) it is time- and resource-consuming and potentially not required for

all patients, shorter pre-therapy risk assessments have been developed, i.e. the CRASH (Chemotherapy Risk Assessment Scale for High-Age Patients (8)) and the CARG (Cancer and Age Research Group, (9)) score.

While the CRASH score contains variables for clinical and geriatric assessment, the CARG score comprises geriatric assessment questions and clinical questions concerning items retrieved from everyday practice. Both scores are considered as useful toxicity prediction tools, appropriate for implementation in routine clinical practice, with a potential impact on the optimization of therapy selection for elderly patients with cancer (10).

With the advent of immune-oncology, new options have become available. Currently, checkpoint inhibition therapies targeting PD-1 and PD-L1 are advancing up to 1st-line treatment in metastatic lung cancer. This is based on several impressive efficacy results of anti-PD-1/PD-L1 antibodies in clinical trials in NSCLC that have led to the approval of nivolumab, pembrolizumab and atezolizumab (11–14) first in advanced therapy lines and later in the 1st line setting (mono-immunotherapy for PD-L1 $\geq 50\%$ or regardless of PD-L1 tumor expression in combination with a combination chemotherapy) (15,16). However, clinical evidence about the tolerability and safety of checkpoint inhibition as a treatment option in frail and elderly patients is still lacking.

In addition, it remains an unresolved question whether efficacy of checkpoint inhibitors in older patients is affected by a still poorly characterized phenomenon referred to as immunosenescence, i.e. the global and progressive remodeling of immune functions with aging (13,14,17,18). Age-related alterations such as, for example, impaired T cell activation, reduced T cell receptor diversity, altered antigen-uptake and -presenting functions, or the increased generation of immune suppressive cells, may impair the antitumor response and thus could be one of the reasons for a higher incidence and prevalence of most cancers in older people.

Furthermore, a paradoxical stimulation of tumor growth upon initiation of treatment with checkpoint inhibitors, the so-called hyperprogressive disease, has been reported in a recent retrospective analysis in up to 19% of patients older than 65 years. This could potentially be caused by an altered immune function due to immunosenescence (19).

In conclusion, with the increasing use of immunotherapy in everyday clinical practice there is a growing interest in immunosenescence and how it may correlate with outcomes of immunotherapy in elderly patients (17,20). However, data derived from randomized trials are lacking to investigate safety and tolerability of checkpoint inhibitors in this specific population of lung cancer patients.

Methods/design

Study design

The DURATION study is an open label, treatment stratified, and randomized phase II study (Figure 1) enrolling patients with histologically confirmed NSCLC (adenocarcinoma and squamous) stage four

(metastatic) prior to any systemic treatment. All procedures and time frames displaced in figure 1 and shedule of assessment (Table 3) are developed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT). Additional file 1 contains the complete SPIRIT checklist.

Study setting

The DURATION trial is a multicenter trial recruiting patients from approximately 30 sites across Germany. A full list of sites can be obtained at clinicaltrials.gov (NCT03345810).

Study objectives

Primary objective

The primary objective is to investigate the safety and tolerability of sequential therapy consisting of standard of care single agent or doublet chemotherapy followed by durvalumab in comparison to standard of care single-agent or doublet chemotherapy in frail and/or elderly patients.

Secondary objectives

Secondary objectives are to collect information on efficacy, safety and quality of life parameters and to investigate the utility of geriatric assessments for treatment guidance.

Exploratory objectives

Exploratory objectives are to identify potential predictive biomarkers for efficacy variables. To this end, tissue collection and blood sampling will be performed before and during course of disease/treatment. The blood and tissue samples will be subjected to molecular analyses to search for markers of immune response in this population.

Analysis of biomarker data will include correlations with clinical phenotype and tumor PD-L1 expression.

Characteristics of patients

200 frail and/or elderly patients with metastatic non-small cell lung cancer with no targetable molecular alterations ($EGFR^{wt}$, $EML4ALK^{transl-}$) before 1st-line treatment will be included.

