cancers

MDPI

Addendum

Addendum: Perri et al. Electrochemotherapy as a First Line Treatment in Recurrent Squamous Cell Carcinoma of the Oral Cavity and Oropharynx PDL-1 Negative and/or with Evident Contraindication to Immunotherapy: A Randomized Multicenter Controlled Trial. *Cancers* 2021, *13*, 2210

Francesco Perri [1,*], Francesco Longo [2], Roberta Fusco [3], Valeria D'Alessio [3], Corrado Aversa [4], Ettore Pavone [4], Monica Pontone [1], Maria Luisa Marciano [1], Salvatore Villano [4], Pierluigi Franco [4], Giulia Togo [5], Gianluca Renato De Fazio [5], Daniele Ordano [5], Fabio Maglitto [4], Giovanni Salzano [4], Maria Grazia Maglione [4], Agostino Guida [6] and Franco Ionna [4]

1 Medical and Experimental Head and Neck Oncology Unit, Istituto Nazionale Tumori IRCCS Fondazione Pascale-IRCCS di Napoli, Via M. Semmola, 80131 Naples, Italy; m.pontone@istitutotumori.na.it (M.P.); m.marciano@istitutotumori.na.it (M.L.M.)
2 Head and Neck Surgery Unit, Ospedale Casa Sollievo della Sofferenza, S. Giovanni Rotondo, 71013 Foggia, Italy; frlongo@hotmail.com
3 IGEA SpA Medical Division—Oncology, Via Casarea 65, Casalnuovo di Napoli, 80013 Napoli, Italy; r.fusco@igeamedical.com (R.F.); v.dalessio@igeamedical.com (V.D.)
4 Head and Neck Surgery Unit, Istituto Nazionale Tumori IRCCS Fondazione Pascale-IRCCS di Napoli, Naples, Via M. Semmola, 80131 Naples, Italy; c.aversa@istitutotumori.na.it (C.A.); e.pavone@istitutotumori.na.it (E.P.); s.villano@istitutotumori.na.it (S.V.); p.franco@istitutotumori.na.it (P.F.); f.maglitto@istitutotumori.na.it (F.M.); g.salzano@istitutotumori.na.it (G.S.); m.maglione@istitutotumori.na.it (M.G.M.); f.ionna@istitutotumori.na.it (F.I.)
5 School of Specialization in Maxillo-Facial Surgery, University of Naples Federico II, Via Sergio Pansini, 80131 Naples, Italy; g.togo@istitutotumori.na.it (G.T.); g.defazio@istitutotumori.na.it (G.R.D.F.); d.ordano@istitutotumori.na.it (D.O.)
6 U.O.C. Odontostomatologia, AORN A. Cardarelli, 80131 Naples, Italy; a.guida@istitutotumori.na.it
* Correspondence: f.perri@istitutotumori.na.it

Citation: Perri, F.; Longo, F.; Fusco, R.; D'Alessio, V.; Aversa, C.; Pavone, E.; Pontone, M.; Marciano, M.L.; Villano, S.; Franco, P.; et al. Addendum: Perri et al. Electrochemotherapy as a First Line Treatment in Recurrent Squamous Cell Carcinoma of the Oral Cavity and Oropharynx PDL-1 Negative and/or with Evident Contraindication to Immunotherapy: A Randomized Multicenter Controlled Trial. *Cancers* 2021, *13*, 2210. *Cancers* **2021**, *13*, 3412. https://doi.org/10.3390/cancers13143412

Received: 4 June 2021
Accepted: 2 July 2021
Published: 8 July 2021

Comments: We have some additional considerations about the recent published article by Perri et al. [1] in *Cancers* titled "Electrochemotherapy as a First Line Treatment in Recurrent Squamous Cell Carcinoma of the Oral Cavity and Oropharynx PDL-1 Negative and/or with Evident Contraindication to Immunotherapy: A Randomized Multicenter Controlled Trial". The primary objective of the clinical trial is to verify the objective response rate of patients included in the two arms: the control arm involves the treatment of head and neck squamous cell carcinoma (HNSCC) with systemic treatment (cetuximab + platinum-based therapy + 5-fluorouracil), while the treatment arm involves the Electrochemotherapy (ECT) with bleomycin. All patients have histologically confirmed local recurrence, and are not eligible to surgery or irradiation. Recently, the results of KEYNOTE-048 study were published and a new combination of a monoclonal antibody named pembrolizumab and chemotherapy emerged as a standard first line therapy for recurrent or metastatic HNSCC that overexpress tissue programmed death 1 ligand (PDL-1). The keynote study was a randomized, phase 3 study of patients with untreated locally incurable HNSCC tumors [2] stratified by PDL-1 expression, p16 status, and performance status and randomly assigned (1:1:1) to pembrolizumab, pembrolizumab plus a platinum and 5-fluorouracil (pembrolizumab with chemotherapy), or cetuximab plus a platinum and 5-fluorouracil (cetuximab with chemotherapy). After a median follow-up of approximately 13 months, an increase in overall survival in patients with CPS (combined positive score) $\geq$ 20 (median 14.7 versus 11.0 months, two-year OS 35% versus 19%) and in those with CPS $\geq$ 1 (median 13.6 versus 10.4 months, two-year OS 31 versus 17%) was observed

