Research Article

Cost-Effectiveness of Pembrolizumab in Combination with Platinum-Based Chemotherapy in First-Line for Squamous and Nonsquamous Non Small-Cell Lung Cancer. Far from Economic Sustainability

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Abstract

Objectives: To assess the pharmacological costs of pembrolizumab in association with chemotherapy as first-line treatment in non small-cell lung cancer (NSCLC).

Methods: Pivotal phase III randomized controlled trials (RCTs) were considered. Differences in progression free survival (PFS) between the different arms were calculated and compared with the pharmacological costs needed to get one month of PFS (incremental cost-effectiveness ratio, ICER).

Results: One thousand one hundred and seventy five patients were included.Differences in costs between the 2 arms with the use of pembrolizumab were 37 009 € for squamous NSCLC and 45 234 € for nonsquamous NSCLC, with a cost of 23 131 € and 11 598 € per month of PFS-gain in the overall population for squamous and nonsquamous NSCLC, respectively and with a progressively lower cost per month of PFS-gain in the transition from PD-L1< 1% (37 009 €) to PD-L1 of 1 to 49% (18 505 €) to PD-L1≥ 50% (9739 €) in squamous and NSCLC.

Conclusion: At the actual prize, pembrolizumab in combination with chemotherapy is not cost-effective in first-line for both squamous and nonsquamous NSCLC. A reduction in pharmacy cost is mandatory.

Keywords: Cost of drugs, NSCLC, pembrolizumab

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Recently, the topic of costs has become preponderant in oncology, also in relation to the introduction of target immunotherapy, with their greatest budgetary impact.[1] One of the most recent examples is represented by pembrolizumab in first-line treatment for advanced non small-cell lung cancer (NSCLC). In this setting, pembrolizumab in association with chemotherapy has shown both a prolonged progression free survival (PFS) and overall survival (OS) in both the intention-to-treat population and the PD-L1-positive subgroup versus (vs.) platinum-based chemotherapy in squamous and nonsquamous NSCLC.[2,3] The introduction of pembrolizumab in this setting is associated with a relevant increase of costs and it is therefore important to make a balance between the costs of treatment and the added value represented by the improvement of the clinical parameters of interest such as OS and PFS. The pres-

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ent analysis was conducted to assess the pharmacological costs of pembrolizumab in association with platinum-based chemotherapy as first-line treatment in squamous and nonsquamous NSCLC.

Materials and Methods

Pivotal phase III randomized controlled trials (RCTs) were considered.[2,3] Differences in PFS (expressed in months) between the different arms were calculated and compared with the pharmacological costs needed to get one month of PFS. Combining the costs of therapy with the measure of efficacy represented by the PFS, we get the costs for obtaining the advantage in PFS, for each arm of the analyzed trials. Incremental cost-effectiveness ratio (ICER) was calculated as the ratio between the difference of the costs in the intervention and in the control groups (pharmacy costs) and the difference between the effect in the intervention and in the control groups (PFS). The costs of drugs are at the Pharmacy of our Hospital (Italy) and are expressed in euros (€), updated to September 2020. 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 the pivotal phase III RCT2. For pembrolizumab we assumed the following pharmacy cost: 2056.08 € for 100 mg vial. All data were reviewed by 2 investigators (J.G., A.B.) and separately computed by 2 investigators (J.G., A.B.). We have subsequently applied the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) to the above RCTs,[4] to derive a relative ranking (from grade 1 to grade 5) of the magnitude of clinically meaningful benefit that can be expected in this setting [5]; adjustments (upgrade or down-grade) are planned based on quality of life (QoL) or grade 3-4 toxicities impacting daily well-being.

Results

One thousand one hundred and seventy five patients were included, in two phase III RCTs.[2,3] ESMO-MCBS reached grade 3 in both RCTs. Differences in costs between the 2 arms with the use of pembrolizumab were 37 009 € for squamous NSCLC and 45 234 € for nonsquamous NSCLC, with a cost of 23 131 € and 11 598 € per month of PFS-gain in the overall population for squamous and nonsquamous NSCLC, respectively (Table 1) and with a progressively lower cost per month of PFS-gain in the transition from PD-L1< 1% (37 009 €) to PD-L1 of 1 to 49% (18 505 €) to PD-L1≥ 50% (9739 €) in squamous and NSCLC (Table 1); the same kind of considerations could not be made in the nonsquamous NSCLC, because the stratification for PD-L1 was not made (only PFS of PD-L1< 1% population was reported).

Discussion

Two main variables are able to condition pharmacy costs: the efficacy of treatment and the price of drugs. The first variable is related to the patient's inclusions criteria and we know that results from RCTs could be not representative of daily clinical practice (that is of patients treated outside such trials). In facts, there may be a cost standardization problem within different European countries (in our country there are no significant pharmacy cost differences between the different regional realities), due to the use of local pharmacy cost. In this case, this bias is minimize by the reference to only a single immune check point inhibitor (pembrolizumab) and the comparison with placebo. Another limit is related to the consideration of only direct costs (which account for about 55% of total medical expenses).

