Immuno-oncological treatment of Non-Small-Cell Lung Cancer (NSCLC) in advanced stage with Nivolumab

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Abstract

Immuno-oncology marked a therapeutic revolution in the treatment of cancer. Thanks to the new strategy that aims to awaken the immune system to fight cancer cells, there has been a change in the clinical course in the treatment of advanced Non-Small Cell Lung Cancer (NSCLC). Our study aimed to evaluate the therapeutic efficacy of nivolumab monotherapy in the treatment of patients with advanced stage IIIB/IV non-small cell lung cancer beyond the second line. The results showed a progression-free survival of 7.35 months and an improvement in the quality of life of patients compared to other treatments. In addition, no type 3 and type 4 adverse reactions were detected in patients treated with Nivolumab. We hope that these results, already promising, will lead to an increase in overall survival in the future.

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Introduction

Lung cancer is still the most common cancer with the highest incidence and mortality rate in the world.[1] In recent years, in Italy there has been a significant increase in new cases of lung cancer, so it remains in the first place among the causes of tumor death in men and in the third place in women.[2] Due to the lack of suitable screening methods and the absence of characteristic clinical symptoms, in most cases this type of tumor is diagnosed only in an advanced or metastatic phase, when the only therapeutic option is systemic chemotherapy, with 2-5 years survival rate at stage IV and definitely unfavorable prognosis.[1,3,4] The new frontier in the treatment of lung cancer is represented by immuno-oncology, which has led to the development of new drugs capable of enhancing the immune response through the action on specific regulatory molecules called immuno-checkpoints.[5-8] Nivolumab is a fully human IgG4 monoclonal antibody, and the first Programmed Death-1 (PD-1) immune checkpoint inhibitor approved by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and Agenzia Italiana del Farmaco (AIFA), for the second line treatment of patients with both squamous and nonsquamous histology of NSCLC.[9] In particular, the results obtained from two clinical trials (CheckMate-017 and CheckMate057) have shown a significant improvement in overall survival, progression-free survival, and objective responses rate, associated with an extremely favorable toxicity profile.[9,10] To confirm this, we conducted a study at the Unità Operativa Complessa (UOC) of Pharmacy of "Ospedali Riuniti Villa Sofia – Cervello" Hospital in Palermo, to evaluate the efficacy of Nivolumab in the second line treatment of patients with NSCLC.

Materials and Methods

Our work aimed to evaluate the therapeutic efficacy of monotherapy with Nivolumab in the treatment of patients with advanced stage IIIB/IV non-small-cell lung cancer beyond the second line.

The data was collected at the UOC of Medical Oncology of the "Ospedali Riuniti Villa Sofia-Cervello" Hospital, between February 2016 and May 2017; 24 patients (with written, signed and dated informed consent) with stage IIIB/IV NSCLC underwent experimental treatment. All patients had received platinum chemotherapy in the first line, except for one patient with adenocarcinoma who was treated with Gefitinib due to EGFR mutation. After first stopping previous chemotherapy, they were treated with Nivolumab at a dose of 3mg/kg of body weight administered intravenously. In total, a median of 16.8 cycles (9.9 AD; 6.8 SQ) were administered for a treatment median of 8.7 months (5.1 AD; 3.6 SQ), according to previous studies.[9,10]

Of these 24 patients, 14 suffered from Adenocarcinoma (AD), 8 from Squamous cell carcinoma (SQ), 1 from Not Otherwise Specified (NOS) carcinoma, 1 from squamous and neuroendocrine large cell carcinoma (LNC/SQ).

Results

Most patients enrolled were men 95.5% (Figure 1) and smokers 91% (Figure 2).

The average age of the patients was 66.4 years. In terms of Performance Status (PS), the distribution of patients was as follows: 13 with PS 0 (92.9%), 8 with PS 1 (50%) and 3 with PS 2 (21.4%; Figure 3).