in the pembrolizumab with chemotherapy group, compared with the cetuximab with chemotherapy group. A not statistically significant improvement in OS in the total study population (median 13.0 versus 10.7 months, two-year OS 29% versus 19%) was present. No relevant differences in-progression free survival in patients with CPS $\geq$ 20 (median 5.8 versus 5.2 months) or CPS $\geq$ 1 (median 5.0 months each) were observed. Similar objective response rates (43 versus 38 percent for CPS $\geq$ 20, 36 percent each for CPS $\geq$ 1), but longer duration of response in patients with any positive CPS (7.1 versus 4.2 months for CPS $\geq$ 20, 6.7 versus 4.3 months for CPS $\geq$ 1) were found. Therefore, the study showed that therapy with pembrolizumab combined with chemotherapy is able to improve OS in the PDL-1 CPS of 20 or more, CPS of one or more, and total populations, and that it was associated with a longer duration of response, with a comparable objective response, PFS and safety profile compared to cetuximab with chemotherapy. Based on the observed efficacy and safety, pembrolizumab with platinum and 5-fluorouracil can be considered a new standard-of-care treatment for patients with recurrent or metastatic HNSCC [2].

For these reasons, we requested and obtained the authorization (0051703-28/04/2021-AIFA-AIFA_USC-P), from the Italian Medicines Agency, for a substantial amendment to the clinical trial [1] in order to extend the study also to PDL-1-positive patients. These patients will be treated with a combination of pembrolizumab + systemic treatment (platinum and 5-fluorouracil). Inclusion and exclusion criteria were already described in [2], with the difference that the patients with recurrent HNSCC of the oral cavity and oropharynx should be candidate either to systemic therapy with cetuximab (PDL-1-negative and/or with evident contraindication to immunotherapy) or to immunotherapy with pembrolizumab (PDL-1-positive patients, CPS of 1 or more) [2]. The primary endpoint is to verify whether the treatment with ECT and bleomycin is superior in terms of objective response to treatment with cetuximab + therapy based on platinum + 5 fluorouracil, or alternatively to pembrolizumab + therapy based on platinum + 5 fluorouracil. The clinical response will be evaluated by RECIST 1.1 criteria on Computed Tomography and/or Magnetic Resonance images at 2 months from baseline.

Moreover, the study design foresees a cross-over to failure from the experimental arm and this would allow, in theory, an interesting treatment sequence, i.e., ECT followed by immunotherapy [3]. Recently, the combination of locoregional/cytoreductive therapeutic methods (such as stereotaxic/hypofractionated radiotherapy and ECT) and immunotherapy is being studied, the rationale of which would be given by a possible "abscopal" immunostimulating effect of cytoreductive treatment [4]. The study by Perri et al. would pave the way for a possible in vivo test related to this therapeutic approach.

References

1. Perri, F.; Longo, F.; Fusco, R.; D'Alessio, V.; Aversa, C.; Pavone, E.; Pontone, M.; Marciano, M.L.; Villano, S.; Franco, P.; et al. Electrochemotherapy as a First Line Treatment in Recurrent Squamous Cell Carcinoma of the Oral Cavity and Oropharynx PDL-1 Negative and/or with Evident Contraindication to Immunotherapy: A Randomized Multicenter Controlled Trial. *Cancers* **2021**, *13*, 2210. [CrossRef] [PubMed]
2. Burtness, B.; Harrington, K.J.; Greil, R.; Soulières, D.; Tahara, M.; de Castro, G., Jr.; Psyrri, A.; Basté, N.; Neupane, P.; Bratland, A.; et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): A randomised, open-label, phase 3 study. *Lancet* **2019**, *394*, 1915–1928. [CrossRef]
3. Ionna, F.; Bossi, P.; Guida, A.; Alberti, A.; Muto, P.; Salzano, G.; Ottaiano, A.; Maglitto, F.; Leopardo, D.; De Felice, M.; et al. Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck: A Big and Intriguing Challenge Which May Be Resolved by Integrated Treatments Combining Locoregional and Systemic Therapies. *Cancers* **2021**, *13*, 2371. [CrossRef] [PubMed]
4. Longo, F.; Perri, F.; Caponigro, F.; Della Vittoria Scarpati, G.; Guida, A.; Pavone, E.; Aversa, C.; Muto, P.; Giuliano, M.; Ionna, F.; et al. Boosting the Immune Response with the Combination of Electrochemotherapy and Immunotherapy: A New Weapon for Squamous Cell Carcinoma of the Head and Neck? *Cancers* **2020**, *12*, 2781. [CrossRef] [PubMed]