Key inclusion criteria are age ≥ 70 years and/or CCI >1 and/or ECOG >1 , previously untreated NSCLC with no targetable molecular alterations ($EGFR^{wt}$, $EML4ALK^{transl-}$) and the availability of a formalin-fixed, paraffin-embedded (FFPE) tumor tissue block (fresh or archival less than three years old or recent) or a minimum of ten unstained slides of tumor sample for biomarker (PD-L1) evaluation. Key exclusion criteria include mixed small cell lung cancer and NSCLC histology, and history of another primary active malignancy or active autoimmune disease.

For a full list of inclusion and exclusion criteria see Table 1.

Procedures for stratification

Patients are stratified according to modified Cancer and Age Research Group (CARG) with the following cut-offs (9,21):

- Total risk score $\leq 3 \rightarrow$ doublet chemotherapy
- Total risk score $> 3 \rightarrow$ single-agent chemotherapy

The aim is to prevent >50% of standard chemotherapy toxicities (CTCAE grade III/IV). The risk score will be determined according to Table 2.

Study procedures

According to a chemotherapy toxicity tool (modified CARG score, Table 2), patients are classified as suitable for doublet chemotherapy (arm A and B) or suitable for a single-agent chemotherapy (arm C and D). Patients are then randomized to receive either four cycles of single agent or doublet chemotherapy or two cycles of single-agent or doublet chemotherapy followed by two cycles of immunotherapy. After four cycles of standard chemotherapy patients receive either follow-up care (arm A and D) or a maintenance therapy with durvalumab for a maximum of two years in the experimental arms B and C. Dose modification and Toxicity management is detailed described in the chapter “Treatment plan” of the protocol. Furthermore, detailed information about permitted or prohibited concomitant treatment is obtained in the protocol. A data safety monitoring board (DSMB) is installed to control, modify or terminate the study. Details are provided in the protocol referring to the DSMB Charta. An overview of all study procedures is presented in table 3.

Treatment arms A and D: standard of care single agent or doublet chemotherapy

Arm A: *nab*-paclitaxel 100mg/m² on days d1 and d8 and carboplatin area under the curve (AUC) 5 on day 1, every 3 weeks up to four cycles

Arm D: Gemcitabine 1000mg/m² on days d1 and d8, given every 3 weeks, or vinorelbine 30mg/m² on days d1 and d8 every 3 weeks up to four cycles

Treatment arms B and C: 2 cycles of single agent or doublet chemotherapy followed by durvalumab

Arm B: Two cycles of *nab*-paclitaxel 100mg/m² on days d1 and d8 and carboplatin area under the curve (AUC) 5 on day 1, every 3 weeks followed by durvalumab 1125 mg every 3 weeks for two cycles followed by maintenance with durvalumab 1500 mg every 4 weeks

, Arm C: Two cycles of gemcitabine 1000mg/m² on days d1 and d8, given every 3 weeks or vinorelbine 30mg/m² on days d1 and d8 every 3 weeks up to four cycles followed by durvalumab 1125 mg every 3 weeks for two cycles followed by maintenance with durvalumab 1500 mg every 4 weeks

Tissue and blood collection for exploratory endpoints

Tissue collection

For each patient a FFPE tumor tissue block (archival or recent) or a minimum of ten unstained slides of tumor sample (2-3 µm sections; slices must be recent and collected on slides provided by the sponsor) must be available for biomarker (PD-L1) evaluation as stated in the inclusion criteria. Biopsy should be excisional, incisional or core-needle. Fine-needle aspiration is insufficient. Tumor PD-L1 expression is measured by an immunohistochemistry assay using SP263 antibody. If a re-biopsy upon tumor progression under study treatment is performed, submission of this tumor material is highly valued.

Blood collection

Participation of patients in the biomarker program is voluntary and must be documented in the informed consent form. The time points for blood sampling are before start of any treatment at baseline and after two cycles of chemotherapy, as well as after 20 weeks of study participation for all patients with stable disease or tumor regression and at the time point of detection of tumor growth in patients with disease progression. In arms B and C, blood is additionally collected after the first cycle of durvalumab.

