

AIO-KHT-0115: A randomized phase II study comparing pembrolizumab with methotrexate in elderly, frail or cisplatin-ineligible patients with head and neck cancers (ELDORANDO)

AIO-Studie

Studiennummer/-Code:	AIO-KHT-0115 - ELDORANDO	
Status:	Rekrutierung vorzeitig beendet am 19.12.2019	
Rekrutierungszeitraum	2017 – 2020+	
Zentren:	geplant: 10	initiiert: 10
Patienten:	geplant: 100 rand.	aktuell eingeschlossen: 47 rand.
Weitere Zentren:	aktuell nicht erforderlich	
Letzte Aktualisierung	Oktober 2020	

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Study design	The study is designed as an open-label, randomized, prospective, multicenter, phase II study of pembrolizumab or methotrexate in elderly, frail or cisplatin-ineligible patients with squamous carcinoma of the head and neck (HNSCC)
Indication	Squamous carcinoma of the head and neck (SCCHN)
Proposed countries / Total number of sites	Germany Number of sites total: 10
Primary objective	To assess antitumor activity of pembrolizumab in SCCHN.
Secondary objectives	To assess quality of life (QoL), predictive biomarkers, and efficacy of pembrolizumab in SCCHN.
Exploratory objectives	To assess: <ul style="list-style-type: none"> • predictive value of PD-L1 expression • exploration of molecular-genetic pro-inflammatory markers in archival tumor specimen
Planned sample size	A total of 100 patients will be randomized, 50 per treatment arm, Recruiting not started yet.
Number of patients	45 randomized patients (10/2019)
Inclusion criteria	<ol style="list-style-type: none"> 1. Cooperation and willingness to complete all aspects of the study including participation in the translational research 2. Signed and dated written informed consent must be given prior to study inclusion 3. Histological or cytological confirmed recurrent or metastatic squamous cell carcinoma of the head and neck (HNSCC) not amenable to local therapies 4. Progressive disease at study entry 5. At least 1 measurable lesion according to RECIST 1.1 6. No previous systemic treatment for metastatic disease 7. Not eligible for cisplatin-based chemotherapy, defined as: <ul style="list-style-type: none"> - ECOG 2 and/or

	<ul style="list-style-type: none"> - calculated CrCl <60 mL/min (measured by MDRD) 8. Age ≥18 years 9. ECOG performance status 0 - 2 10. Brain metastases require completion of local therapy with discontinuation of steroids prior to start of treatment 11. If of childbearing potential, willingness to use effective contraceptive method (double barrier method) for the duration of the study and 2 months after last dose 12. Adequate bone marrow function, liver and renal function: <ul style="list-style-type: none"> a. Absolute neutrophil count ≥ 1.5 x 10⁹/L b. Thrombocytes ≥ 100 x 10⁹/L c. Hemoglobin ≥ 9 g/dL d. INR ≤ 1.5 and PPT ≤ 1.5 x upper limit during the last 7 days before therapy e. Bilirubin < 1.5 x lower limit and f. AST (GOT) and ALT (GPT) < 3 x lower limit (5 x lower limit in case of liver metastases) 13. Tumor block must be available at study inclusion for central pathology testing
Exclusion criteria	<ul style="list-style-type: none"> 1. Live expectancy less than 3 months 2. Nasopharynx carcinoma 3. Anticancer treatment during the last 30 days prior to start of treatment, including systemic therapy, radiotherapy or major surgery 4. Participation in a clinical trial within the last 30 days prior to study treatment 5. History of allogeneic tissue/solid organ transplant 6. History of pneumonitis that has required oral or i.v. steroids 7. Evidence of interstitial lung disease 8. Minor surgery ≤ 24 hours prior first dose of study treatment 9. Symptomatic acute cardiovascular or cerebrovascular disease 10. Known active HBV, HCV or HIV infection 11. Has any other active infection requiring systemic therapy. 12. Patients with active tuberculosis 13. Prior therapy with an anti-programmed cell death protein 1 (anti-PD-1), anti-PD-L1, anti-programmed cell death-ligand 2 (anti-PD-L2), anti-CD137 (4-1BB ligand, a member of the Tumor Necrosis Factor Receptor [TNFR] family), or anti-Cytotoxic T-lymphocyte-associated antigen-4 (anti-CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) 14. A diagnosis of immunodeficiency or patient is receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. 15. Patient has had a prior monoclonal antibody, which does significantly interfere with the immune system or which does have a systemic therapeutic effect on the tumor within 4 weeks prior to randomization 16. Patient has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events any toxicities due to agents administered more than 4 weeks earlier. [Subjects with ≤ Grade 2 neuropathy or alopecia are an exception to this criterion and may qualify for the study.] 17. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study 18. Has received a live vaccine within 30 days prior to the first dose of trial treatment. 19. Has known hypersensitivity to methotrexate or pembrolizumab or any of constituent of the productsits.

