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Letter to the editor

Immune-checkpoint inhibitors in head and neck squamous cell carcinoma: cost-efficacy in second-line treatment based on programmed death-ligand 1 (PD-L1) level

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Dear Editor,

Recently Hirschmann et al. [1] have assessed the cost-effectiveness of nivolumab as second-line treatment for recurrent and/or metastatic head and neck squamous cell cancer (r/mHNSCC) in their country (Switzerland), based on the perspective of the Swiss health system with a 60 months' time horizon. Incremental cost-effectiveness ratios (ICER) resulted in CHF 102,957 per QALY gained. They concluded that reducing the price of nivolumab according to a consented payback by 4.75%, resulted in an ICER of CHF 98,325/QALY gained (below the informal willingness-to-pay of 100,000 CHF/QALY). In light of the relevant expenses of these new pharmacological interventions it might be interesting to make a balance between the cost of immune check point inhibitors (ICIs) and the added value represented by the improvement of the clinical parameters of interest, such as overall survival (OS). The present analysis was conducted to assess the pharmacological costs of second-line treatments with ICIs (nivolumab and pembrolizumab) for r/mHNSCC.

The present evaluation was restricted to phase III RCTs in second-line treatments with nivolumab and pembrolizumab for r/mHNSCC. We calculated differences in OS (expressed in months) between the different arms of each trial. Then, we calculated the pharmacological costs necessary to get the benefit in OS, for each trial. Calculations were based on an “ideal patient” (BSA 1.8 sqm; weight 70 kg). The dosage of drugs were considered according to those reported in each RCT. The costs of drugs are at the Pharmacy of our Hospital and are expressed in euros (€), updated to May 31st, 2019. We assumed the following costs: nivolumab = 1108.80 € for 100 mg, pembrolizumab = 2828.10 € for 100 mg, docetaxel = 3.52 € for the cost of 20 mg, cetuximab = 168.91 € for 100 mg, methotrexate = 2.09 € for 50 mg. We have also applied the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) [2] to the above pivotal phase III RCTs; adjustments (upgrade or down-grade) are planned based on QoL or grade 3–4 toxicities impacting daily well-being. All data were reviewed by 2 investigators (J.G., A.B.) and separately computed by 2 investigators (J.G., A.B.).(See Table 1.)

Our analysis evaluated 2 phase III RCTs [3,4], including 1372 patients. Progression free survival (PFS) ranged from 2.0 months of nivolumab [3] to 3.5 months of pembrolizumab in Programmed Death-Ligand 1 (PD-L1) > = 50% population [4]; OS ranged from 5.1 months of standard single-agent sistemic therapy [3] to 11.6 months of pembrolizumab in PD-L1 > = 50% population [4]. ESMO-MCBS reached medium-high score (grade 3–5) for both RCTs [3,4]. The lowest cost per month of OS-gained in the overall population (independent from PD-L1) was associated with the use of nivolumab (from 2539.28 € towards cetuximab to 4145.77 € towards methotrexate). The lowest cost per month of OS-gained in the PD-L1 > = 50% population was associated with the use of pembrolizumab (from 2314.87 € towards cetuximab to 3559.94 € towards methotrexate).

In this paper we performed a review of the literature, limited to phase III RCTs that reported the effect second-line treatments with ICIs (nivolumab and pembrolizumab) for r/mHNSCC, to find out the incremental costs necessary to get the benefit in OS, for each trial. We have limited our evaluation to phase III RCTs for different reasons: first, phase II trials are plagued by patient's selection biases and this reduce the possibility to define “credible” measures of efficacy (PFS, OS); second, RCTs are needed to allow comparison of efficacy. So, data showed that the pharmacological costs were influenced by two main factors: the efficacy of the therapies (strictly associated with the patient's inclusions criteria) and the price of drugs used. Combining the costs of therapy with the measure of efficacy represented by OS, we get the costs for obtaining the advantage in OS. It results that nivolumab had the lowest cost per month of OS-gained in the overall population (independent from PD-L1) and pembroluzumab in the PD-L1 > = 50% population. Concerning pembrolizumab, the economic advantage in PD-L1 > = 1% population is not so clear.

Our review has several limitations, first of all cross-trial comparisons. Moreover, we have considered only the direct costs, but there are other important cost elements that are not considered here (e.g. outpatient/inpatient administration costs or treatment-related adverse event costs or health-related quality of life between different first-line treatments). In facts, the data we have reported are not a real cost-effectiveness analysis (that would imply not only direct medical costs, but also indirect medical costs), but an analysis of pharmacological costs. Moreover, using PFS and OS are unconventional but raises interesting issues. We decided to consider OS because PFS will likely

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Table 1
Pharmacological costs and differences in OS with immune check point inhibitors (pembrolizumab and nivolumab) in second-line for r/mHNSCC.