In the AD group, 1 patient had mutated Epidermal Growth Factor Receptor (EGFR) and was treated with a Tyrosine Kinase Inhibitor (TKI), which was suspended after disease progression; the remaining 13 were wild-type EGFR. Anaplastic Lymphoma Kinase (ALK) translocation was not found in any patient. Genetic investigations of EGFR and ALK were not performed in the SQ group. The patients who underwent surgery were 11 (45.8%); radiotherapy was performed for the treatment of primary lung injury in 3 patients (1 AD, 2 SQ) and metastases (brain in 5 patients with AD, elsewhere in 2 patients with AD and in 2 patients with SQ). The maintenance therapy was performed in 10 patients (41.7%). The patients receiving Nivolumab in the second line were 10 (41.7%) of which 2 with adenocarcinoma and 8 with squamous carcinoma; in the third line and beyond there were 14 (58.3%), of which 12 with AD and 2 with SQ. In total, a median of 16.8 cycles (9.9 AD, 6.8 SQ) was administered for a treatment median of 8.7 months (5.1 AD, 3.6 SQ; Table 1).

Evaluating the state of the patients, we can see that in the group of subjects affected by AD: 4 patients continue to receive Nivolumab, 3 patients have stopped the treatment with Nivolumab due to disease progression and continue chemotherapy, 1 had brain radiation therapy, 6 patients have died. In the group of subjects with SQ, 2 patients continued to receive Nivolumab, 4 patients have stopped the treatment with Nivolumab, 1 by choice and the other 3 by progression and continued chemotherapy, 4 have died (Figure 4).

It was not possible to make an accurate assessment of the median Overall Survival (OS) due to the death of half of the population examined. The average was 5.6 months for AD and 7.4 months for SQ, Progression-Free Survival (PFS) was 7.35 months.

Overall, survival and progression-free survival are not related to the histotype (AD vs SQ), smoking status, site of metastases (brain *vs.* liver vs bone), line of therapy (second *vs.* third and beyond).

The Objective Response (OR) is represented by a Complete

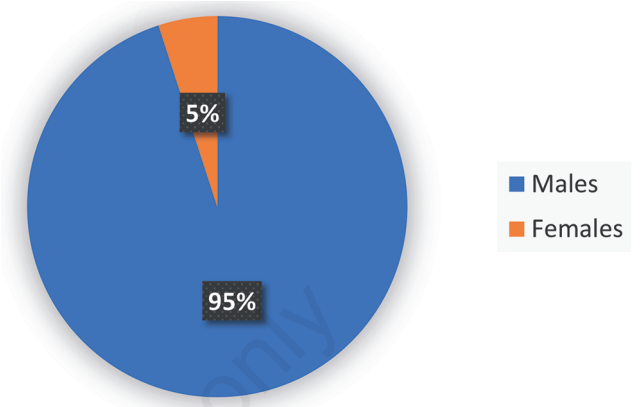

Figure 1. Gender of recruited patients.

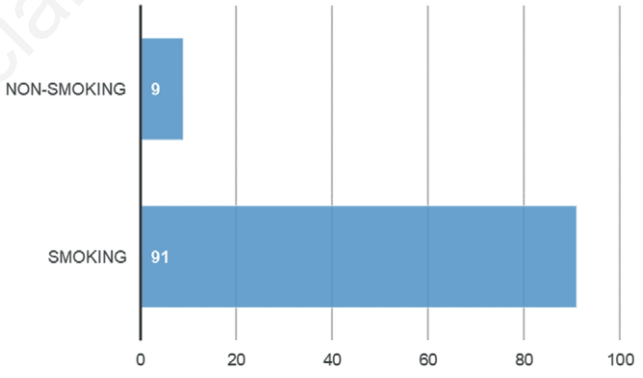

Figure 2. Percentage of smokers.

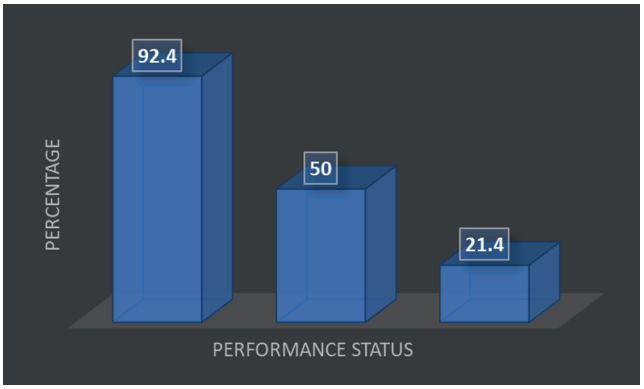

Figure 3. Performance status of patients.

Response (CR), achieved in only 1 patient with AD (4.2%), and gives Partial Responses (PR) achieved in 6 patients (25%), of which 3 with AD (12.5%) and 3 with SQ (12.5%).

