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Financial Toxicity and Non-small Cell Lung Cancer Treatment: The Optimization in the Choice of Immune Check Point Inhibitors*

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Abstract. *Background/Aim: Immune check point inhibitors (ICIs) are changing cancer treatment in several malignancies, including non-small cell lung cancer (NSCLC). The introduction of these active new agents is associated with a relevant increase of costs and it is, therefore, important to create a balance between the costs of treatment and the added value represented by the improvement of the clinical parameters of interest such as overall survival (OS). This analysis was conducted to assess the pharmacological costs of first- and second-line treatments with ICIs (pembrolizumab, nivolumab and atezolizumab) for metastatic NSCLC. Materials and Methods: The present evaluation was restricted to phase III randomized controlled trials (RCTs). We calculated the pharmacological costs necessary to get the benefit in OS. Results: Six phase III RCTs were evaluated. Concerning first-line, the lowest cost per month of OS-gain was associated with the use of pembrolizumab at 2,734 €. Concerning second-line, the lowest cost per month of OS-gain was associated with the use of atezolizumab at 3,724 €. Conclusion: Pembrolizumab and atezolizumab are cost-effective in both first and second-line treatment for metastatic NSCLC, respectively.*

Immune check point inhibitors (ICIs) are changing cancer treatment in several malignancies, including squamous and non-squamous non-small cell lung cancer (NSCLC) (1). In particular, the introduction of ICIs, such as pembrolizumab, nivolumab and atezolizumab, in first and second-line treatment of metastatic NSCLC with no targetable alterations, such as epidermal growth factor receptor (EGFR)-activating mutations, anaplastic lymphoma kinase (ALK)-translocations or the proto-oncogene tyrosine-protein kinase ROS1 translocation/re-arrangements, have demostrated improvements in survival relative to standard chemotherapy (2). In light of the relevant expenses of these new pharmacological interventions it might be interesting to examine the balance between the cost of 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 first and second-line treatments with ICIs (pembrolizumab, nivolumab and atezolizumab) for metastatic NSCLC.

Materials and Methods

The present evaluation was restricted to phase III randomized controlled trials (RCTs) in first and second-line treatments with pembrolizumab, nivolumab and atezolizumab for metastatic NSCLC without EGFR-activating mutations, ALK-translocations or ROS1 translocation/re-arrangements. 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 m^2, weight 70 Kg). The dosage of drugs was considered according to what is reported in each RCT.

The costs of drugs at the Pharmacy of our Hospital are expressed in Euros (€). Currently, no drug dosage is available per single vial in our Country. We assumed the following costs: i) nivolumab at 240 mg flat dose every 2 weeks (Q2W), with each administration at 3,225 euros (each medication vial is 100 mg and the cost of each vial was 1,075 €, so 3 vials were used for each administration), ii) docetaxel at 18 € for the cost of 1 cycle, iii) pembrolizumab at 2,056.08 € for 100 mg [in the calculation of costs only pembrolizumab at 2 mg/Kg was considered (single dose recorded in the data sheet)], and iv) atezolizumab at 3,139.08 € for 1200 mg. We have also applied the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) (3) to the above pivotal phase III RCTs, with adjustments (upgrade or down-grade) planned based on quality of life (QoL) or grade 3-4 toxicities impacting daily well-being (3). The last available update of each trial was considered as the original source. The deadline for trial publication and/or presentation was

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Key Words: NSCLC, first-line, second-line, phase III RCTs, pembrolizumab, nivolumab, atezolizumab, cost of drugs.

January 31th, 2019. All data were reviewed by 2 investigators (JG and AB) and separately computed by 2 investigators (JG and AB).