	<p>20. Other active malignancy requiring treatment</p> <p>21. Lactating or pregnant women, women of child-bearing potential who do not agree to the usage of highly effective contraception methods (allowed methods of contraception, meaning methods with a rate of failure of less than 1% per year are implants, injectable contraceptives, combined oral contraceptives, intrauterine pessars (only hormonal devices), sexual abstinence or vasectomy of the partner). Women of childbearing potential must have a negative pregnancy test (serum β-hCG) at Screening.</p> <p>22. Any psychiatric illness that would affect the patient's ability to understand the demands of the clinical trial</p> <p>23. Patient has already been recruited in this trial (does not include screening failures)</p> <p>24. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.</p> <p>25. 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].</p>
Randomization criteria	<p>Randomization will be performed 1:1</p> <p>Strata:</p> <ul style="list-style-type: none"> • ECOG performance status (PS 0-1 vs. 2) • HN-CCI index (<2 vs. \geq2)
Investigational drug	Pembrolizumab at fixed dose
Treatment phase	<p>Arm A: Pembrolizumab 200 mg q3w i.v. until disease progression or non-tolerable toxicity (maximum 2 years)</p> <p>Arm B: Methotrexate (MTX) 40 mg/m² weekly i.v. until disease progression or non-tolerable toxicity (maximum 2 years)</p>
Study rationale	<p>Standard of care (SOC) for palliative chemotherapy for SCCHN consists of a platinum-combination, mostly combined with cetuximab. However, platinum-therapy may not apply to a number of patients because of age (approx. 30% >70y.) or comorbidities (36%) [Bøje et al. Radiother Oncol. 2014 Jan;110(1):91-7]. This fraction of patients is underrepresented in clinical trials. It remains a challenge to define the optimal palliative treatment benefit/risk ratio in the clinic and prospective data is scarce in order to guide the choice of the clinician. Hence, no SOC is defined and treatment recommendations for this cohort of patients vary among treating physicians (Mountzios et al. Head Neck Oncol. 2013 Feb 27;5(3):27).</p> <p>Comorbidities have been shown to be associated with a poor OS in SCCHN (Sanabria et al. Ann Surg Oncol. 2007 Apr;14(4):1449-57). The EORTC QLQ-H&N35 questionnaire has been shown to be prognostic in localized disease (Osthus et al. Oral Oncol 47(10): 974-979, 2011). The ELAN-UNFIT trial tests the role of cetuximab or methotrexate in elderly patients (>70 years) (NCT01884623) using a composite endpoint TTFS for efficacy and tolerability (Guigay J; ASCO 2014). However, age per se does not seem to affect treatment outcome, underscoring the relevance to differentiate fit and frail patients rather than an age limit for treatment selection (Mountzios et al. Head Neck Oncol. 2013 Feb 27;5(3):27).</p> <p>The Charlson Comorbidity Index (CCI) detected poor tumor specific survival in SCCHN with increasing comorbidities (Singh et al. Laryngoscope. 1997 Nov;107(11 Pt 1):1469-75). Based on these results an adapted version has been created for localized SCCHN - the HN-CCI, which includes 6 prognostic items: congestive heart failure, cerebrovascular disease, chronic pulmonary disease, peptic ulcer disease, liver disease, and diabetes (Bøje et al. Radiother Oncol. 2014). This data underscores the relevance of non-cancer associated mortality in SCCHN patients. A more recent publication identified age, comorbidity, tumor recurrence, and secondary primaries to be prognostically relevant (Kwon et al. Ann Oncol 2014), emphasizing comorbidity as a key</p>

