EMERGING TRENDS IN THE MANAGEMENT OF NSCLC PD-L1+ PATIENTS IN ITALY

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INTRODUCTION

Lung cancer is deemed as the leading cause of cancer-related deaths worldwide and Non-Small-Cell Lung Cancer (NSCLC) represents the most common histologic variant (80% of cases)[1]. Despite advances in the understanding of the molecular biology of NSCLC, this malignancy shows a considerably poor survival rate. Literature studies report the cancer cells to overexpress a protein called programmed-death-ligand 1 (PD-L1) that enables cancer to evade the immune system[1]. Over the past decade, a huge paradigm shift in the treatment of cancer arose, driven by a significant breakthrough in personalized medicine and immuno-oncology disease treatment[2]. As a matter of fact, PD-L1 on both tumor cells and infiltrating immune cells seems to help preventing T cells from attacking tumor cells. For this reason this molecular mechanism has became a crucial area of cancer-immunotherapy research[3].

OBJECTIVE

The primary aim of this study was to assess and identify the major changes occurred after Immunotherapies introduction in the treatment of Non-Small-Cell Lung Cancer (NSCLC) Programmed Death Ligand 1 (PD-L1) positive patients in Italy and the new approach towards a systematic testing of this biomarker.

METHODS

A desk research was performed to gather international and national treatment guidelines. The methodology used to assess and weight the impact of immunotherapies in the NSCLC market was grounded on a quantitative market research - called IQVIA Biomarker tracking- and on a continuative study about oncological treatments in hospitals - called OncoView - based on the quarterly data collection of patients records. The IQVIA Biomarker tracking evaluated the rate of biomarkers testing within a sample of 197 clinical wards with a specific focus on the PD-L1 testing. OncoView study relied on a panel of 480 specialists (including 250 Oncologists), clinicians were selected across all Italian regions in order to be representative of local prescription dynamics; On average, 3.755 NSCLC patients' records were collected over one year period of observation from 255 responding clinicians. The data collected from this Sample of patient were then projected to a national level and were analysed in order to provide specific estimations of patients' prevalence and treatments approaches in Italy, from January 2016 until June 2018.

RESULTS

The recent guidelines showed the shift of NSCLC treatment to immunotherapies, initially by replacing 2nd line standard chemotherapy with docetaxel and subsequently by replacing platinum-based chemotherapy in the 1st line, and the establishment of patient treatment protocol based on the identification of biomarkers. The analysis of IQVIA Biomarker tracking data showed a striking increase of the PD-L1 testing rate (up to 50%) during the past 2 years, with a growth of 41% after pembrolizumab 1st line approval in June 2017. All patients tested for PD-L1 mutation, were also tested for ALK and EGFR (Figure 1). In 98% of cases, PD-L1 test was performed at diagnosis and in 2018 principal mutations were tested together. The PD-L1 test reached a main selection test status, being tested alongside EGFR and ALK; across the mapped hospitals, 32% of the respondents stated the main diagnostic sequence adopted was EGFR/ALK/PD-L1 (Figure 2). Overall testing rate grew from 68% to 72%: particularly, EGFR and ALK showed a *plateau*, while PD-L1 arose from 9% to 58% (Table 1). The main drivers in testing algorithm were: the drug effectiveness, the availability of diagnostic tests and mutation incidence. In two years time immunotherapies prescriptions in NSCLC disease doubled by eroding chemotherapy market share, supporting the crucial role acquired by this type of therapy within the NSCLC market (Figure 3). Patient profile analysis highlighted that PD-L1+ patient was prevalent between 51-75 years old with a ECOG 0-1 and the metastasis mainly affecting lung, liver, kidney and bones. PD-L1+ patient was prevalent and this drove the increase of 1st and 2nd Line patients with ECOG 0-1 (Table 2).

CONCLUSION

The approval of immunotherapies has opened a new era, giving patients remarkable antitumor responses with limited side effects compared to chemotherapy. In fact, immunotherapies have received "innovativeness designation" by numerous Drug Agencies including the Italian Authority (AIFA), remarking their high promising results.

The comprehension of cancer immunology has advanced together with the increased availability of biomarkers-based treatments. However, many challenges as results' interpretation and treatment complexity still need to be overcome.

This study provides up to date real-world evidence about treatment changes in the management of the NSCLC PD-L1 patients in Italy. Also, it highlights the characteristics of eligible patients with a deep dive in treatment algorithm, with the aim of supporting the development of a bulk of evidence that could help clinicians and decision makers to further understand NSCLC PD-L1 treatments and strengthen new therapeutic paradigms.