Results

Our analysis evaluated 6 phase III RCTs (2 RCTs in first-line and 4 RCTs in second-line) (4-10), including 3,545 patients. Regarding first-line treatment (Table I), progression free survival (PFS) ranged from 4.2 months of nivolumab in the CheckMate026 trial (6) to 10.3 months of pembrolizumab in the KEYNOTE-024 trial (4). OS was 14.4 months of nivolumab in the CheckMate026 trial (6) and 30.0 months of pembrolizumab in the OS update of KEYNOTE-024 trial (5). ESMO-MCBS reached high score (grade 5) for the KEYNOTE-024 trial (4,5), while nivolumab otained low score (grade 1) ESMO-MCBS in the CheckMate026 trial (6). Concerning the second-line treatments (Table II), OS ranged from 2.3 months of nivolumab in the CheckMate 057 (8) to 4.2 months of docetaxel in the same trial (8), and from 6 months of docetaxel in the CheckMate 017 (7) to 13.8 months of atezolizumab in the OAK (10). ESMO-MCBS reached high score (grade 5) for the CheckMate 017 (7) trial, KEYNOTE-010 (9) trial and OAK trial (10), while CheckMate 057 (8) reached grade 4 in the ESMO-MCBS. Concerning the first-line treatment, the most relevant increase of costs were associated with the use of nivolumab, with 18,813 € per month of OS-gain, while the lowest cost per month of OS-gain was associated with the use of pembrolizumab with 2,734 € (Table I). Concerning the second-line treatment, the most relevant increase of costs was associated with pembrolizumab with 15,122 € per month of OS-gain, while the lowest cost per month of OS-gain was associated with the use of atezolizumab with 3,724 € (Table II).

Discussion

In this study we reviewed phase III RCTs that reported the effect of first and second-line treatments with the ICIs, pembrolizumab, nivolumab and atezolizumab, for metastatic NSCLC, 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 reduces the possibility to define “credible” measures of efficacy, such as PFS and OS. Second, RCTs are needed to allow comparison of efficacy. So, data showed that the pharmacological costs were influenced by two main factors: i) the efficacy of the therapies (strictly associated with the patient's inclusions criteria) and ii) the price of drugs used. Combining the costs of therapy with the measure of efficacy represented by OS, we got the costs for obtaining the advantage in OS. The use of atezolizumab was associated with the lowest cost per month OS-gain in first-line for metastatic NSCLC (2,734 €). In second-line treatment for metastatic NSCLC, atezolizumab had the lowest cost per month of OS-gain (3,724 €).

Our review has several limitations, first of which involves the 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 the different first-line treatments). In fact, 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 as part of the analysis is unconventional but raises interesting issues. We decided to consider OS because PFS on its own would likely underestimate the life-years saved (11-13). In addition, ESMO-MCBS considers the QoL in the definition of the clinical benefits of each RCT, and adjustments (upgrade or down-grade) are planned based on QoL or grade 3-4 toxicities impacting daily well-being (3).

The annual costs of ICIs treatment are in line with those reported by Azimi and Welch (14), that found a favored implementing intervention for thresholds of less than $ 61,500 per life-year gained, only for pembrolizumab in first-line ($ 28,779) and atezolizumab in second-line ($ 39,200) treatment. At current prices, nivolumab cannot be considered cost-effective for metastatic NSCLC, both in first (negative results of CheckMate026 (6)) and second-line treatments for both non-squamous ($ 72,474) and squamous ($ 84,695) metastatic NSCLC. The cost of nivolumab would be economically sustainable with a dosage at 3 mg pro Kg [currently nivolumab is approved at 240 mg flat dose Q2W, based on data of comparable efficacy and safety towards nivolumab at 3 mg/kg Q2W schedule (15, 16)], with 4,809 € and 5,623 € per month of OS-gain in non-squamous (8) and squamous NSCLC (7), respectively, and with $ 50,621 and $ 59,189 of annual perspective, respectively. Concerning pembrolizumab, recently a flat dose of 200 mg was approved also for second-line treatment for NSCLC (17). There are no differences in terms of costs per month OS-gain also for 200 mg flat dose (15,122 €) *versus* pro-Kg dosage.