Study endpoints

Primary endpoint

The primary endpoint will be the rate of treatment related grade III/IV adverse events (CTCAE V4.03).

Secondary endpoints

Secondary endpoints will be:

- ORR according to RECIST 1.1 criteria
- Progression-free survival (PFS)
- Overall survival (OS)
- AEs/SAEs according to CTCAE 4.03
- Health-related quality of life (HR-QoL)

Exploratory endpoints

Exploratory analysis on tissue samples

Tumor PD-L1 assessment using SP263 antibody will be performed as part of the clinical study. The results will be used to correlate PD-L1 staining intensity (proportion of positive tumor and immune cells) with durvalumab efficacy.

Exploratory analysis on blood samples

Blood samples that are collected at different time points will be used to characterize the immune response and investigate biological processes before, during and after the administration of the treatment. Phenotypic fluorescence activated cell sorter (FACS) analysis will be used to analyse whole blood samples with respect to the changes in the T-cell composition. Abundances of immunostimulatory cytokines will be quantified by measuring serum pro- and anti-inflammatory cytokines. Analysis of mutational load on cfDNA will be performed.

Statistical analysis

The primary safety endpoint for the study is the occurrence of CTC grade III/IV toxicities assessed from the first dose to 90 days after the last dose of durvalumab. This is also the primary study endpoint on which the sample size calculation is based. According to the results presented at ASCO 2015 by *Rizvi* it is assumed that the probability for a CTC grade III/IV toxicity for patients from the pooled experimental arms B+C receiving durvalumab amounts to $P_{B+C}=0.18$ (22). Based on reported data of selected treatment related adverse events (combination chemotherapy *nab*-paclitaxel/carboplatin (23), mono-chemotherapy gemcitabine/vinorelbine: (6) it is furthermore assumed that the rate of patients with a CTC grade III/IV toxicity in the pooled control arms A+D receiving chemotherapy only amounts to $P_{A+D}=0.35$. With the planned number of patients of $N=200$, the assumed difference between these two groups can be detected using a Chi-square test at a two-sided significance level of $\alpha=10\%$ with a probability of $1-\beta=0.80$, also taking into account a dropout rate of 15%. Sample size calculation was performed using ADDPLAN v6.1.

It should be noted that the study is not powered to detect significant differences with regard to the efficacy endpoints, since its primary aim is to assess safety and tolerability. Hence, no confirmatory evidence can be drawn from the efficacy evaluation. Accordingly, all p-values for efficacy outcomes are only to be interpreted descriptively and no adjustment for multiple testing will be done.

The null hypothesis for the primary (safety) endpoint of the trial is defined as $H_0: P_{B+C} = P_{A+D}$ (i.e., the rate of patients with a CTC grade III/IV toxicity is equal in the pooled experimental arms B+C and the pooled control arms A+D), which is tested against its alternative $H_1: P_{B+C} \neq P_{A+D}$ (i.e., there is a difference between the pooled experimental arms B+C and the pooled control arms A+D with regard to the rate of patients with a CTC grade III/IV toxicity). These hypotheses will be assessed at a two-sided significance level of $\alpha=0.1$ using a Mantel-Haenszel Chi-square test adjusting for the stratum “adopted combination/not prone to combination”. Missing data for the primary outcome variable will be replaced by using multiple imputation (24). The analysis of the primary endpoint will be based on the Safety Population comprising all patients enrolled who received at least one dose of study medication. Secondary endpoints will be analyzed descriptively. Subgroup analyses according to PD-L1 expression will be performed. A detailed methodology for the statistical analysis will be described in the statistical analysis plan (SAP), which will be finalized before data base lock. Statistical analysis will be done using SAS v9.4 or higher (SAS Institute, Cary, NC).

Discussion

Lung cancer is the most common cause of cancer related death worldwide and it is predominantly a disease of the elderly, with about 50% of patients diagnosed aged 70 years or older and with about 14% of these being older than 80 years (2). Due to the fact that lung cancer is mostly diagnosed at an advanced stage, prognosis is very poor.

