Kopf-Hals Tumor – präoperative Therapie

Window of opportunity study of preoperative immunotherapy with atezolizumab (Tecentriq in local squamous cell carcinoma of the head and neck – an imCORE Study

AIO-assoziierte Studie

Studiennummer/-Code:	**AIO-KHT-0220/ass - PIONEER**		
Status:	rekrutierend		
Rekrutierungszeit:	von: Q3/2021	bis: Q1/2023	
Anzahl Zentren:	geplant: 3	aktuell initiiert: 1 (Essen)	aktiv rekrutierend: 1
Weitere Zentren:	leider nicht möglich		
Anzahl Patienten:	geplant: 20	aktuell eingeschlossen: 6	
Letzte Aktualisierung	31.03.2022		

STUDY TYPE	phase II
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SPONSOR	University Hospital Essen Hufelandstraße 26 45147 Essen
CONDITION	Histologically proven resectable squamous cell carcinoma of the head and neck (SCCHN)
DESIGN	International, open-label, multicenter, single arm non-randomized window of opportunity study
INDICATION	Resectable squamous cell carcinoma of the head and neck (SCCHN)
OBJECTIVE(S)	**Primary objectives** • Effect of atezolizumab on tumor-infiltrating immune cells in resectable SCCHN • Feasibility of preoperative short time immunotherapy
INTERVENTION(S)	▪ atezolizumab 1200 mg intravenously (i.v.) on day 1 Resection will be perfomed on day 21 to 28.

OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	**Secondary objectives** • Safety of preoperative short time immunotherapy and assessment of postoperative complication rates • To assess dynamics in tumor immunity • Exploratory analyses of predictive biomarker by gene and protein expression to establish correlation with pathological response • Characterization of changes in frequency and numbers of circulating immune cells • Resectability after immunotherapy • Influence of immunotherapy on histo-morphological assessment • (optional) set up of a registry for follow up of patients and subsequent documentation of relapse free survival (RFS) rate • and overall survival (OS) rate **Exploratory objectives** • Clinical response • Pathological regression
BACKROUND/RATIONALE	In patients with SCCHN, the time period between primary biopsy and resection represents an ideal window for neoadjuvant therapeutic studies. Furthermore, SCCHN tumors amenable to surgical resection with curative intent can yield large quantities of tissue, far beyond the requirements for pathological analysis and clinical staging, providing an invaluable resource for translational research, which would not be possible with the limitations of small biopsies from patients with metastatic disease. Window of opportunity studies assessing the potential anti-tumoral biological effects of novel therapeutic agents administered for a short-duration (2 – 4 weeks) in the preoperative setting constitute an efficient proof of concept strategy, allowing to rapidly evaluate and prioritise novel CIT. Pharmacodynamic and correlative studies on tumor tissue obtained pre-, on- and post-treatment can provide important insights into the mechanisms of action, differences in activity and potential predictors of response and resistance to define the optimal patient population. While a considerable number of immunotherapiesare currently in clinical development in SCCHN, most studies lack a thorough translational research program that would allow to better understand the dynamics of immune cell populations leading to an effective antitumor response. The relatively large volume of tissue available at resection allows performing a standardized series of assays with state-of-the-art technologies to interrogate the immunological consequences of immunotherapies in SCCHN. In addition, serial analyses of peripheral immune cell populations will assess the impact on systemic immune responses. This study will assess the importance of targeting mechanisms of immune escape through immune cell priming and activation, tumor infiltration, and/or recognition of tumor cells for elimination.
KEY EXCLUSION CRITERIA	**Exclusion criteria** 1. Evidence of metastatic disease

	2. Prior treatment with immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies 3. Treatment with investigational therapy within 28 days prior to initiation of study treatment 4. Any anti-cancer therapy, including chemotherapy or hormonal therapy, within 4 weeks prior to initiation of study treatment 5. Bilateral pleural effusion 6. Treatment with systemic immunosuppressive medications (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) within 2 weeks prior to Day 1, Cycle 1. Note: The use of inhaled corticosteroids, physiologic replacement doses of glucocorticoids (i.e. for adrenal insufficiency) and mineralocorticoids (e.g. fludrocortisone) is allowed 7. Treatment with a live-attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during the course of the study, and for 5 months after the last dose of atezolizumab 8. Treatment with systemic immuno-stimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or five half-lives of the drug (whichever is longer) prior to initiation of study treatment 9. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins; known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or to any component of the atezolizumab formulations 10. Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the course of the study 11. Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium or Ca > 12 mg/dL or corrected serum calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab 12. Uncontrolled tumor-related pain. Patients requiring narcotic pain medication must be on a stable regimen at study entry 13. Pregnant and lactating women 14. Acute toxicities from previous therapy that have not resolved to Grade ≤ 1, except for alopecia 15. Infections a. Positive human immunodeficiency virus (HIV) test Known HIV+ patients may be included but must have: A stable regimen of highly active anti-retroviral therapy (HAART) No requirement for concurrent antibiotics or antifungal agents for the prevention of opportunistic infections A CD4 count above 250 cells/mcL and an undetectable HIV viral load on standard PCR-based tests b. Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test at screening Patients with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test at screening followed by a negative HBV DNA test, are eligible for the study. The HBV DNA test will be performed only for patients who have a positive total HBcAb test. c. Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test followed by a positive HCV ribonucleic acid (RNA) test at screening.

