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Immunotherapy for Head and Neck Cancer in the Era of Exponentially Increasing Health Care Expenditure

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Disclosures of potential conflicts of interest may be found at the end of this article.

Recurrent and/or metastatic head and neck squamous cell carcinomas (RMHNSCC) are associated with very poor clinical outcomes. Cytotoxic chemotherapy regimens have activity but come with substantial side effects that may adversely impact quality of life. The Checkmate 141 study demonstrated a survival advantage with nivolumab compared to investigators choice chemotherapy for patients previously treated with cisplatin-based chemotherapy, leading to U.S. Food and Drug Administration approval [1]. Quality-of-life endpoints collected during this trial were also observed to be superior in patients receiving nivolumab [2]. However, the cost of this drug is substantial, underscoring the importance of examining financial implications of its use in health-care systems.

Zargar et al. [3] performed a cost-utility analysis that compared nivolumab with docetaxel. A state transition model was utilized and applied to clinical data obtained from the Checkmate 141 study, using costs from a Canadian health care perspective. The authors found that nivolumab adds only 0.13 additional quality-adjusted life years (QALY) compared to docetaxel. At the current price estimate, the incremental cost–effectiveness ratio (ICER) of $144,744 CAD per QALY for nivolumab exceeds the currently accepted willingness to pay threshold of $100,000 CAD per QALY—a conclusion similar to other independently performed economic analysis in head and neck [4], lung [5], and kidney cancers [6].

Cost-effectiveness analyses are tools used by policy makers to understand and compare the cost and outcomes of different therapeutic strategies. To place this study's conclusion in context for the practicing oncologist, it is key to review the basics of these types of economic analyses. A cost-utility analysis compares two different treatment strategies and estimates the ratio between the cost of a health-related intervention and the benefit it produces in terms of the number of years lived in full health. Full health is estimated by calculating QALY, a measure of disease burden that includes both the quality and the quantity of life lived. QALYs are obtained by multiplying the amount of time lived by a utility weight that ranges from 0.0 (death) to 1.0 (perfect health). The difference between the cost of two interventions is then divided by the difference in their QALYs to obtain an ICER, which represents the average incremental cost associated with one additional QALY. An ICER that ranges from

$50,000 to $100,000 in U.S. dollars (or is less than three times the per capita gross domestic product), is generally accepted as cost-effective. One can easily see how the values used to obtain QALYs can dramatically alter the ICER and therefore the conclusion of a study.

Zargar et al. conclude that patients treated with nivolumab only gain 0.13 QALY compared with patients treated with docetaxel. The reliability and reproducibility of utility weights used to arrive at this QALY might be questioned, because there is currently no set standard for these values [7]. There is significant debate on how best to estimate these, with some proposing that patients with the disease in question be surveyed, as they have direct experience. Alternatively, proponents of estimates obtained from the general public or medical providers cite a potentially less biased valuation. Zargar et al. obtained these utility weights from published Canadian and U.S. studies of adverse events associated with systemic cytotoxic therapy, most of which were generated by surveys of medical oncologists treating various malignancies [8, 9]. An example of how these utility weights may not accurately reflect the two treatments' impact on health is hyperthyroidism. One of the most common adverse events from immune checkpoint inhibitors, hyperthyroidism is typically detected by screening thyrotropin levels in asymptomatic patients. Because there is no utility value for hyperthyroidism, the authors assigned fatigue as the utility weight, with the rationale that this is hypothyroidism's most common clinical presenting symptom. The utility weight for fatigue was obtained using a survey of gastrointestinal (GI) medical oncologists treating metastatic colorectal cancer [8]. Although fatigue can also be observed in patients receiving immune checkpoint inhibitors, the degree to which it can be used as a surrogate for hyperthyroidism is questionable at best and unlikely to be comparable with the fatigue observed during cytotoxic chemotherapy for GI malignancies. Because immune checkpoint inhibitors can result in unique and nonoverlapping toxicities compared with cytotoxic chemotherapy, careful attention to and refinement of utility weights to reflect these differences are important.