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 on the cost topic, but also on the method, which is to combine the pharmacological costs of drugs with the measures of efficacy (OS).

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

Combining pharmacological costs of drugs with the measure of efficacy represented by OS, pembrolizumab and atezolizumab are cost-effective in first and second-line

Table I. *Pharmacological costs and difference in PFS and OS with immune check point inhibitors (pembrolizumab and nivolumab) in first-line for advanced NSCLC.*

Trials	Comparative regimens	Total N patients	Primary endpoint	PFS (months)	*p*-Value	OS (months)	*p*-Value	PFS/OS gain (months)[a] /increase in 2 years survival alone (%)	OS HR (95% CI)	ESMO-MCBS	Median of doses received	Costs of therapy (€)	Difference in costs (€)	Difference in OS (months)	Difference in costs per month-OS gained (€)
KEYNOTE-024 (4)	Platinum-based chemotherapy[b]	151	PFS	6.0	< 0.001	14.2[c]	0.002[c]	15.8/NR	0.63 (0.47-0.86)	5	4	x	10 045	15.8	2734
	Pembrolizumab	154		10.3		30.0[c]					10.5	x + 43 192			
CheckMate 026 (6)	Platinum-based chemotherapy[b]	270	PFS	5.9	NS	13.2	NS	-1.7/NR	1.15 (0.91-1.45)	1	5	x	22 575	1.2	18 813
	Nivolumab	271		4.2		14.4					7	X + 22 575			

N: Number; PFS: progression-free survival; OS: overall survival; 95% CI: 95% Confidence Interval; NS: not significant; NR: not reached; ESMO-MCBS: European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (from grade 1 to grade 5); [a]referring to the primary endpoint (except when OS as a secondary endpoint shows improvement, it will prevail and the new scoring refers to OS); [b]based on the investigator's choice: carboplatin plus pemetrexed, cisplatin plus pemetrexed, carboplatin plus gemcitabine, cisplatin plus gemcitabine, or carboplatin plus paclitaxel; [c]data from the update on OS of KEYNOTE-024 trial (5).

Table II. *Pharmacological costs and difference in PFS and OS with immune check point inhibitors (pembrolizumab, nivolumab and atezlizumab) in second-line treatment for advanced NSCLC.*

Trials	Comparative regimens	Total N patients	Primary endpoint	PFS (months)	*p*-Value	OS (months)	*p*-Value	OS gain (months)	OS HR (95% CI)	ESMO-MCBS	Median of doses received	Costs of therapy (€)	Difference in costs (€)	Difference in OS (months)	Difference in costs per month-OS gained (€)
CheckMate 017 (7)	Nivolumab	131	OS	3.5	<0.001	9.2	<0.001	3.2	0.59 (0.44-0.79)	5	8	25 800	25 746	3.2	8046
squamous	Docetaxel	129		2.8		6.0					3	54			
CheckMate 057 (8)	Nivolumab	287	OS	2.3	NS	12.2	0.002	2.8	0.73 (0.59-0.89)	4	6	19 350	19 278	2.8	6885
squamous	Docetaxel	268		4.2		9.4					4	72			
KEYNOTE-010 (9)	Pembroli-Zumab$_2$	345	OS, PFS	3.9	NS	10.4	0.0008[a]	1.9[a] 4.2[b]	0.71 (0.58-0.88)[a]	5	7 3	28 785[c] 54	28 731c	1.9	15 122c
NSCLC	Pembrolizumab$_{10}$	346		4.0		12.7	<0.0001[b]		0.61						
	Docetaxel	343		4.0		8.5			(0.49-0.75)[b]						
OAK (10)	Atezolizumab	425	OS	2.8	NS	13.8	0.0003	4.2	0.73)	5	5	15 695	15 641	4.2	3724
NSCLC	Docetaxel	425		4.0		9.6			(0.62-0.87						