Chemotherapy is effective in elderly NSCLC patients. However, they might convey an increased risk of experiencing and deteriorating due to side effects. The Elderly Selection on Geriatric Index Assessment (ESOGIA) trial was the first prospective study to investigate comprehensive geriatric assessment (CGA) incorporation into cancer treatment decisions and its impact on survival outcomes (25). The study randomly assigned 192 stage IV NSCLC patients with a median age of 77 years to a standard arm or a CGA arm, where patients received either one of two chemotherapy regimens or best supportive care (BSC) based on performance status (PS) and age or on the CGA evaluation, respectively. Importantly, the treatment allocation based on CGA reduced treatment toxicities and the number of toxicity-related treatment failures, although it was not able to improve treatment failure-free survival or OS. This trial for the first time demonstrated the feasibility of incorporating CGA in a multicenter clinical trial setting and that CGA-based treatment is associated with decreased toxicity in elderly NSCLC patients. In clinical practice, however, the implementation of CGA has been difficult because it is rather time- and resource-consuming. Consequently, alternative pre-therapy risk assessment tools have been developed to predict chemotherapy toxicity, the CRASH and CARG scores being the two most promising tools for assigning patients to varying chemotherapy intensities based on pre-therapy risk assessment.

In the DURATION trial, the CARG toxicity prediction tool will be used to guide treatment intensity with the intention to improve outcomes of elderly and frail patients. The CARG score has been developed to stratify patients and identify those at higher risk for chemotherapy toxicity (9). It consists of eleven questions, including five geriatric assessments questions and six clinical questions concerning items retrieved from everyday practice. The CARG score was validated in lung cancer, showing its value in better distinguishing the risks of chemotherapy toxicity in older patients compared to the Karnofsky performance status (KPS) (26). Its value in treating and predicting mortality in elderly patients with cancer is now broadly accepted. Minor modifications of the CARG score in the DURATION trial include the removal of the default scoring items “polychemotherapy” and standard dose as well as the items “GI” or “GU cancer”, which do not apply to this study. The predictive properties of the CARG score remain unchanged.

According to this modified CARG toxicity tool, patients in the DURATION trial will be classified as “fit” or as “less fit” with regard to receiving a platinum-based combination chemotherapy. “Less fit” patients will be treated with a single-agent chemotherapy of either vinorelbine or gemcitabine. Both single-agent chemotherapy regimens were established as the standard of care over best supportive care for 1st-line therapy of advanced NSCLC patients aged 70 years or older (5,27). Patients that are stratified as “fit” will receive treatment according to current ESMO guidelines for advanced NSCLC that recommend platinum-based combination chemotherapy for patients aged >70 years with PS 0-2 and adequate organ function based on a recent systematic review (28). The combination chemotherapy applied in the DURATION trial consists of a combination of *nab*-paclitaxel with carboplatin as inferred from clinical trials and

retrospective analyses that demonstrated superiority of carboplatin/*nab*-paclitaxel over carboplatin/paclitaxel with respect to efficacy and safety in elderly patients (23,29). Both patient groups treated with either single-agent or doublet chemotherapy will be subjected to randomization for treatment with the PD-L1 inhibitor durvalumab.

Based on promising results from clinical trials, immuno-oncology agents such as PD-1 - or PD-L1 inhibitors have found their way into frequent clinical use, even in the 1st-line setting and have revolutionized the treatment landscape of NSCLC. However, due to underrepresentation of older patients in large trials that led to approval of checkpoint inhibitors, all available efficacy and safety data for this patient group is derived from subgroup analyses. Such analyses of 2nd-line trials revealed no differences in response rates and survival between patients aged less or more than 65 years (11,13,17,30,31). Similarly, KEYNOTE-024, a 1st-line clinical trial comparing pembrolizumab with combination chemotherapy in advanced NSCLC patients with PD-L1 expression >50%, indicated no differences in the beneficial effect of pembrolizumab when comparing patients aged <65 years and >65 years (15). Of note, no differences regarding toxicities between age groups were observed (13). However, to date no data from randomized phase III trials assessing the efficacy of PD-1/PD-L1 targeting agents in elderly patients with advanced NSCLC are available.