Another potential limitation is the assumption made with regard to the efficacy of nivolumab, especially because the trial data only extended out to 16 months, with a median

follow-up for overall survival of only 5.1 months (range 0– 16.8 months). In order to project the overall and progression-free survival to 5 years, a Weibull survival distribution was used, which assumes that there will be no long-term survivors. Although it is generally accepted that therapeutic strategies for RMHNSCC are palliative, with long-term survival being exceedingly rare, this may change with the introduction of immune checkpoint inhibitors. In other malignancies with longer-term follow-up and more mature data using immune checkpoint inhibitors, a subset of long-term survivors is increasingly recognized. In a recent pooled analysis of 1,861 patients with melanoma treated with the CTLA-4 checkpoint inhibitor ipilimumab, in 10 prospective and 2 retrospective studies, the overall survival curve began to plateau at 3 years with a 22% survival rate [10]. It is unknown if this same phenomenon will be observed in RMHNSCCs with longer follow-up. It is possible that a cost-effectiveness analysis using utility weights specific to immunotherapy and survival approximations that account for long-term survivors [11] might reach a different conclusion than that of Zargar et al.

Not exclusive to this study is the fact that the external validity of cost-effectiveness analyses based on randomized control trials is a legitimate concern. The applicability of these cost-effectiveness results in the "real world," nontrial scenario can be argued, especially because the population with non-human papilloma virus-related head and neck squamous cell carcinoma is enriched with tobacco and alcohol use, socioeconomic disparity, and under- or uninsured ethnic minorities with significant vascular, pulmonary, and cardiac comorbidities. This population, which is commonly seen in regular clinical practice, deviates significantly from the select treatment population enrolled in the Checkmate 141 study. Furthermore, therapeutic standards for second-line therapy are largely undefined in this patient population. Zargar et al. do take this issue into consideration and justify the use of docetaxel as the comparator arm in their analysis. Clinicians are very familiar with the challenges of offering second-line therapy in this often infirm group of patients, whose performance status and comorbidities often preclude the use of second-line systemic therapy after cisplatin. It is difficult to predict if nivolumab, with its generally more favorable toxicity profile compared with cytotoxic chemotherapy, would be more cost-effective than a nondocetaxel regimen or supportive care alone in a less fit patient population. It would be interesting to look at the trends of use of these agents in the community setting using registry data.

The rapidly escalating costs of cancer therapeutics highlight the urgency of exploring avenues for minimizing costs outside of drug pricing legislation. Revisiting dosing strategies is an obvious route, given the extended half-lives of these monoclonal antibodies. There is a growing body of evidence suggesting extended dosing intervals are just as effective as intravenous dosing every 2 weeks [12]. Another strategy is to establish which patients are likely to benefit from immune checkpoint inhibition prior to initiating therapy. Although treatment with nivolumab can drastically change the natural history of this disease in a subset of patients, this subset represents a small proportion of patients with RMHNSCC. The identification of a robust biomarker that correlates with response could aid in appropriate patient selection for such costly therapeutic approaches. Available correlative data on the utility of p16 status, programmed cell death ligand 1 status, and tumor mutational burden as treatment criteria are conflicting and difficult to apply in this population at the current time; however, further investigation is ongoing and may inform therapeutic decision-making in the future [13–15]. Because the majority of patients with newly diagnosed head and neck cancer will present with locally advanced disease and are potential candidates for curative-intent therapy, an immunotherapy approval in the locally advanced setting would have an even greater impact on healthcare expenditure. Therefore, thoughtfully designed clinical trials, ideally with biomarker, quality-of-life, and economic endpoints, are critical. There are numerous upcoming and ongoing clinical trials exploring the addition of nivolumab or pembrolizumab to curative intent therapy, with several large phase III registrational international trials underway (NCT03040999, NCT02952586, and NCT02999087). These clinical trials are designed to administer the immune checkpoint inhibitors during and for protracted periods after curative-intent therapy is completed. These trials do not include comparator arms in which immune checkpoint inhibition is given with curative intent therapy without extended adjuvant therapy. This extended adjuvant approach is not a current standard among patients treated with curative intent and has not been shown to be of benefit when other biological agents, such as epidermal growth factor receptor inhibitors, are used after treatment for locally advanced disease [16]. Oversight into appropriate clinical trial design, ideally by entities free of conflicts of interest, are essential for making these breakthrough agents available to patients with the least financial impact to society.

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Editor's Note:

See the related article, "Cost-Effectiveness of Nivolumab in Recurrent Metastatic Head and Neck Squamous Cell Carcinoma," by William W.L. Wong et al. on page 225 of this issue.