N: Number; RR: response rate; PFS: progression free survival; OS: overall survival; 95% CI: 95% Confidence Interval; ESMO-MCBS: European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (from grade 1 to grade 5); NS: not significant; pembrolizumab$_2$: pembrolizumab at 2 mg/Kg; pembrolizumab$_{10}$: pembrolizumab at 10 mg/Kg; [a]pembrolizumab$_2$ *versus* (*vs.*) docetaxel; [b]pembrolizumab$_{10}$ *vs.* docetaxel; [c]with pembrolizumab at 2 mg/Kg.

treatment for metastatic NSCLC, respectively. The price of newly registered oncologic drugs is continuously increasing, which poses a serious threat 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 (18).

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

JG and AB contributed equally to the conception and design of the study, acquisition, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, as well as for its final approval to be published.

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References

1 Clarke JM, George DJ, Lisi S and Salama AKS: Immune Checkpoint Blockade: The New Frontier in Cancer Treatment Target Oncol *13(1)*: 1-20, 2018. PMID: 29441437. DOI: 10.1007/s11523-017-0549-7

2 Assi HI, Kamphorst AO, Moukalled NM and Ramalingam SS: Immune checkpoint inhibitors in advanced non-small cell lung cancer. Cancer *124(2)*: 248-261, 2018. PMID: 29211297. DOI: 10.1002/cncr.31105

3 Cherny NI, Sullivan R, Dafni U, Kerst JM, Sobrero A, Zielinski C, de Vries EG and Piccart MJ: A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Ann Oncol *26(8)*: 1547-1573, 2015. PMID: 26026162. DOI: 10.1093/annonc/mdv249

4 Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leiby MA, Lubiniecki GM, Shentu Y, Rangwala R and Brahmer JR; KEYNOTE-024 Investigators: Pembrolizumab *versus* chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med *375(19)*: 1823-1833, 2016. PMID: 27718847. DOI: 10.1056/NEJMoa1606774

5 Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Vandormael K, Riccio A, Yang J, Pietanza MC and Brahmer JR. Updated Analysis of KEYNOTE-024: Pembrolizumab *versus* platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. J Clin Oncol *37(7)*: 537-546, 2019. PMID: 30620668. DOI: 10.1200/JCO.18.00149

6 Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, Felip E, van den Heuvel MM, Ciuleanu TE, Badin F, Ready N, Hiltermann TJN, Nair S, Juergens R, Peters S, Minenza E, Wrangle JM, Rodriguez-Abreu D, Borghaei H, Blumenschein GR Jr., Villaruz LC, Havel L, Krejci J, Corral Jaime J, Chang H, Geese WJ, Bhagavatheeswaran P, Chen AC and Socinski MA; CheckMate 026 Investigators: First-Line nivolumab in stage IV or recurrent non-small-cell lung cancer. N Engl J Med *376(25)*: 2415-2426, 2017. PMID: 28636851. DOI: 10.1056/NEJMoa1613493

7 Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, Waterhouse D, Ready N, Gainor J, Arén Frontera O, Havel L, Steins M, Garassino MC, Aerts JG, Domine M, Paz-Ares L, Reck M, Baudelet C, Harbison CT, Lestini B and Spigel DR: Nivolumab *versus* docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med *373(2)*: 123-135, 2015. PMID: 26028407. DOI: 10.1056/NEJMoa1504627

8 Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, Barlesi F, Kohlhäufl M, Arrieta O, Burgio MA, Fayette J, Lena H, Poddubskaya E, Gerber DE, Gettinger SN, Rudin CM, Rizvi N, Crinò L, Blumenschein GR Jr., Antonia SJ, Dorange C, Harbison CT, Graf Finckenstein F and Brahmer JR: Nivolumab *versus* docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med *373(17)*: 1627-1639, 2015. PMID: 26412456. DOI: 10.1056/NEJMoa1507643

