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LETTER TO THE EDITOR

# In reply to Swain et al.: Re-evaluation of updated meta-analysis including trials RTOG 1016 and De-ESCALaTE

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We would like to thank Swain et al. [1] for their constructive comments considering our meta-analysis [2]. In their correspondence, authors [1] concluded that there are several shortcomings with the reported article that merit further discussion. One of them was inappropriateness of combining data from prospective and retrospective studies, according to Cochrane handbook for systematic reviews of interventions. While we agree that it is preferable to separately analyse prospective and retrospective data when conducting meta-analysis, in special circumstances, combining different types of studies may be performed. In our meta-analysis, randomised controlled trials (RCTs) and retrospective studies had similar results. To make it more clear, there was no significant heterogeneity among examined studies with respect to both of analysed endpoints [overall survival (OS) and locoregional recurrence (LRR)], and including them together provides a consistent point estimate. We agree that safety profiles and quality of life (QoL) are important parameters of drug evaluation, however, this was not the aim of our study which was clearly stated in the introduction and methodology section. Furthermore, toxicity profiles and QoL measurements were reported in RCTs and they show similar overall severe toxicity (acute and late) between the two treatment regimens. Also, authors have stated that the data from the study by Riaz et al. [3] was extracted only from an abstract without information considering survival, despite the availability of full-text publication with reported survival outcomes at the later date. However, full-text does not provide information regarding survival in p16/HPV-positive subjects receiving CDDP or C225 with irradiation, which makes this data irrelevant considering the design of our meta-analysis. On the contrary, abstract provided an information regarding LRR in HPV-driven oropharyngeal cancer (OPC) patients treated with CDDP or C225, which justified its inclusion in our meta-analysis. At the end, authors concluded that ''lack of a formal risk-of-bias assessment, integral to quality assessment for grading the strength of recommendation raises further questions regarding the robustness of interpretation of results and conclusions in such pooled analysis''. Limitations of our meta-analysis were stated in discussion sections which reflects afore-mentioned objection. Additionally, we have used strict inclusion criteria to avoid potential biases and provide better evidence considering the investigated issue. The main reason for performing preliminary [4] and updated meta-analysis [2] was to guide decision-making in HPV-positive subjects receiving definitive chemoradiotherapy or bioradiotherapy due to the lack of studies which directly compare efficacy of CDDP vs C225 in conjunction with radiotherapy. When our initial meta-analysis of retrospective studies was presented at ESMO Congress 2018 [4], there were no prospectively collected data with respect to the examined issue. It was the first evidence of significant superiority of CDDP over C225 in the p16/HPV-positive OPCs. Since the Bonner's registration study [5], C225 joined CDDP as category 1 option in NCCN guidelines for concurrent use with radiotherapy in patients with head and neck cancer. While the efficacy of CDDP-based radiotherapy was demonstrated through numerous prospectively conducted trials which compared it to radiotherapy alone, C225-based radiotherapy showed superior efficacy in only one RCT where subgroup analysis suggested one of the most

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pronounced effects in OPC patients. In conclusion, our both analyses [2, 4], suggested significant superiority of CDDP-based radiotherapy over C225-based radiotherapy in p16/HPV-positive OPC and are consistent with the data obtained through the RCTs.

## Compliance with ethical standards

**Conflict of interest** We disclose any commercial associations that might pose a potential, perceived or real conflict of interest with the content of this article. These include grants, patent licensing arrangements, consultancies, stock or other equity ownership, donations, advisory board memberships, or payments for conducting or publicizing the study.

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