	The HCV RNA test will be performed only for patients who have a positive HCV antibody test. d. Active tuberculosis e. Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia f. Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment g. Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study. 16. Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, anti-phospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 12.1 for a more comprehensive list of autoimmune diseases and immune deficiencies) with the following exceptions: - Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study - Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., no psoriatic arthritis) may be eligible provided that they meet the following conditions: – Rash must cover less than 10% of the body surface area. – Disease is well controlled at baseline and only requires low potency topical steroids. – There are no acute exacerbations of underlying condition within the last 12 months (e.g., not requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency, or oral steroids) 17. Adverse events (AE) related to any previous radiotherapy, chemotherapy, targeted therapy or surgical procedure that have not reolved to Grade ≤1, except alopecia (any grade) and Grade 2 neuropathy 18. Prior allogeneic stem cell or solid organ transplantation 19. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computer tomography (CT) scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted. 20. Active malignancy or a prior malignancy within the past 3 years. Patients with completely resected basal cell carcinoma, cutaneous squamous cell carcinoma, cervical carcinoma in-situ, breast carcinoma in-situ, and patients with isolated elevation in prostate-specific antigen in the absence of radiographic evidence of metastatic prostate cancer are eligible for the study. 21. Any Grade ≥ 3 hemorrhage or bleeding event within 28 days of Day 1 of Cycle 1 22. Increased corrected QT (QTc) interval (QTc > 470 ms)

	23. Family history of long QT syndrome or other risk factors for torsades de pointes 24. History of stroke, reversible ischemic neurological defect, or transient ischemic attack within 6 months prior to Day 1 25. Significant cardiovascular disease, such as New York Heart Association (NYHA) cardiac disease (Class II or greater), myocardial infarction within 6 months prior to Cycle 1 Day 1, severe cardiac arrhythmia requiring medication or severe conduction abnormalities, unstable arrhythmias, acute coronary syndromes (including unstable angina), or history of coronary angioplasty/stenting/bypass grafting within past 6 months. a. Patients with a known left ventricular ejection fraction (LVEF) < 40% will be excluded b. patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF < 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate 26. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications 27. Criteria which in the opinion of the investigator preclude participation for scientific reasons, for reasons of compliance, or for reasons of the subject's safety Participation in another clinical study within the last 3 months prior to inclusion or simultaneous participation in other clinical studies with an exception of studies evaluating radiological imaging.
KEY INCLUSION CRITERIA	**Inclusion criteria** 1. 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 has to be obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening examinations and laboratory results must have been obtained within 14 days before first study drug administration (initial tumor imaging: within 28 days before first study drug administration). 2. Only patients for whom sufficient tumor material to be judged by the local investigator and which is of adequate quality can be included into the trial. Please refer to section 6.5 for further details on quantity and quality of tumor samples. 3. Histologically or cytologically proven SCCHN (cT1-4a, cN0-3, cM0) that is amenable to surgical resection with curative intent based on the decision of the local multidisciplinary tumorboard. 4. Patients with relapse after primary radio(chemo)-therapy are allowed if a salvage surgery is possible (maximum 20% in each arm). Patients should have recovered from the effects of radiation: AE/sequelae should resolves to ≤ grade 2 (no minimum recovery period required). 5. Male or female, 18 years of age or older on day of signing informed consent 6. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1 7. Life expectancy >12 weeks