9 Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, Molina J, Kim JH, Arvis CD, Ahn MJ, Majem M, Fidler MJ, de Castro G Jr, Garrido M, Lubiniecki GM, Shentu Y, Im E, Dolled-Filhart M and Garon EB: Pembrolizumab *versus* docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet *387(10027)*: 1540-1450, 2016. PMID: 26712084. DOI: 10.1016/S0140-6736(15)01281-7

10 Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, Gadgeel SM, Hida T, Kowalski DM, Dols MC, Cortinovis DL, Leach J, Polikoff J, Barrios C, Kabbinavar F, Frontera OA, De Marinis F, Turna H, Lee JS, Ballinger M, Kowanetz M, He P, Chen DS, Sandler A and Gandara DR; OAK Study Group: Atezolizumab *versus* docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet *389(10066)*: 255-265, 2017. PMID: 27979383. DOI: 10.1016/S0140-6736(16)32517-X

11 Olchanski N, Zhong Y, Cohen JT, Saret C, Bala M and Neumann PJ: The peculiar economics of life-extending therapies: a review of costing methods in health economic evaluations in oncology. Expert Rev Pharmacoecon Outcomes Res *15(6)*: 931-940, 2015. PMID: 26478989. DOI: 10.1586/14737167.2015.1102633

12 Cohn DE, Kim KH, Resnick KE, O'Malley DM and Straughn JM Jr: At what cost does a potential survival advantage of bevacizumab make sense for the primary treatment of ovarian cancer? A cost-effectiveness analysis. J Clin Oncol *29(10)*: 1247-1251, 2011. PMID: 21383297. DOI: 10.1200/JCO.2010.32.1075

13 Shi Q, de Gramont A, Grothey A, Zalcberg J, Chibaudel B, Schmoll HJ, Seymour MT, Adams R, Saltz L, Goldberg RM,Punt CJ, Douillard JY, Hoff PM, Hecht JR, Hurwitz H,

Díaz-Rubio E, Porschen R, Tebbutt NC, Fuchs C, Souglakos J,Falcone A, Tournigand C, Kabbinavar FF, Heinemann V, Van Cutsem E, Bokemeyer C, Buyse M and Sargent DJ: Individual patient data analysis of progression-free survival *versus* overall survival as a first-line end point for metastatic colorectal cancer in modern randomized trials: findings from the analysis and research in cancers of the digestive system database. J Clin Oncol *33(1)*: 22-28, 2015. PMID: 25385741. DOI: 10.1200/JCO.2014.56.5887

14 Azimi NA and Welch HG: The effectiveness of cost-effectiveness analysis in containing costs. J Gen Intern Med *(13810)*: 664-669, 1998. PMID: 9798812. DOI: 10.1046/j.1525-1497.1998.00201.x

15 Zhao X, Suryawanshi S, Hruska M, Feng Y, Wang X, Shen J, Vezina HE, McHenry MB, Waxman IM, Achanta A, Bello A, Roy A and Agrawal S: Assessment of nivolumab benefit-risk profile of a 240-mg flat dose relative to a 3-mg/kg dosing regimen in patients with advanced tumors. Ann Oncol *28(8)*: 2002-2008, 2017. PMID: 28520840. DOI: 10.1093/annonc/ mdx235

16 Opdivo Prescribing Information. Opdivo U.S. Product Information. Last updated: March 2018. Princeton, NJ: Bristol-Myers Squibb Company.

17 Freshwater T, Kondic A, Ahamadi M, Li CH, de Greef R, de Alwis D and Stone JA: Evaluation of dosing strategy for pembrolizumab for oncology indications. J Immunother Cancer *5*: 43, 2017. PMID: 28515943. DOI: 10.1186/s40425-017-0242-5

18 Giuliani J and Bonetti A: FOLFIRINOX is a cost-effective combination chemotherapy in first-line for advanced pancreatic cancer. Pancreatology *19(2)*: 325-330, 2019. PMID: 30704852. DOI: 10.1016/j.pan.2019.01.014

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