1. AIOM – AIRTUM Guidelines for Lung Cancer, 2017
2. D'Errico et al. A current perspective on cancer immune therapy: step-by-step approach to constructing the magic bullet. Clin Transl Med. 2017 Dec; 6(1):3
3. Alsaab et al. PD-1 and PD-L1 Checkpoint Signaling Inhibition for Cancer Immunotherapy: Mechanism, Combinations, and Clinical Outcome. Front Pharmacol. 2017; 8: 561

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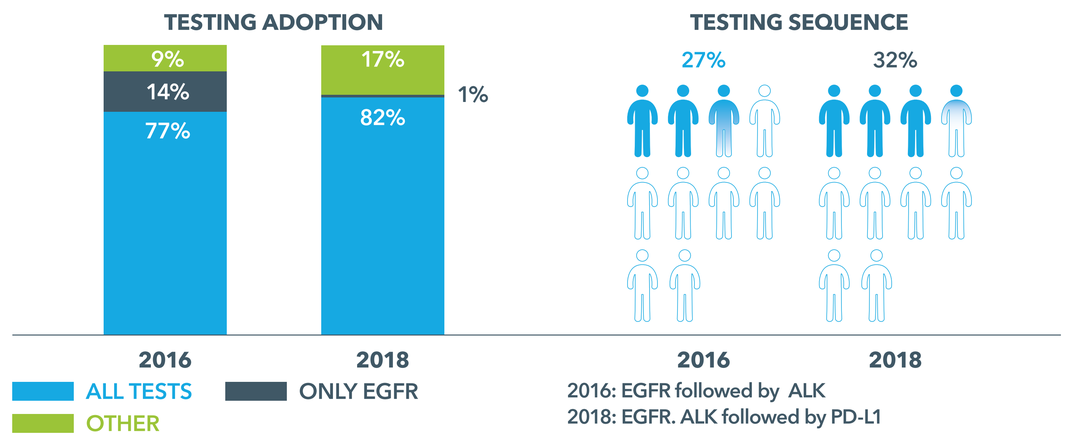
FIGURE 1
Evolution of the NSCLC testing rates during two years

	JUN 2016	DEC 2016	JUN 2017	DEC 2017	JUN 2018
EGFR	77%	82%	98%	99%	99%
ALK	65%	65%	82%	94%	95%
KRAS	48%	49%	57%	56%	57%
BRAF	46%	36%	43%	48%	43%
ROS1	37%	41%	59%	73%	73%
PD-L1	22%	22% **+16%**	38% **+41%**	79% **+5%**	83%
RET	27%	19%	34%	33%	30%

Source: Biomarker Tracking

FIGURE 2
NSCLC testing adoption and sequence: before and after immunotherapies launch



"Other" includes: testing based on tumor histotype, no predefined sequence, only one test

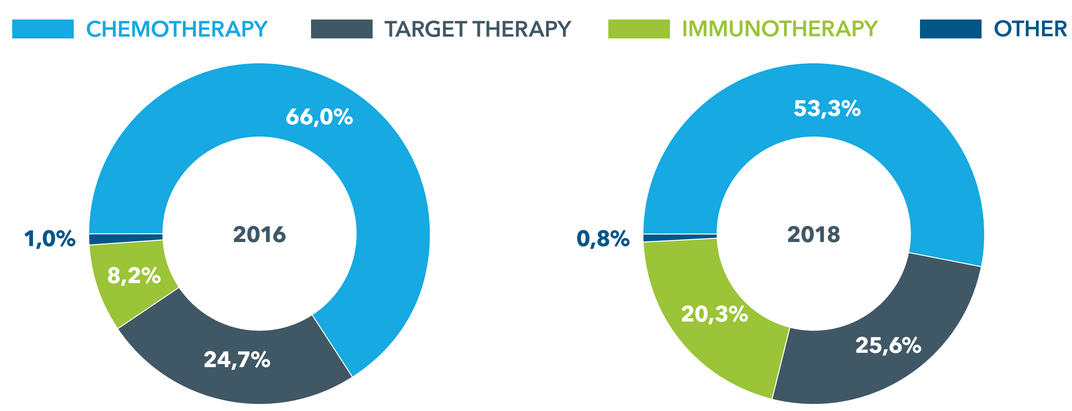
Source: Biomarker Tracking

TABLE 1
Evaluation of NSCLC testing rate: overall rate and specific biomarkers

TESTING RATE	2016	2018	TREND
OVERALL	68%	72%	↑
EGFR	100%	100%	=
ALK	45%	45%	=
PD-L1	**9%**	**58%**	↑

Source: Oncoview

FIGURE 3
Prescribed treatments for NSCLC in 1st and 2nd line, clustered for years of record



"Other" includes: bevacizumab, target therapies and immunotherapies not yet approved in Italy for NSCLC

Source: Oncoview

TABLE 2
NSCLC patient characteristics grouped by year of record and treatment administered

VARIABLES	1ST LINE			2ND LINE		
	2016	2018	IMMUNO 18	2016	2018	IMMUNO 18
ECOG						
<50	8%	7%	**7%**	6%	7%	**4%**
51-65	35%	35%	**47%**	39%	37%	**38%**
65-75	35%	37%	**34%**	41%	41%	**45%**
>75	22%	21%	**12%**	14%	15%	**13%**
AGE						
0	31%	32%	**39%**	28%	29%	**30%**
1	54%	54%	**55%**	57%	59%	**60%**
2	14%	12%	**6%**	14%	10%	**8%**
3	1%	2%	**-**	1%	2%	**2%**
TESTING						
EGFR-T	72%	76%	**74%**	65%	69%	**60%**
ALK-T	46%	59%	**72%**	48%	60%	**57%**
PD-L1-T	9%	48%	**100%**	7%	40%	**44%**
METASTASES	LUNG, LIVER, KIDNEY, BONES			LUNG, LIVER, KIDNEY		

Source: Oncoview