The best response to Nivolumab was in total: disease stability (DS) for 7 patients (29.2%), including 5 with AD (20.8%) and 2 with SQ (8.3%); Disease Progression (DP) for 7 patients (29.2%), including 5 with AD (20.8%) and 2 with SQ (8.3%). Furthermore, no response was determined for 3 patients with adenocarcinoma (12.5%; Figure 5).

Regarding the toxicity profile, there were no Grade 3 or 4 adverse events. Only Grade 1 adverse reactions were found, and they are, in order of frequency: nausea, constipation, thyroiditis, rash, weight loss, gynecomastia, alopecia and hyperglycaemia, dyspnoea, peripheral edema and itching.

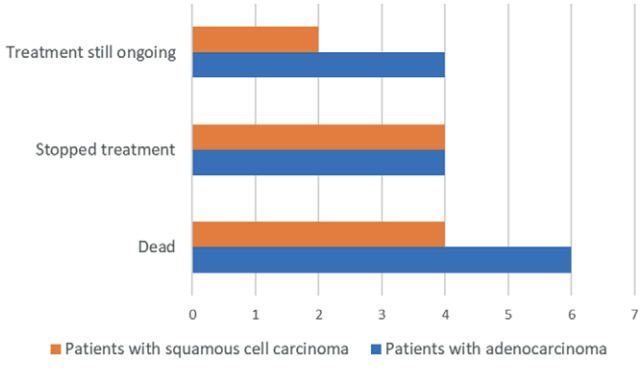

Figure 4. Current patient status.

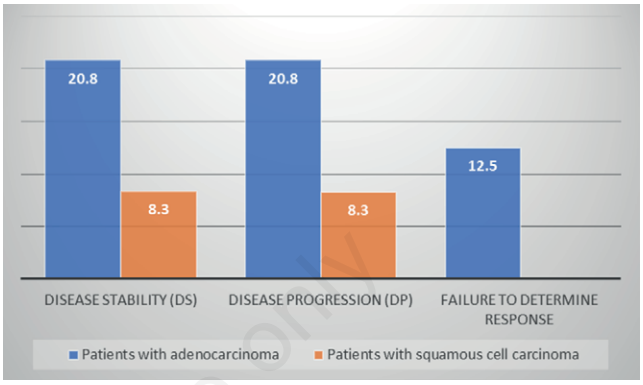

Figure 5. Total response to Nivolumab.

Table 1. Comparison of the status of patients with adenocarcinoma in treatment with Nivolumab.

Pt	Sex	Age	Hysto	PS	St	Sm py	Brain Mts	Prev Surg	RT x	CT x I line	CT x mant	Prev Lines	Cycle nivo	Dur treat	Best Resp	Current Status	OS	PFS
1 CD	M	74	AD	0	IV	45	no	lobect	no	carb/pem	erlot	3	27	20	rp	susp	nev	15
2 LA	M	65	AD	0	IV	15	yes	lobect	br	cis/vnr	no	2	13	7.3	pd	rtbr	8.7	8
3 LFS	M	45	AD	0	IV	0	no	nodulect	no	cis/gem	beva	3	28	18	sd	nivo	nev	nev
4 DCG	M	63	AD	1	IV	30	yes	lobect	br-adr	cis/vnr	pem	3	35	14	pd	susp	nev	17
5 PG	M	75	AD	1	IV	70	yes	lobect	br	cis/rt	no	3	33	17	rp	nivo	nev	nev
6 GA	M	62	AD	0	IIIB	30	no	no	no	carb/pem	pem	1	29	17	rc	nivo	nev	nev
7 SP	M	66	AD	0	IV	2.5	no	lobect	no	cis/pem	pem	2	28	15	rp	nivo	nev	nev
8 SMM	M	67	AD	1	IV	30	no	no	no	cis/etop	pem	1	6	3.1	nev	dec	4	4
9 LNF	M	81	LCN/SQ	1	IV	37	no	lobect	lg-lym	carb/gem	no	2	18	15	sd	susp	nev	9
10 ID	M	59	SQ	2	IIIB	40	no	no	no	carb/gem	no	1	9	8	sd	dec	8	8
11 TP	M	67	SQ	0	IIIB	90	no	lobect	mediast	carb/gem	no	1	10	4.5	sd	susp	4.8	4.8
12 AG	M	69	NOS	0	IV	45	no	no	no	carb/gem	no	1	15	9	sd	dec	9	8
13 CV	M	63	SQ	0	IV	45	no	no	no	carb/gem	no	1	13	7	pd	dec	7	6
14 GC	M	65	SQ	1	IV	nv	yes	no	br	cis/gem	no	1	13	6	rp	susp	6	6
15 DMG	M	68	SQ	1	IV	30	no	no	bone	carb/gem	no	1	15	8.1	sd	dec	11.2	7.7
16 TS	M	70	AD	1	IV	20	no	no	lg-adr	cis/pem	pem	2	6	2.3	pd	nav	6	2.6
17 SA	M	65	AD	0	IV	nv	no	lobect	no	cis/vnr	no	2	12	6.4	sd	dec	11.2	6.9
18 PS	M	66	AD	0	IV	nv	yes	lobect	br	gefit	gefit	3	6	2.1	nev	dec	2.3	2.3
19 VI	M	70	AD	0	IV	0	yes	no	br	cis/pem	pem	5	6	3.6	pd	dec	6.8	4
20 PR	F	55	AD	2	IV	20	no	no	no	cis/gem	no	8	3	0.9	nev	dec	1.2	8.7
21 PFP	M	61	AD	2	IV	15	no	no	no	carb/gem	no	2	6	3.9	pd	dec	4.7	4.4
22 AP	M	79	SQ	0	IV	45	no	no	br	carb/gem	no	1	44	22	rp	nivo	nev	nev
23 IG	M	70	SQ	0	IIIB	35	no	no	no	carb/gem	vnr	1	14	8	pd	susp	nev	8
24 PF	M	71	SQ	1	IIIB	30	no	lobect	br	carb/gem	no	3	14	8	rp	nivo	nev	nev