Authors	Comparative regimens	Total N patients	Primary endpoint	ORR	p-value	PFS (months)	p-value	OS (months)	p-value	OS gain (months)	OS HR (95% C.I.)	ESMO-MCBS	Median duration of treatment (months)	Costs of therapy (€)	Difference in costs (€)	Difference in costs per month-OS gained (€)
Ferris et al. [3]	Nivolumab	240	OS	13.3	NR	2.0	NS	7.5	**0.001**	2.4	0.70	**3**	1.9	9979.20	9949.94–6094.27	2539.28–4145.77
	Standard single-agent sistemic therapy[a]	121		5.8		2.3		5.1			(0.51–0.96)		1.9	29.26[b]-3884.93[c]		
Coehn et al. [4]	Pembrolizumab	247[d]	OS	14.6[d]	NS[d]	2.1[d]	NS[d]	8.4[d]	**0.032**[d]	1.5[d]	0.82	**3**[d,e]	2.8	17 824.80	17 799.72–11 574.33	7716.22–11866.48[d]
		196[e]		17.3[e]	**0.017**[e]	2.2[e]	NS[e]	8.7[e]	**0.078**[e]	1.6[e]	(0.67–1.01)[d]	**5**[f]				7233.96–11 124.83[e]
		64[f]		26.6[f]	**0.001**[f]	3.5[f]	**0.034**[f]	11.6[f]	**0.001**[f]	5.0[f]	0.74					2314.87–3559.94[f]
	Standard single-agent sistemic therapy[a]	248[d]		10.1[d]		2.3[d]		6.9[d]			(0.58–0.93)[e]		1.4[b]	25.08[b]-6249.67[c]		
		191[e]		9.9[e]		2.3[e]		7.1[e]			0.53		1.7 [g]			
		65[f]		9.2[f]		2.2[f]		6.6[f]			(0.35–0.81)[f]		2.3[c]			

N = number; ORR = overall response rate; PFS = progression free survival; OS = overall survival; ESMO-MCBS = European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (from grade 1 to grade 5); NS = not significant; NR = not reported.

[a] Methotrexate, docetaxel or cetuximab.
[b] Methotrexate.
[c] Cetuximab.
[d] Overall population.
[e] PD-L1 > = 1%.
[f] PD-L1 > = 50%.
[g] Docetaxel.

underestimate the life-years saved [5–7].

The annual costs of treatment are in line with those reported by Azimi and Welch [8], that found a favored implementing intervention for thresholds of less than $ 61,500 per life-year gained, for both nivolumab in the overall population (from 34169.82 $ to 55787.55 $) and pembrolizumab in PD-L1 > = 50% population (31150.05 $). Similar projection for nivolumab were obtained also by Hirschmann et al [9], with an incremental cost-effectiveness ratios (ICER) of around 100,000 Swiss Francs (CHF) (considered as an informal willingness-to-pay) per QALY gained.

The pharmacological costs are transferred to the Italian reality and, more generally, to Europe (free movement of patients and goods). The idea is to emphasize not only the cost topic, but also the method, which is to combine the pharmacological costs of drugs with the measures of efficacy (OS), in order to achieve a given objective as possible.

However, to our knowledge, this is the first time an analysis of the pharmacological costs of regimens in second-line treatments with ICIs for r/mHNSCC is integrating with OS and clinical benefit.

In conclusion, combining pharmacological costs of drugs with the measure of efficacy represented by OS, nivolumab and pembrolizumab are cost-effective in second-line treatment for r/mHNSCC in different subgroups of patients: pembrolizumab in PD-L1 > = 50% population and nivolumab in the remaining overall population. The price of newly registered oncologic drugs is continuously increasing posing a serious treat to the sustainability of the National Health Systems, especially in Countries in which the public control and oversight over the prices is limited. Medical Oncologists and the society as a whole are becoming more and more concerned with the issues of the costs of the cure of cancer patients and are able to bring attention to the “just price” of new treatments that must reflect the reality of their true benefits and societal and personal costs [10].

Authorship

Jacopo Giuliani and Andrea Bonetti contributed equally to (1) conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the version to be published.

Disclosure

No founds were received to support this article.

Research involving human participants and/or animals

No human participants and/or animals were involved.

Informed consent

Not needed (no human participants were involved).

Declaration of Competing Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. In particular:

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