Annals of Clinical Otolaryngology

Editorial
Published: 04 Nov, 2017

Immunotherapy in Head and Neck Cancer: A New Paradigm

*Thibaut Reverdy, Andy Karabakakian, Max Gau and Jérôme Fayette**

Department of Medical Oncology, Centre de Lutte Contre le Cancer Léon Bérard, Lyon-I University, France

Editorial

Immunotherapy has shown efficiency in multiple tumor types with implementation of new paradigms. Head and neck squamous cell carcinoma (HNSCC) is also revolutionized. Based on the concept of immunoevasion, these molecules stimulate the immune system by inhibiting immune checkpoint receptors such as PD-1 and CTLA-4 which are believed to be the most exploited by tumor cells. To date, three antibodies showed benefice in recurrent or metastatic HNSCC, after failure of platinum-based chemotherapy (possibly given in curative intent for localized disease in one study). Nivolumab and pembrolizumab, anti-PD1 agents, were both tested in a phase III study vs chemotherapy at the choice of the investigator with similar results: no better progression free survival than chemotherapy (about 2 months); increase of overall survival (OS) 7.7 vs 5.1 months HR=0.71 (95% CI: 0.55-0.90) for nivolumab and 8.4 vs 7.1 months HR=0.81 (95% CI : 0.66-0.99, currently not significant, p superior to the unilateral born of 0,0175) for pembrolizumab; and similar response rates of about 14% [1,2]. Interestingly, efficacy is clearly higher for PDL1+ tumors. Comparisons are difficult since the cut-off is different for each study. HR for OS was 0.55 for PDL1+>1% with nivolumab (59% of the tested patients) and 0.54 for PDL1+>50% with pembrolizumab (26% of the patients). For PDL1 negative patients there is no clear benefit in OS, but analysis of the quality of life favored nivolumab regardless of PDL1 status [3]. It seems that HPV infection could lead to sensitivity to nivolumab whether or not the tumor expresses PDL1. Durvalumab, an anti-PDL1 agent, showed similar response rate of 16.5% in a phase II monoarm study for PDL1+ tumors [4].

More than median OS, it should be underlined that a fraction of patients benefit strongly from immunotherapy with 21.5% of patients alive at 18 months with nivolumab vs 8.3% with chemotherapy. Tolerability is excellent with less than 14% of grade 3/4 toxicities with all the three antibodies. So, immunotherapy is now the current standard after failure of platin-based chemotherapy, certainly for PDL1+ patients and probably in terms of quality of life for those that are PDL1 negative. Today, better biomarkers are needed and are largely explored without a clear emergence of a crucial one. The IFN-γ 6 gene signature, which was explored with pembrolizumab, seems to be predictive of ORR, PFS and OS. This signature is a composite score calculated by averaging normalized values of 6 genes implicated in the immune response: CXCL9, CXCL10, IDO1, IFNG, HLA-DRA and STAT1. In the near future, a cancer immunogram could help select the best candidates for immunotherapies. Which type of immunotherapy? Monotherapy with anti-PD1/PDL1 could perhaps be improved and a current phase III study is comparing in the second line setting chemotherapy to anti-PDL1 alone (durvalumab) or combined with anti-CTLA4 (tremelimumab).

A stringent question concerns the attitude at progression: treatment beyond progression or stopping treatment and starting a new line? Among progressive patients under nivolumab, 42% pursue the treatment and in this population the OS reached 12.7 months and interestingly 24% of these patients experimented tumor shrinkage [5]. So while hyperprogression under immunotherapy has been described [6], pseudoprogression could be a real phenomenon. Biomarkers analysis of this population who benefit from treatment beyond progression suggests that they experience a decrease of Treg cells after an initial increase and like responders have less CTLA4+ T cells at baseline. This new paradigm is not definitive yet and immunotherapies are tested in first line versus the standard comparator (EXTREME schedule: cisplatin 5FU cetuximab) and with various approaches: anti-PD1/PDL1 alone, anti-PD1/PDL1 + anti-CTLA4, anti PD1 + chemotherapy with cisplatin and 5FU. Responses are awaited to these crucial questions: Can the addition of an anti-CTLA4 agent increase survival despite added toxicity? For all populations? Only for PDL1 negative patients? Is an anti-PD1/PDL1 agent alone sufficient for PDL1+ patients? Can the addition of chemotherapy increase overall survival? The question will become even more complicated with the launch of phase III studies (versus EXTREME) testing a combination of anti-PD1/PDL1 with anti-IDO (inducible

OPEN ACCESS

Correspondence:
Jérôme Fayette, Department of Medical Oncology, Centre de Lutte Contre le Cancer Léon Bérard , 69008 Lyon, France,
E-mail: jerome.fayette@lyon.unicancer.fr

Received Date: *06 Oct 2017*
Accepted Date: *02 Nov 2017*
Published Date: *04 Nov 2017*

Citation:
Reverdy T, Karabakakian A, Gau M, Fayette J. Immunotherapy in Head and Neck Cancer: A New Paradigm. Ann Clin Otolaryngol. 2017; 2(5): 1027.

mechanism of resistance to anti-PD1/PDL1) whom preliminary data suggest very good safety and promising efficacy. Immunotherapies are also tested for localized disease with variable approaches: in combination with chemoradiation with cisplatin (q1w or q3w), alone in potentiation of radiotherapy, in adjuvant setting after chemoradiation, in combination with TPF in induction.

Nobody can predict the future five years. Should Immunotherapy be used earlier than second line? Which setting? Neoadjuvant? Exclusive (chemo) radiation, adjuvant after multimodality initial treatment? First line? Which combination? After use for localized disease is there a place for recurrence? The next few years are very challenging. More trials and ancillary analysis are needed but what is more exciting than embarking to the unknown and build the future?

References

1. Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med. 2016;375(19):1856-1867.
2. Cohen EWHKJ, Le Tourneau C, Dinis J, Licitra L, Ahn MJ, Soria A, et al. Pembrolizumab (pembro) vs standard of care (SOC) for recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC): Phase 3 KEYNOTE-040 trial. ESMO Congress, 2017.
3. Harrington, Ferris RL, Blumenschein G Jr, Colevas AD, Fayette J, Licitra L et al.Nivolumab versus standard, single-agent therapy of investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck (CheckMate 141): health-related quality-of-life results from a randomised, phase 3 trial. Lancet Oncol. 2017;18(8):1104-1115.
4. Zandberg DPAA, Jimeno A, Good JS, Fayette J, Bouganim N, Ready NE, et al. Durvalumab for recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): Preliminary results from a single-arm, phase 2 study. ESMO Congress, 2017.
5. Haddad RBG, Fayette J, Guigay J, Colevas AD, Licitra L, Kasper S, et al. Treatment beyond progression with nivolumab in patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) in the phase 3 checkmate 141 study: A biomarker analysis and updated clinical outcomes. ESMO Congress, 2017.
6. Saâda-Bouzid E, Defaucheux C, Karabajakian A, Coloma VP, Servois V, Paoletti X, et al. Hyperprogression during anti-PD-1/PD-L1 therapy in patients with recurrent and/or metastatic head and neck squamous cell carcinoma. Ann Oncol. 2017;28(7):1605-1611.