In addition, addressing immuno-oncology agents specifically in older patients is of particular interest as a phenomenon called immunosenescence has to be considered. This age-related decline in the immune system includes reductions in B- and T-cell proliferation and function, quantitative differences in cellular subsets, functional impairment, and qualitative changes in APCs and an accumulation of regulatory T cells – processes that eventually could be associated with impaired immune response to pathogens and tumor cells (17).

Considering the growing number of immune checkpoint inhibitors that are available for the treatment of NSCLC patients, it is also important to learn about potential differences between PD-1 and PD-L1 targeting agents. Although each drug has shown activity in NSCLC, comparing these agents in terms of efficacy and toxicity is subject of current research. A recent systematic review of clinical trials that tested both PD-1 and PD-L1 antibodies did not find significant differences between the two types of checkpoint inhibitors regarding the reported response rates and toxicity profiles (32). The most notable difference was observed regarding grade III/IV immune-mediated pneumonitis that was slightly higher with PD-1 inhibitors compared with PD-L1 inhibitors. This could possibly be explained by the fact that anti-PD-L1 antibodies still allow for the interaction of PD-1 with its other ligand PD-L2, thus resulting in a weaker blockade of the negative inhibitory signal and reduced autoimmunity (32). The development of autoimmune pneumonitis has to be carefully monitored in NSCLC patients as this has led to a few treatment-related deaths in early-phase studies of PD-1 targeting agents (12,33,34) and patients with lung cancer are more vulnerable to toxicities given the older age of the patient population and the presence of comorbid conditions. Given the putatively lower risk of developing autoimmune-mediated toxicities with PD-L1 targeting agents, the use of durvalumab, a selective, high-affinity, human IgG1 monoclonal anti-PD-L1 antibody (35–37), is expected to be more suitable for treatment of a more vulnerable patient group such as old or frail NSCLC patients that

are included in the DURATION trial. Encouraging antitumor activity of durvalumab has already been shown in an early-phase clinical study involving multiple advanced solid tumors, including NSCLC, and recently it has been approved for patients with locally advanced NSCLC after chemoradiotherapy (35,38).

In the DURATION trial, checkpoint inhibition by durvalumab is combined sequentially with cytotoxic chemotherapy. It is thought that modulation of the immune response through PD-1 inhibition may be enhanced by the potential immunogenic effects of cytotoxic chemotherapy, e.g. by increasing the potential for antigen cross-presentation by dendritic cells after the destruction of tumor cells, inhibiting myeloid-derived suppressor cells, increasing the ratio of cytotoxic lymphocytes to regulatory T cells, and blocking the STAT6 pathway to enhance dendritic-cell activity (39–42). Thus, the two cycles of induction chemotherapy that are applied in the DURATION trial are expected to lead to a prompt disease stabilizing effect, which can be efficaciously extended by a consecutive PD-L1 immunotherapy with durvalumab. In frail and elderly NSCLC patients two cycles of chemotherapy are well feasible, side effects are manageable, and impairments in quality of life are avoided.

Current treatment guidelines recommend a standard administration of immunotherapy also for elderly lung cancer patients despite to the lack of adequate data for this patient group. Importantly, this recommendation neglects the potential role of higher age on response to or toxicity of immune checkpoint inhibitors. The DURATION trial will help to close the current gap in knowledge about safety and tolerability of checkpoint inhibitors in elderly and frail lung cancer patients, an important cohort that has been underrepresented in clinical trials for too long.

Trial Status

Patient accrual started in December 2017 and is currently ongoing according to the protocol version number 7 of May 23, 2019. At present, 30 centers are participating in this study. The approximate end of recruitment will be in December 2020.