	<p>prognostic element. Clearly, novel therapeutic strategies are needed in order to deliver optimal palliation in patients who are not fit for platinum treatment.</p> <p>In bladder cancer, The EORTC 30986 study established an adapted regimen as a new standard in patients with WHO PS of 2 and/or impaired renal function (GFR >30 but <60 mL/min) (De Santis JCO 2012), which may serve as a backbone for the definition of cisplatin-ineligible patients.</p> <p>Criteria for cisplatin-ineligibility:</p> <ul style="list-style-type: none"> • ECOG 2 and/or • CrCl <60 mL/min <p>The modulation of the immune system has been identified as a promising treatment approach in cancer patients. SCCHN has been shown to respond to checkpoint inhibitors in early clinical trials and have triggered a number of phase III studies, which explore PD-1 or PD-L1 inhibitors in patients with failure after platinum-based therapy. Pembrolizumab showed an ORR of 19.6%, irrespective of HPV status in PD-L1 positive SCCHN (Seiwert et al. ASCO 2014). Overall, tolerability remained good in this study, with an AE incidence of 58% (all grades), and 17% grade 3/4 AEs.</p> <p>We test the hypothesis that pembrolizumab is superior to methotrexate treatment in patients unfit to receive cisplatin-based chemotherapy.</p>
<p>Rationale for sample size and tests to be used</p>	<p>In order for a chi-squared test to detect a difference of 25% vs. 50% (Methotrexate vs. Pembrolizumab) in the 1-year overall survival between the two treatment arms with 80% power and a one-sided significance level alpha=5%, 46 evaluable patients per arm are needed. Hence, a total of 100 patients will be enrolled (incl. 9% uninformative drop-outs).</p>
<p>Interim analyses</p>	<p>No interim analyses planned.</p>
<p>Statistical analysis</p>	<p>Primary endpoint and hypothesis: 1-year overall survival rate We test the hypothesis that with regard to 1-year-OS, pembrolizumab is superior to methotrexate treatment in patients unfit to receive cisplatin-based chemotherapy (50% Arm 1 (Pembrolizumab) vs. 25% Arm 2 (MTX)).</p> <p>Key secondary:</p> <ul style="list-style-type: none"> • Time to failure of strategy (TTFS) at 1 year, defined as death, progressive disease (PD), treatment discontinuation (due to toxicity) or deterioration of Instrumental Activities of Daily Living (IADL score) by 2 points • objective response rate (ORR) according to modified RECIST 1.1 <p>other secondary:</p> <ul style="list-style-type: none"> • progression free survival (PFS) • median overall survival (OS) • ORR according to RECIST 1.1 • duration of response • duration of treatment beyond progression • treatment discontinuation rate • safety and tolerability <p>Exploratory:</p> <ul style="list-style-type: none"> • predictive value of PD-L1 expression • prognostic value of tumor shrinkage • QoL response, defined as improvement of 5-10 points in QLQC30 and HN35

Study plan	Study start (FPI): Q3/2017 Recruitment end (LPI): Q3/2020 (likely to be extended) Reaching the primary endpoint: Q3/2021 Planned analysis of primary endpoint: Q4/2021 Publication date: Q3/2021 End of maximum treatment period for last patient [24 months]: Q3/2022 Follow up period for the last patient: 12 months Study end (LPLV): Q3/2023 Data base lock: Q3-Q4/2024 Completion of Clinical Study Report (CSR): Q2/2023 Publication date: Q1/2024
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