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Point Reached in Targeted Therapy; Where are we?

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ABSTRACT
Lung cancer is a very important public health problem. Identification of new molecular targets and development of novel therapies related to activated immune cytotoxic cells are significant steps in achieving the goal of personalized therapy in lung cancer.
Keywords: Epidermal growth factor receptor (EGFR), Anaplastic lymphoma kinase (ALK), immunotherapy, lung cancer

INTRODUCTION

Lung cancer is a major health problem all over the world and Turkey. Today, lung cancer is the leading cause of cancer-related deaths all over the world. It is a very important public health problem in terms of mortality and morbidity burden. There are 1.8 million new cases per year in the world. According to Turkey Cancer Institute Department of Public Health of 2014 cancer statistics, lung cancer was first place with 21.1% in men and fifth with 5.0% in women with all cancers (1).

Lung cancer is divided into two main subgroups as small cell lung cancer and non-small cell lung cancer (NSCLC). NSCLC constitutes approximately 85% of all lung cancer cases (2).

Histologically, NSCLC has several subtypes, including adenocarcinoma, squamous cell carcinoma, large cell carcinoma and mixed histology. Genotyping studies have revealed genetic/molecular abnormalities in the various subtypes of lung cancer (3). The result of genetic changes, tumors can become dependent for proliferation and survival, on a single oncogene, known as "driver oncogene" (4). Some studies have also shown that these genetic changes may not only be necessary for development or progression of a tumor but are also required for tumor survival, being referred to as "oncogene addiction" (5). This is a rational reason for the development of targeted therapies. In lung cancer cases, the discovery of a number of driver mutations and the therapeutic use of interactions between the immune system and tumor cells in the tumor microenvironment leading to longer survival outcomes (6). The frequency of these mutations and possible therapeutic agents used for these mutations are shown in Table 1. Identification of new molecular targets and development of novel therapies related to activate immune cytotoxic cells are significant steps in achieving the goal of personalized therapy in lung cancer.

In this review, activity and safety data of targeted therapies, biological agents and immunotherapy which used in lung cancer were presented.

CLINICAL AND RESEARCH CONSEQUENCES

Epidermal Growth Factor Receptor (EGFR)

Epidermal growth factor receptor is a growth signal receptor that controls cell proliferation and survival. It is a member of a family of cell surface receptors that dimerize on ligand binding and then activate the intracellular tyrosine kinase domain and trigger downstream pathways that lead to cell proliferation, angiogenesis, and metastases. Targeting the EGFR pathway represents a novel approach to treating NSCLC (7).

Epidermal growth factor receptor mutation frequency is higher in Far East countries (30-40%) than European and American societies (8). The frequency of EGFR mutation can change according to smoking status. While 40-60% patients with EGFR mutation consisted of nonsmokers, mutation frequency is decreasing in the smoking population with older age (9). This mutation is also more frequent in women and young patients. Although many EGFR mutations identified at different locations, the most common mutations are exon 19 deletions (45%) and exon 21 L858R point mutations (10). These two mutations are activating mutations and patients with this mutation are more likely to have to benefit from EGFR tyrosine kinase inhibitors (TKIs). Along with that, another activating mutation is exon 18 mutation. However, because of the low frequency of this mutation due to lack of a sufficient number of patients in clinical trials activity has not been evaluated. Resistance mutations associated with treatment other than activating mutations is monitored. Among these mutations, the best described the T790M mutation in exon 20. In recent years, the new generation of EGFR TKIs is also used effectively in treatment. The first-generation TKIs targeting the EGFR mutation is erlotinib and gefitinib (competitive inhibitors); the second generation is afatinib (non-competitive inhibitor) and the third generation is osimertinib. The clinical studies and their results of EGFR mutation-positive metastatic non-small cell lung cancer (mNSCLC) are presented in Table 2.