List Of Abbreviations

AE	Adverse event
AIO	Arbeitsgemeinschaft Internistische Onkologie
APC	Antigen presenting cells
ASCO	American society of clinical oncology
AUC	Area under the curve
BSC	Best supportive care
CARG	Cancer and aging research group

CCI	Charlson comorbidity index
CD	Cluster of differentiation
cfDNA	cell-free Deoxyribose nucleic acid
CGA	comprehensive geriatric assessment
CRASH	Chemotherapy Risk Assessment Scale for High-Age Patients
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EML4ALK	Echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase
ESMO	European Society for Medical Oncology
FACS	Fluorescence activated cell sorter
FFPE	Formalin-fixed, paraffin-embedded
GI	Gastrointestinal
GU	Genitourinary
G8	Geriatric 8
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HR-QoL	Health related quality of life
IHC	Immunohistochemistry
IMP	Investigational medical product
irRECIST	Immune-related response evaluation criteria in solid tumors
MRI	Magnetic resonance imaging
6MWT	Six minute walk test

NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
RECIST	Response evaluation criteria in solid tumors
SAE	Severe adverse event
QoL	Quality of life

Declarations

Ethics approval and consent to participate

Central ethical approval has been confirmed from the Ethics Committee of the Medical Faculty of the University of Heidelberg 24.10.2017 (AFmu-681/2016) and we will not begin recruiting at other centres in the trial until local ethical approval has been obtained.

Written informed consent is obtained from all participants. Additionally, the Paul Ehrlich Institute (competent authority for approval of clinical trials using medicinal products for human use in Germany) approved the study on 03.07.2017

Consent for publication

Not applicable – as no individual patient data are contained in this manuscript.

Availability of data and material

Not applicable – as no primary data are contained, generated or analysed.

Competing interests

The DURATION trial received funding from AstraZeneca and Celgene. AstraZeneca and Celgene have not been involved in the study design, and has no role in data collection, management, data analysis and interpretation, or in the decision to submit this protocol for publication.

All authors declare that there are no competing conflicts of interest.

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Authors' contributions

JK1, MT developed the study idea, wrote the protocol and coordinated funding, regulatory permission and approval processes. JK1 is lead investigator of this study. FB is substitute lead investigator. AH developed preclinical, translational and biomarker exploratory projects, derived from DURATION. JK2 calculated (bio-) statistical models for sample size, study hypothesis, and endpoint determinations. FL and AS performs tissue-based biomarker evaluation strategies and will perform all respective analysis. MM is representative of the AIO-Studien-gGmbH (Kuno-Fischer-Str. 8, 14,057 Berlin, Germany, info@aio-studien-ggmbh.de) and substantially contributed to conception, design and preparation of study protocol. The AIO-Studien-gGmbH is sponsor of the study and responsible for study management, logistics and counselled in study design.

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Authors' information (optional)

not provided

Availability of data and materials

Not applicable.

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Tables

Table 1 : Complete list of inclusion / exclusion criteria

Inclusion criteria
<ul style="list-style-type: none"> · Written informed consent and any locally-required authorization (EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations. · Age ≥ 70 years at time of study entry and / or Charlson-Comorbidity-Index (CCI) > 1 and / or Performance status PS > 1 · Histologically confirmed diagnosis of metastatic NSCLC and no targetable molecular alterations (EGFR WT; ALK transl-) · Patients with measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) · A formalin fixed, paraffin-embedded (FFPE) tumor tissue block or a minimum of 10 unstained slides of tumor sample · No prior chemotherapy or any other systemic therapy for metastatic NSCLC. Patients who received prior platinum-containing adjuvant, neoadjuvant, or definitive chemoradiation for locally advanced disease are eligible, provided that progression has occurred > 6 months from last therapy. · Prior radiotherapy and surgery are allowed if completed 4 weeks prior to start of treatment and patient recovered from toxic effects or associated adverse events. · Adequate blood count ,liver-enzymes, and renal function <ul style="list-style-type: none"> o Haemoglobin ≥ 9.0 g/dl o Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$ (>100 per mm^3) o platelet count $\geq 100 \times 10^9 / L$ ($>100,00$ per mm^3) o Serum bilirubin $\leq 1.5 \times ULN$. This will not apply to subjects 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) $\leq 2.5 \times$ institutional upper limit of normal unless liver metastases are present, in which case it must be $\leq 5 \times ULN$ o Serum 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 o Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits, examinations including follow up and appropriate contraception.
Exclusion criteria
<ul style="list-style-type: none"> · Mixed small-cell lung cancer and NSCLC histology

