

Abbreviated Title	PACE ACE
Trial Phase	II
Clinical Indication	Recurrent and/or metastatic head and neck cancer after checkpoint inhibitor failure
Trial Type	Interventional prospective, multicenter, single-arm, phase II AIO-associated trial; 7 study sites in Austria (5) and Germany (2)
Route of administration	Intravenous
Study treatment	Cetuximab intravenously 400mg/m <sup>2</sup> loading dose followed by 250mg/m <sup>2</sup> weekly in combination with paclitaxel 175mg/m <sup>2</sup> three weekly for up to six cycles followed by biweekly cetuximab maintenance 500mg/m <sup>2</sup>
Trial Blinding	Unblinded open label
Treatment Groups	1
Number of patients	50
Sample size calculation	<p>The primary objective of this Phase II study is to evaluate the proportion of patients responding to cetuximab plus paclitaxel. An exact binomial test with a nominal 0.025 one-sided significance level will have 83.6% power to detect the difference between the null hypothesis of an ORR <math>\pi_0 \leq 0.10</math> (assumed based on Checkmate 141 trial and Keynote 040 trial; SoC arm) and the alternative hypothesis of an ORR <math>\pi_A \geq 0.25</math> (assumed based on Saleh et al. <i>J Clin Oncol</i> 2018)<sup>23</sup> when the sample size is 50.</p> <p>If there are 10 or more successes (CR or PR) out of the 50 patients the study is considered to be a success and the null hypothesis will be rejected in favour of the alternative hypothesis of a higher Overall Response Rate.</p>
Estimated enrollment period	21 months (Estimated end date 31.12.2023)
Study Rationale	<p>The pivotal randomized phase III KEYNOTE 048 study evaluated the efficacy of pembrolizumab alone or in combination with platinum/5-FU compared to the EXTREME (SoC) regimen in untreated R/M SCCHN patients. The median OS for pembrolizumab+/-chemotherapy was superior to SoC in CPS<math>\geq</math>1 patients. Based on this practice changing results pembrolizumab +/- chemotherapy was approved in this setting worldwide.</p> <p>From the clinical point of view, however, the optimal management of patients progressing on or after immune checkpoint-inhibitor therapy (CPI) is still a challenge. While it is well known that both taxanes and cetuximab exert clinical activity both in the first line, but also in the second line setting after failure of conventional platinum-based therapy, the activity of these drugs after CPI failure has not been studied in a prospective trial so far. Interestingly, it has been demonstrated that taxanes also interact with the immune system separately from their cytotoxic effects. Likewise, cetuximab modulates the immune response besides its activity towards the EGFR signalling pathway and</p>

	<p>retrospective data demonstrated promising response rates with chemotherapy +/- cetuximab in this population. Although the underlying molecular mechanism is still unclear, it is tempting to speculate that checkpoint inhibitor mediated modulation of the tumor immune landscape can re-sensitize the tumor to conventional chemotherapy (taxane) plus cetuximab in SCCHN patients.</p> <p>In summary the combination of paclitaxel and cetuximab after CPI failure seems to be an interesting approach as a salvage therapy in recurrent and/or metastatic SCCHN patients, might boost the immune response and exert superior anti-tumor activity.</p>
Objectives	<p><b>Primary objective</b></p> <ul style="list-style-type: none"> <li>• To evaluate the confirmed Overall Response Rate (CR/PR) rate according to RECIST V 1.1, in patients treated with cetuximab plus paclitaxel for recurrent and/or metastatic SCCHN after pembrolizumab based first-line therapy</li> </ul> <p><b>Secondary objectives</b></p> <ul style="list-style-type: none"> <li>• To describe Best Overall Response categories (CR, PR, SD, PD) according to RECIST V 1.1, in patients treated with cetuximab in combination with paclitaxel in patients diagnosed with recurrent and/or metastatic SCCHN after pembrolizumab based first-line therapy</li> <li>• To describe duration of response</li> <li>• To evaluate changes in health-related quality-of-life assessments from baseline in patients with R/M SCCHN using the EORTC QLQ C-30 and EORTC QLQ-H&amp;N35 questionnaires.</li> <li>• To assess median Overall Survival (OS) and Progression Free Survival (PFS) in this patient population</li> <li>• To evaluate the safety of cetuximab in combination with paclitaxel in patients diagnosed with recurrent and/or metastatic SCCHN.</li> </ul>
Selection criteria	<p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• The patient has provided written informed consent prior to any study-related procedure.</li> <li>• The patient is at least 18 years of age</li> <li>• Histologically proven locally advanced unresectable, recurrent and/or metastatic squamous cell carcinoma of the oropharynx, hypopharynx, larynx or oral cavity not amenable for salvage surgery</li> <li>• p16 status has to be determined for oropharyngeal carcinomas</li> <li>• Documented progressive disease based on investigator assessment according to RECIST 1.1, following receipt of a pembrolizumab based regimen given as first line therapy in the platinum sensitive setting</li> </ul>