	8. Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment: • Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L without granulocyte colony-stimulating factor support • Lymphocyte count $\geq 0.5 \times 10^9$/L • Platelet count $\geq 100 \times 10^9$/L without transfusion • Hemoglobin $\geq$ 90 g/L o Patients may be transfused to meet this criterion but patients in need of chronic or repeated RBC transfusion should be discussed with the sponsor before. • Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 2.5 \times$ upper limit of normal (ULN) • Serum bilirubin $\leq 1.5 \times$ ULN with the following exception: o Patients with known Gilbert disease: direct serum bilirubin level $\leq$ ULN for patients with total bilirubin levels>1.5 ULN. • Serum creatinine $\leq 1.5 \times$ ULN or Creatinine clearance ≥30 mL/min (calculated using the Cockcroft-Gault formula) • Serum albumin $\geq$ 2.5 g/dL • International normalized ratio (INR) or activated Partial Thromboplastin Time (aPTT) $\leq 1.5 \times$ ULN (This applies only to patients who do not receive therapeutic anticoagulation; patients receiving therapeutic anticoagulation (such as low−molecular weight heparin or warfarin) should be on a stable dose 9. Women of childbearing potential: • Should have a negative urine or serum pregnancy test within 14 days prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. • Agreement to remain abstinent (refrain from heterosexual intercourse) or use a non-hormonal contraceptive method with a failure rate of $<$ 1% per year during the treatment period and for at least 5 months after last study drug administration • A woman is considered to be of childbearing potential if she is post-menarchal, has not reached a postmenopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). • Examples of contraceptive methods with a failure rate of $<$ 1% per year include bilateral tubal ligation, male sterilization, and copper intrauterine devices. • The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception. For men: with female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 5 months after the last dose in arm A and B to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

<table>
<tr><td>OUTCOME(S)</td><td>Primary variables
Percentage of patients with at least 2-fold increase of GzmB+/CD8+ T cells by immunohistochemistry (IHC) after 1 administration of atezolizumab between pre-treatment biopsy specimens and post-treatment resection specimens
Number of patients with completion of pre-operative immunotherapy and resection of SCCHN</td></tr>
<tr><td>STATISTICAL ANALYSIS</td><td>At least 20 consecutive patients will be included in the study.Interims analysis for safety will be done after 6 patients were resected. In addition if the first 3 patients will have a delay in surgery for more than 3 weeks an additional safety analysis will be done in these patients and the study will be temporarily paused. All primary and secondary analyses are based on pre-vs. post-treatment comparisons.
The primary objective of this study is to determine the change in tumor infiltrating GzmB+/CD8+ T cells after 1 cycle of preoperative atezolizumab.
The fold-change (FC) of the immune cells between pre-treatment biopsy and post-treatment resection specimens is the primary observable. It appears reasonable to assume log(FC) to be normally distributed (Wei et al. 2004). A change of the mean value of FC by one unit of its a-priori unknown distribution width, i.e. an effect of size 1, is deemed to be a minimum result size we would like to capture with a probability of 80% (power = 0.8). For this study we deem a significance level of α = 0.05 to be appropriate.
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Summary of the parameters:
<table><tr><th>Parameter</th><th></th></tr><tr><td>effect size</td><td>1</td></tr><tr><td>α</td><td>5%</td></tr><tr><td>β</td><td>20%</td></tr><tr><td>power (1- β)</td><td>80%</td></tr><tr><td>test</td><td>two-sided, one group</td></tr></table>
The primary endpoint will be positive if the 2-fold increase of GzmB+/CD8+ T-cells is observed in ≥30% of patients..

The sample size calculation for these parameters gives a minimum of n = 17 evaluable study participants in each arm, in order to detect a true effect of size one with 80% probability and only a 5% chance of a signal to be false positive. Assuming 10% attrition and non-evaluability, we estimate our need to enroll at least 20 patients to ensure 17 evaluable patients.

Patients could be included after prior radio-(chemo) therapy in case of salvage surgery. A maximum of 20% of patients with previous radio-(chemotherapy) will be included in each arm.

Co-primary endpoint will be the feasibility of a pre-operative short time immunotherapy in patients with resectable SCCHN. The endpoint will be positive if 15 out of 17 evaluable patients (>85%) have completed the pre-operative immunotherapy and have been resected.

All other parameters and secondary endpoints will be evaluated in an explorative or descriptive manner, providing means, medians, ranges, standard deviations and/or confidence intervals. If any p values are calculated (e.g. in subgroup comparisons), they are considered to be descriptive and will be presented explicitly without referring to hypotheses or a significance level. Usually, no error adjustment for multiple testing will be</td></tr>
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	performed. Thus the p values will reflect the comparison-wise error and not the experiment-wise error.
SAMPLE SIZE	20
TRIAL DURATION	**For the individual patient:** Approximately 3 months (up to 2 weeks screening, 3 weeks study therapy and follow up visit / end of study visit 37±10 days after standard of care surgery. An optional registry study will be launched for additional follow up (up to 36 months after last study drug administration) **Planned study schedule** First Patient In Q3/2021 Last Patient In Q2/2023 Last Patient EoT Q2/2023 LPLV Q4/2023 DBL Q2/2024 End of study Q2/2024
PARTICIPATING CENTERS	Two centres in Germany (University Medicine Essen, West German Cancer Center, National Center for Tumor Diseases (NCT) Heidelberg) and one center in The Netherlands (Netherlands Cancer Institute, Antoni Van Leeuwenhoek Hospital Amsterdam)
FURTHER CENTERS DESIRED?	no
NUMBER of PATIENTS	20
CURRENT NUMBER of PATIENTS	2
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