Legend: Nivo: Nivolumab, Hysto: Histology, Sm py: smoke packyears, St: stage, Surg: surgery, RTx: radiotherapy, CTx: chemotherapy, CTx maint: CT maintenance, D treat: duration treatment, BestReasp: best response, Lcn: large cell neuroendocrine cancer, lobect: lobectomy, adr: adrenal, br: brain, lg: lung, lym: lymphnodes, cis: cisplatin, carb: carboplatin, vnr: vinorelbine, germ: gemcitabine, etop: etoposide, pem: pemetrexed, erlot: erlotinib, gefit: gefitinib, nav: navelbine, dec: deceased.

Discussion

Immuno-oncology has started a new era in the treatment of tumors, allowing to combine traditional methods with a therapy that aims to enhance the immune response against cancer cells. The results that are reported in this study agree with what was expressed in a clinical study previously conducted.[10] Median overall survival was not achieved due to the failure of half of the sample examined to die. Progression-free survival had a lower outcome than the data reported in the literature.[9] The objective response rate was 25% according to the data reported in the literature. The drug is equally active in both histotypes, considering the small number of the sample under examination. The study revealed a good tolerance to treatment, as no grade 3 and 4 adverse events were detected. We can therefore conclude that in the treatment of NSCLC, the use of Nivolumab improves the prognosis and the quality of life of the patient, without causing serious side effects compared to other treatments. We hope that in the future the combination of predictive biomarker research combined with the improvement of immuno-oncology protocols will lead to ever greater overall survival data.[9]

In a study conducted by Murdaca *et al.* five Tumour Necrosis Factor-alpha (TNF-α) inhibitors are analyzed, available for the clinical use: infliximab, adalimumab, etanercept, golimumab and certolizumab pegol. All these agents block the biologic effects of TNF-α although there are some differences in their structure, pharmacokinetics, and mechanisms of action. The efficacy and safety profile of the TNF-α blockers can be considered, in general, as a class effect. The differences in the mechanism of action of the TNF-α inhibitors are also reflected by the variable response rate observed in patients with Crohn Disease (CD) who respond well to infliximab and adalimumab but not to etanercept. Of note, infliximab binds specifically to TNF-α, whereas etanercept binds and neutralizes both TNF-α as well as lymphotoxin-α, which might yield differential immunomodulatory effects and contribute to the varying efficacy between the two agents in the treatment of CD. Patients who fail to tolerate one TNF-α inhibitor can be switched to another TNF-α inhibitor if allowed by the nature of the adverse event. Although TNF-α inhibitors are generally well tolerated, physicians should be aware of the potential adverse events of these drugs. TNF-α inhibitors represent a new class of drugs that have revolutionized the clinical management of chronic inflammatory diseases. Physicians need to be aware of the potential efficacy and risks of treatment with these agents.[11]

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