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Table 1. Molecular targets and treatment agents in non–small cell lung cancer

	Frequency		
Target molecule	**Adenocarcinoma**	**Squamoz cell carcinoma**	**Drugs**
KRAS	15–33	0	Selumetinib
EGFR	15	0	Erlotinib, Gefitinib, Afatinib, Osimertinib, Dacotinib
ALK	3–13	–	Crizotinib, Alectinib, Ceritinib, Brigatinib, Lorlatinib, Ensartinib
ROS1	1–2	–	Crizotinib, Lorlatinib
BRAF	1–3	0	Dabrafenib, Vemurafenib
MET amplification	3–4	–	Crizotinib, Cabozantinib
Her2	1–3		Afatinib, Trastuzumab, Neratinib, Temsirolimus
MEK	<1	<1	Cobimetinib, Trametinib
RET	1–2	–	Cabozantinib, Vandetanib, Sunitinib, Alectinib
PTEN	2	8	Buparsilib
NTRK1	<1–3	0	Entrectinib
RB1	3–4	7	Palbosiklib
FGFR1	1	20	Dovitinib, nindetanib

Table 2. Anti–EGFR treatments and results used in the treatment of mNSCLC

Study	**Drug**	**Patient number**	**Response Rate (%)**	**Median PFS (month)**	**Median OS (month)**
EURTAC	Erlotinib vs Cisplatin/Docetaxel	173	58 vs 15	9.7 vs 5.2	19.3 vs 19.5
OPTIMAL	Erlotinib vs Gemcitabine/Carboplatin	154	83 vs 36	13.7 vs 4.6	22.7 vs 28.9
ENSURE	Erlotinib vs Cisplatin/Docetaxel	217	63 vs 34	11.0 vs 5.5	26.3 vs 25.5
IPASS	Gefitinib vs Gemcitabine/Paclitaxel	261	71 vs 47	9.5 vs 6.3	21.6 vs 21.9
WJTOG	Gefitinib vs Cisplatin/Docetaxel	172	62 vs 32	9.2 vs 6.3	34.8 vs 34.3
NEJGS002	Gefitinib vs Carboplatin/Paclitaxel	224	74 vs 31	10.8 vs 5.4	30.5 vs 23.6
LUX–Lung 3	Afatinib vs Cisplatin/Pemetrexed	345	56 vs 23	11.1 vs 6.9	28.2 vs 28.2
LUX–Lung 6	Afatinib vs Gemcitabine/Cisplatin	364	67 vs 23	11.0 vs 5.6	23.1 vs 23.5
LUX–Lung 7	Afatinib vs Gefitinib	319	70 vs 56	11.0 vs 10.9	27.9 vs 24.5
FLAURA	Osimertinib vs Erlotinib/Gefitinib	556	80 vs 76	18.9 vs 10.2	Unreached

OPTİMAL was a phase 3 study that comparing erlotinib versus carboplatin/gemcitabine in the first line treatment of EGFR exon 19 and 21 mutant mNSCLC. In this study, a longer progression-free survival advantage was observed in the erlotinib arm (13.6 vs 10.1 months). The event was more prominent in patients with exon 19 deletions (11).

The European Tarceva vs Chemotherapy (EURTAC) trial randomized Europian and American patients with advanced NSCLC with EGFR mutations (exon 19 deletions or L858R mutation in exon 21) to receive erlotinib or cisplatin/docetaxel chemotherapy regimen. The primary endpoint of the study was progression-free survival (PFS). Median PFS was 9.7 months vs 5.2 months favoring erlotinib (HR 0.37; 95% CI 0.25-0.54; p<0.0001) (12).

Another study published in 2015 was the ENSURE. In Asian, EGFR mutant patients, erlotinib and gemcitabine/cisplatin treatments were compared in first-line treatment. Median PFS for erlotinib and chemotherapy were 11.0 and 5.5 months (13).

In all these studies, the PFS benefit was favorable for EGFR TKI and the overall survival (OS) difference could not be shown in any study. The main reason for this situation is that all the studies have been allowed to cross over and thus the patients in the chemotherapy arm have also been used erlotinib. Similar results with erlotinib have been found in studies with gefitinib. The IPASS trial was the first study to compare gefitinib with chemotherapy. When analyzed according to EGFR mutation, gefitinib was found superior to chemotherapy in terms of PFS and response rate (PFS 9.5 vs 6.3 months) (14).

Table 3. ALK inhibitors in the treatment of mNSCLC

Study	Drug	Patient number	Response ratio (%)	Median PFS (month)
PROFILE 1014	Crizotinib vs Platin/Pemetrexed	343	74 vs 45	10.9 vs 7.0
ALEX	Alectinib vs Crizotinib	303	83 vs 75	Unreached vs 11.1
J–ALEX	Alectinib vs Crizotinib	207	92 vs 78	25.9 vs 10.2
ALUR	Alectinib vs Chemotherapy	107	37.5 vs 2.9	7.1 vs 1.6
ASCEND	Ceritinib vs Chemotherapy		73 vs 27	16.6 vs 8.1

Gefitinib was found to be superior to combined chemotherapy regimens in WJTOG and NEJGS-002 studies in Far East patients (15, 16). In the case of studies with gefitinib, the advantage of OS was not revealed due to the similar crossing. Afatinib is the second generation EGFR TKI. It is a more potent EGFR inhibitor when compared to other TKIs and irreversibly binds to Erb2, Erb3, and Erb4 receptors.

