Answering Reviewers

First of all, we want to thank Reviewer#1 for the excellent and constructive comments to improve our manuscript. A careful edition was done considering your recommendations. We have separated the topics for a more readable response.

Reviewer #1: Very recently, a comparison of TPEx and EXTREME was published (it should be cited).

> RESPONSE: Thanks for this observation. We had cited the previous publication of this trial. Now we updated the data and citation of the GORTEC 2014-01 TPExtreme study.

Reviewer #1: How do you explain that your ORR was >10% better than that of others'? The frequency of grade 3/4 events was also very low. Presumably, it was a very selected group of patients (private care centers - with unusual, unrevealed premedications, etc.) rather than a real-world study.

> RESPONSE: Notably, compared to other studies (Table 5), our cohort showed a slightly higher response (62.5%) and a lower frequency of grade 3 (25%) and 4 (0%) adverse events.
> Concerning the toxicity findings, it could be explained by a selection bias since all patients were treated in academic centers by specialized head and neck oncologists with experience in using this schema. This may have mitigated potentially non-serious toxicity receiving early symptomatic treatment and preventing a worsening of the event. Of note, Even et al.[21] (Table 5) also report a very low grade 3 and 4 adverse events (17% and 10%, respectively) in 30 patients treated with TPEx in the well-known experienced Head and Neck Department of the Gustave Roussy Institute.
>
> On the other hand, as you timely pointed, the entire population was treated in private care centers with proper access to high-quality health care. Most of our patients had ECOG 0 (58.3%), compared to 26% in the GORTEC study[14] or 32% in the GORTEC 2014-01 TPExtreme trial[19]. Again, a selected population may have been impacted in the higher ORR. Particularly, in concordance with our

findings, the Even et al.[21] retrospective study also showed a superior ORR (87%) compared to the others phase 2 clinical trials.
Following these important observations by Reviewe#1, we explain this potential selection bias in the limitation part of the manuscript (page 10, line 26-30).

Reviewer #1: Why the PFS was not tested for the other variables (similarly to the type of response)? I suggest to reinvestigate PFS at least according to dose changes, tumor site, metastatic vs. advanced, previous treatments, AEs. Moreover, the median follow-up will be longer and the OS can also be reevaluated (e.g. according to the type of immunotherapy).

RESPONSE: following these proper suggestions, we performed extra analyses according to different clinicopathological characteristics and previous treatments.

Relevant prognostic factors were stratified by univariate Cox regression models for first-line TPEx PFS in a new Table 4. Different comparisons were performed including ECOG, primary site, the extent of disease at TPEx initiation, relapse-free survival of the primary treatment, previous treatments, treatment interruption/ discontinuation/dose reduction, and adverse events. For a better illustration of these results, Figures 4 and 5 were added.

Following Reviewer#1 suggestion, we performed the Kaplan–Meier curve for overall survival (Fig. 6). Among the 14 patients who experienced disease progression on TPEx, 13 received second-line treatment with immunotherapy (pembrolizumab [n=9] and nivolumab [n=4]). For that reason, we could not compare the subsequent lines (immunotherapy vs. other treatments). When comparing the OS among patients on Pembro vs. nivolumab, no difference was observed (P-value 0.892).
It should be highlighted that most of our analyses were performed based on PFS since the follow-up for OS was still immature.

Reviewer #1: Try to find out what were the characteristics of a real-world treatment cohort, which differed compared to trials.

RESPONSE: We carefully reviewed the FDA framework eligibility criteria for a Real-World Evidence (RWE) study[1]. Although observational clinical studies might be a valid way to generate RWE, they must provide data from a representative sample of the population. In this context, our study has a multicenter retrospective observational design; however, since it was carried out

[1] Framework for FDA's Real-World Evidence Program. December 2018

exclusively in private centers, it should be noted that a potential selection bias may be underlying. For this reason, after having adequately reviewed all these criteria and taking into account what was underlined by Reviewer#1, we decided to change the design to a "multicenter retrospective cohort".

Reviewer #1: I could not find the institutional ethical approvals for this investigation.

RESPONSE: The Institutional Review Board Approval Document was included in the submitted files. We kindly resubmitted it.

Reviewer #1: Minor Table 1: p16 can be omitted. Table 3: report separately grades 3 and 4. Fig. 1-3: use dot for decimal numbers at y axis. For a better comparison of TPEx trials make a table.

RESPONSE: Following this timely suggestion, p16 status was omitted from Table 1 as it only refers to oropharyngeal carcinomas.

We change the adverse event report separately by grades 3 and 4 (Table 3) since as the reviewer properly pointed, it better describes the toxicity profile. Of note, no patient experienced grade 4 toxicity. This important observation was also remarked in the abstract and the main text.

We changed the dot for decimal numbers at the y axis of all the figures.

We added Table 5 for a more appropriate comparison of TPEx studies.

Re-Reviewer' comment:
I accept your responses, except that about ethical approval. 1. The ethical approval should be included into the text, which I had not found. 2. I don't know what the requirements for multicentre testing are in your country, but you will probably need to get the approval of the national committee. Ethical approval of a single institution is not enough.

RESPONSE: We have sent all the Institutional Reviewer Board approvals.