

2 ARM RANDOMIZED PHASE II TRIAL TO ASSESS THE FEASIBILITY AND EFFICACY OF A TREATMENT WITH DURVALUMAB (MEDI4736) A PDL1-INHIBITOR PLUS TREMELIMUMAB A CTLA-4- INHIBITOR IN COMBINATION WITH RADIOTHERAPY AND A TREATMENT WITH DURVALUMAB IN COMBINATION WITH RADIOTHERAPY AS FIRST-LINE THERAPY FOR PATIENTS WITH NON-RESECTABLE LOCALLY ADVANCED HPV NEGATIVE HNSCC – A COMPARISON WITH A HISTORICAL CONTROL GROUP-

AIO-assozierte Studie	
Studennummer/-Code:	AIO-KHT-0120/ass - DURTRERAD
Status:	Studie ist komplett geschlossen
Rekrutierungszeit:	von:10/2018 bis: 10/2022
Anzahl Zentren:	geplant: 4 initiiert: 3
Weitere Zentren:	sind auf Anfrage an den LKP möglich
Anzahl Patienten:	geplant: 120 eingeschlossen: 18
Letzte Aktualisierung	Oktober 2021

STUDY TYPE	interventionell
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CONDITION	Head and neck cancer
DESIGN	Phase II
INDICATION	Non-resectable locally advanced HPV negative HNSCC
OBJECTIVE(S)	The primary objective is to explore the feasibility and efficacy in terms of treatment discontinuation due to toxicity and in terms of 1-year progression free survival of a PDL1-Inhibitor plus a CTLA-4 Inhibitor in combination with radiotherapy vs a PDL1-Inhibitor in combination with radiotherapy as first-line therapy for patients with non-resectable locally advanced HNSCC in the poor prognostic subgroup.
INTERVENTION(S)	Patients in arm 1 will receive a single dose of durvalumab of 1500 mg administered on day 1, 14 days prior to initiation of the radiotherapy. Radiotherapy with 35 fractions over 7 weeks (administered as daily fractions of 2 Gy given 5 days every week for 7 weeks) will start on day 14.. On week 5, 9, 13 and 17 patients will receive durvalumab (1500 mg) and tremelimumab (75 mg) for up to 4 doses/cycles and then continue 1500 mg durvalumab q4w starting on week 21 to complete a total of 12 months of

	<p>therapy (overall 9 single doses durvalumab including the initial dose on day 1).</p> <p>Patients in arm 2 will receive durvalumab (1500 mg) q4w up to a total of 12 months of therapy (up to 13 doses in total).</p> <p>Radiotherapy with 35 fractions over 7 weeks (administered as daily fractions of 2 Gy given 5 days every week for 7 weeks) will start on day 14.</p>
BACKGROUND/RATIONALE	<p>Despite aggressive initial treatment, the risk of recurrence in HNSCC is high and locoregional recurrence is the predominant pattern of failure. Patterns of failure are changing and distant metastases have been increasingly documented in recent times.</p>
KEY EXCLUSION CRITERIA	<p>Participation in another clinical study with an investigational product during the last 3 months</p> <p>Prior or current anticancer treatment to the head and neck area (e.g. radical attempted or tumor reductive surgery, neo-adjuvant chemotherapy, EGFR inhibitors or radiotherapy).</p> <p>Any previous treatment with a PD1 or PD-L1 inhibitor, including durvalumab or an anti-CTLA4, including tremelimumab</p> <p>Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, 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:</p> <p>Patients with vitiligo or alopecia</p> <p>Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement</p> <p>Any chronic skin condition that does not require systemic therapy</p> <p>Patients without active disease in the last 5 years may be included but only after consultation with the study physician</p> <p>Patients with celiac disease controlled by diet alone</p> <p>History of primary immunodeficiency</p> <p>History of allogeneic organ transplant</p> <p>History of another primary malignancy except for</p> <p>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</p> <p>Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease</p> <p>Adequately treated carcinoma in situ without evidence of disease</p> <p>History of hypersensitivity to durvalumab and/or tremelimumab or any excipient</p> <p>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</p> <p>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.</p> <p>Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results</p> <p>Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control as described in the protocol from screening to 180 days after the last dose of</p>

	<p>durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period</p> <p>Distant metastasis</p> <p>Patients who are institutionalised by official order</p> <p>Mean QT interval corrected for heart rate (QTc) ≥ 470 ms calculated from 3 electrocardiograms (ECGs) using Fredericia's Correction</p> <p>Receipt of live attenuated vaccination within 30 days prior to study entry step 2 or within 30 days of receiving durvalumab or tremelimumab</p>
KEY INCLUSION CRITERIA	<p>Patients with locally advanced histopathologically confirmed HNSCC not candidate for primary surgical treatment</p> <p>Patients that are planned for radiotherapy</p> <p>No distant metastasis (M0)</p> <p>tumor tissue available for central testing</p> <p>Patients with HPV/p16 negative disease ($\leq 70\%$ positively stained cells) as determined by central testing</p> <p>Adequate normal organ and marrow function</p> <p>Measurable tumor according to RECIST</p> <p>Patients must be expected to complete the treatment.</p> <p>Age > 18 years at time of study entry</p> <p>Female patients must either be of non-reproductive potential or must have a negative serum pregnancy test upon study entry and be willing to use adequate contraceptive measurements as described in the protocol</p> <p>Non-sterilized males who are sexually active with a female partner of childbearing potential must be willing to use adequate contraceptive measurements as described in the protocol section 6.5.4</p>
STATISTICAL ANALYSIS	<p>The study is designed as an open-label randomized phase II trial with 2 experimental treatment arms.</p> <p>The primary endpoint is the 1-year progression free survival depicted as the 1-year in-field-progression-free survival and 1-year distant metastasis free survival.</p> <p>As raw data from the historical control are not available the value known from the literature for one year PFS (=30%) will be considered to be the true value in a 1-sample test. Assuming no censored cases the variance of the survival $S(t)$ can be estimated by the binomial variance $[S(t)*(1-S(t))]/n$ (Collet, Modelling survival data in Medical Research, page 25) where n is the sample size. A sample size estimation of the exact binomial test with $H_0 p = 0.3$ and $H_1 p = 0.5$ leads to $n = 54$ (type 1 error 0.025 one-sided, power 82%, software nquery). Assuming a 10% drop out rate, we include 60 subjects. The analysis will not be even driven but done when 54 subjects have reached one year follow up. This will be done separately in both experimental study arms. The Greenwood for the standard error of PFS(one year) will be used for analysis. If the lower bound of the 95% CI of $S(t)$ is above 0.30, H_0 (PFS(one year) = 0.30) will be rejected in favour of the alternative (PFS(one year) > 0.30).</p>
PARTICIPATING CENTERS	Charité Berlin, Universität Essen, Vivantes Berlin