- Mean QT interval corrected for heart rate (QTc) ≥ 470 ms calculated from 3 electrocardiograms (ECGs) using Fredericia's correction
- History of another primary malignancy except local prostate cancer without need for systemic treatment (e.g. active surveillance, operation without need for adjuvant treatment) and malignancies treated with curative intent and with no known active disease >2 years before the first dose of study drug 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 (e.g. cervical cancer in situ)
- Pre-existing peripheral neuropathy of Grade ≥ 2
- Brain metastasis or spinal cord compression unless asymptomatic or treated and stable off steroids and anticonvulsants for at least 1 month prior to study treatment.
- Active or prior documented autoimmune disease within the past 2 years. NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2years) are not excluded.
- Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)
- History of primary immunodeficiency
- History of allogeneic organ transplant
- History of hypersensitivity to durvalumab or any excipient
- History of hypersensitivity to any of the comparator agents
- Medication that is known to interfere with any of the agents applied in the trial
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent
- Clinical diagnosis of active tuberculosis
- Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab
- Male patients of reproductive potential who are not employing an effective method of birth control (failure rate of less than 1% per year)
- Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results
- Participation in another clinical study with an investigational product during the last 30 days before inclusion
- Any previous treatment with a PD-1 or PD-L1 inhibitor, including durvalumab

- Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid
- Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) ≤ 21 days prior to the first dose of study drug or ≤ 4 half-lives of the agent administered, whichever comes first.
- Previous enrollment or randomization in the present study.
- Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff of sponsor and study site)
- Patient who might be dependent on the sponsor, site or the investigator
- Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.
- Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].

Table 2: Risk score determination for treatment stratification. [Modified from Hurria et al. JCO 2011]

Toxicity Factor / Question	Value/Response	Score
Age ≥ 72 years	≥ 72	2
Hemoglobin	$< 11\text{g} / \text{dL}$ (male)	3
	$< 10\text{g/dL}$ (female)	
Creatinine clearance	$< 34\text{mL/min}$	3
Hearing	Fair / worse	2
Number of falls in the past 6 months	1 or more	3
Taking medications	with some help or unable	1
Walking 1 block (100 meters)	somewhat limited or limited a lot	2
Decreased social activity because of physical/emotional health	limited at least sometimes	1

Table 3: schedule of assessments

Schedule of assessments

	All Arms					Arm B & C	All Arms	
Procedure / Assessment	Screening	Treatment (q3w)				Maintenance (q4w)	End of Treatment	Follow-Up
	Inclusion	C1 - C2		C3	C4			
		Day 1	Day 8					
Informed consent, eligibility criteria, demographics, medical and disease history	x							
FFPE tumor tissue (PD-L1)	x							
Vital signs, physical examination	x	x	x	x	x	x	x	
ECOG	x			x		x	x	x ^a
AE / SAE	x	x	x	x	x	x	x	x
CT / MRI of tumor lesions	x			x		x ^b		x ^c
HR-QoL	x			x		x ^b	x	x
Charlson Comorbidity Index	x							
CARG-score	x							
Geriatric assessments	x					x	x	x ^d
Biomarker sample		x ^e		x	x ^f	x ^g	x	x ^a
Treatments								
Arm A		CHT	CHT	CHT	CHT			
Arm B		CHT	CHT	Durvalumab	Durvalumab	Durvalumab		
Arm C		CHT	CHT	Durvalumab	Durvalumab	Durvalumab		
Arm D		CHT	CHT	CHT	CHT			

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