The scenario has become even more complicated over the last few years with the introduction of new drugs (biotechnology), which are completely different towards old drugs (chemical). In facts, the old was of high prevalence, low cost, without extension of indication, without combination therapy and, consequently, without increase in treatment duration. Different, the new is of low prevalence, high costs, with extension of indication, often with combination therapy and, consequently, with increase in treatment duration (exactly the opposite of the old drugs). The biggest problem is certainly linked to the definition of the price of new drugs. So, the choice of price is not based on levels of scientific evidence and/or on measures of expected clinical benefit. To this we must add first, that the cost "per year of life gained" increases over the time and second the Companies perspective (high costs of clinical development, regulatory requirements and reinvestment needs). In this complex situation we can be helped by the introduction of biosimilars (biologic product that have been shown "highly similar" to an already approved reference product, it means no clinically meaningfull differences in terms of safety, purity and potency towards the originator). In facts, we know that biological agents are essential in oncology, but it was one of the main causes of the increase in spending on anticancer drugs. So, the integration of biosimilars into daily clinical practice has the potential to significantly decrease, costs for patients, health-care systems and insurance companies.[1] Unfortunately, few active oncological drugs were produced and approved in daily clinical practice (trastuzumab, bevacizumab and rituximab)[1,6] and what we currently can do as Medical Oncologists (and more generally the whole of the society) are becoming more and more concerned with the issues of the costs of the cure of cancer patients.

Table 1. Pharmacological costs and difference in PFS with pembrolizumab in combination with chemiotherapy vs. chemiotherapy in first-line for both squamous and nonsquamous NSCLC

Trial/Histology	Comparative Regimens	Total N patients	Primary endpoint	OS (months)	p	PFS (months)	p	PFS gain (months)	OS HR (95% C.I.)	ESMO-MCBS	Median duration of treatment (months)	Costs of therapy (€)	ICER (€)
KEYNOTE-407/ squamous NSCLC2	carboplatin plus paclitaxel/nab-paclitaxel plus pembrolizumab -> pembrolizumab	278	OS, PFS	15.9[a]	<0.001[a]	6.4[a] 6.3[b]	<0.001[a]	1.6[a] 1.0[b]	0.64 (0.49-0.85)	3	6.3	x + 37 009	23 131[a] 37 009[b]
	carboplatin plus paclitaxel/nab-paclitaxel plus placebo -> placebo	281		11.3[a] 5.3[b] 5.2[c] 4.2[d]		7.2[c] 8.0[d] 4.8[a]		2.0[c] 3.8[d]			4.7	x	18 505[c] 9739[d]
KEYNOTE-189/ nonsquamous NSCLC3	platinum-based chemotherapy plus pemetrexed plus pembrolizumab -> pembrolizumab	410	OS, PFS	NR[a]	<0.001[a]	8.8[a] 6.1[b]	<0.001[a]	3.9[a]	0.49 (0.38-0.64)	3	7.4	x + 45 234	11 598[a]
	platinum-based chemotherapy plus pemetrexed plus placebo -> placebo	206		11.3[a]		4.9[a] 5.1[b]					5.4	x	

Legend: N= number; 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) ; ICER= incremental cost-effectiveness ratio (expressed as the difference (€) per month-PFSS gained); NSCLC= non small-cell lung cancer; NR= not reached; a= overall population; b= PD-L1 < 1%; c= PD-L1 of 1 to 49%; d= PD-L1≥ 50%.

In Europe expenditure for cancer drugs amounted to €10 billion in the year 2005 and increased more than three times to €32 billion in the year 2018.[7] In this scenario, European Contries negotiate the price of new drugs with the manufacturers with the aim to obtain a discount, so as to allow more patients to be treated. This results on "confidential rebates" (it means not publicly available), that may really hamper access to drugs with a consequent overpayment without improving the value of drugs.

In addition, the annual cost of drug treatment in the overall population (277 572 € in squamous NSCLC and 139 176 € in squamous NSCLC) is not in line with those reported in literature, that found a favored implementing intervention for thresholds of less than $61.500 (57 138 €) per life-year gained.[8] Better results, but not in line with those reported in literature,[7] were obtained in squamous NSCLC for PD-L1 of 1 to 49% (222 060 €) and for PD-L1≥ 50% in squamous NSCLC (116 868 €). An excessive spending (444 108 € in squamous NSCLC and 542 808 € in squamous NSCLC) were obtained in PD-L1< 1% population.

In light of the relevant expenses of these new drugs it might be also interesting to compare the cost of pembrolizumab with the costs of the other immune check point inhibitors (ICIs, nivolumab and atezolizumab), used in advanced NSCLC (among the most expensive new drugs in medical oncology [8-13]) and the costs of the reference elements in international markets, gold 18 karat (K) (currently listed on 46. 90 € per gram) and platinum (currently listed on 21.45 € per gram). Pembrolizumab has the highest cost per gram, with 205 608.00 €, with a Δ toward gold 18K and platinum per gram of 205 561.10 € and 205 586.55 €, respectively (Table 2).

Table 2. A comparison between the costs pembrolizumab and the costs of the others immune check point inhibitors (ICIs, nivolumab and atezolizumab) used in the treatment of advanced NSCLC and the costs of the reference elements in international markets (gold, platinum)

Element/drug	Cost per gram (€)	Δ toward gold 18K per gram (€)	Δ toward platinum 18K per gram (€)
gold 18K	46.90	--	--
platinum	21.45	--	--
nivolumab	107 500.00	107 453.10	107 478.55
pembrolizumab	205 608.00	205 561.10	205 586.55
atezolizumab	1726.03	1680.87	1697.50

Legend: k= Karat; nivolumab= 1070.00 € for 100 mg, pembrolizumab= 2056.08 € for 100 mg, atezolizumab= 2071.24 € for 1200 mg.

In conclusion, at the actual prize, combining pharmacological costs of drugs with the measure of efficacy represented by the PFS, pembrolizumab in combination with chemotherapy is not a cost-effective in first-line for both squamous and nonsquamous NSCLC. There is no doubt that data on pembrolizumab in combination with chemotherapy are good in this setting (confirming also by the grade of clinical benefit with ESMO scale [4]), but a reduction in pharmacy cost is mandatory.

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