(i.e.  $\geq 6$  months since last platinum exposure) for recurrent and/or metastatic SCCHN

- Measurable disease according to RECIST 1.1.
- The patient has a life expectancy of at least 3 months.
- Has a performance status of 0, 1 or 2 on the ECOG Performance Scale
- Female patient of childbearing potential should have a negative urine or serum pregnancy 24 hours prior to treatment initiation if the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
- Female patients of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study until 120 days after the last dose of study medication. Patients of childbearing potential are those who have not been surgically sterilized or have not been free from menses for  $> 1$  year.
- Male patients should agree to use an adequate method of contraception starting with the first dose of study therapy until 120 days after the last dose of study therapy.
- Demonstrate adequate organ function as defined in table 1, all screening labs should be performed within 14 days of treatment initiation.

**Exclusion criteria:**

- Prior taxane therapy is not allowed except as part of induction therapy for locally advanced disease (completed at least 6 months before study entry)
- Prior cetuximab therapy is not allowed except as part of either induction therapy or in combination with radiotherapy treatment for locally advanced disease (completed at least 6 months before study entry)
- Patients with nasopharyngeal carcinomas or salivary glands cancers
- Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy within 4 weeks of the first dose of treatment.
- Has a diagnosis of immunodeficiency including a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
- Has known active Hepatitis A/B or Hepatitis C
- Has had prior pembrolizumab within 1 week prior to study day 1 or who has not recovered (i.e., recovery to  $\leq$  Grade 1 or baseline grade

	<p>prior to pembrolizumab) from (immune- related) adverse events other than endocrine side effects.</p> <ul style="list-style-type: none"> <li>• Has had prior chemotherapy or radiation therapy within 2 weeks prior to study day 1 or who has not recovered (i.e., recovery to <math>\leq</math> Grade 1 or baseline grade prior to chemotherapy or radiation) from adverse events due to a previously administered agent.</li> <li>• Has had chemotherapy, targeted therapy or investigational drugs after checkpoint inhibitor failure for second line therapy.</li> <li>• Has had prior pembrolizumab in the platinum resistant setting (&lt;6 months after last platinum exposure).</li> <li>• Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.</li> <li>• Has an active infection requiring systemic therapy.</li> <li>• Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating investigator.</li> <li>• Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.</li> <li>• Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit until 120 days after the last dose of trial treatment.</li> </ul>
Duration of Participation	Each patient will participate in the trial until death, withdrawal or loss-to-follow-up from the time the patient signs the Informed Consent Form (ICF) until the final contact. Study treatment will continue until disease progression is confirmed.
Principle Investigator	Assoc.Prof. PD. Dr.Thorsten Füreder Department of Medicine I, Division of Oncology Medical University of Vienna
Sponsor	Medical University of Vienna Spitalgasse 23 1090 Vienna, Austria
Protocol Version	5.0; 30.11.2021