LUX-Lung 3 study is an international multicenter study comparing afatinib with cisplatin/pemetrexet. In this study, the duration of PFS was higher in the afatinib arm (11.1 vs 6.9 months) (17). The LUX-Lung 6 study was conducted in the Far East Asian population and the cisplatin/gemcitabine regimen was chosen as the regimen for chemotherapy. In this study, median PFS duration was found to be 5.6 months compared to 11 months of favoring afatinib (18). Although individual studies of these two studies did not reveal overall survival, the combined analysis showed that overall survival could be as high as HR 0.81 in favor of afatinib (19). The LUX-Lung 7 study was phase 2b and afatinib was compared with another EGFR TKI, gefitinib. In this study, PFS was similar in both treatment arms (11.0 vs 10.9 months).The study was not published for the reason that the overall survival data had not completed (20).

Osimertinib is a third generation inhibitor of EGFR and is also effective in patients with the T790M mutation. In the FLAURA trial, the platinum-based chemotherapy regimen and osimertinib efficacy were compared in EGFR mutant patients (21). In this study, osimertinib was shown to provide longer PFS than chemotherapy (18.9 vs 10.1 months). The main problem with patients treated with EGFR TKI is the development of resistance after a while. Drug resistance is developed approximately in 11-12 months (22).

The most common resistance mechanism is exon 20 T790M mutation, which is responsible for about 50% of patients. Other resistance mechanisms include MET amplification, small cell carcinoma transformation and PI3K pathway activation (23). In the case of resistance, a re-biopsy or liquid biopsy should be performed for showing T790M mutation and in this situation, osimertinib is a new treatment option. In patients with the T790M mutation who received first-line EGFR tyrosine kinase inhibitor treatment in the AURA study, median PFS was 10.1 months on the osimertinib arm and 4.4 months on the control arm (24). In this study, it is observed that patients with the T790M mutation have similar median PFS benefit, even for second-line treatment of osimertinib.

Anaplastic Lymphoma Kinase (ALK)

Anaplastic Lymphoma Kinase is a transmembrane tyrosine kinase receptor that is normally expressed in the small intestine, testes, and brain. ALK signaling is activated in NSCLC by the creation of oncogenic fusions of the ALK gene on chromosome 2 with an upstream partner, the echinoderm microtubule-associated protein-like 4 (EML4) (25). The chimeric protein is a potent oncogenic driver. EML4/ALK rearrangements occur in 2-7% of NSCLC patients, usually in non-smokers with adenocarcinoma (26). There are many treatment agents in patients with ALK gene rearrangement positive. Crizotinib, Ceritinib, Alectinib, Brigatinib, and Lorlatinib are molecules that differ from one another with different properties. ALK inhibitor treatments and results were presented in Table 3.

A randomized phase III trial, PROFILE 1007, compared crizotinib with a single agent chemotherapy (pemetrexed or docetaxel) who had received one prior platinum-based regimen (27). The median PFS was 7.7 versus 3.0 months for crizotinib versus chemotherapy (HR 0.49, 95% CI 0.37-0.64). In PROFILE 1014, pemetrexed/cisplatin chemotherapy and crizotinib were compared in the first-line treatment of ALK mutation-positive patients. In this study, PFS benefit was obtained in favor of crizotinib (7.0 vs 10.9 months) (28). The response rate was 74% in the crizotinib arm, 45% in the chemotherapy arm. The most common side effects were visual disturbances, diarrhea, nausea and edema in the crizotinib arm and nausea, vomiting, weakness, and loss of appetite were on the chemotherapy arm. Despite these positive results, the median overall survival was not reached in the two groups due to the 70% ratio of crossover.

The ceritinib and alectinib, which are the second-generation TKI, are used in the crizotinib-resistant ALK-positive patient group. In the ASCEND 2 trial, ceritinib activity was proved to be statistically significant in the group of patients who had progressed after both chemotherapy and first line crizotinib (29). ASCEND 3 study showed that median PFS was increased to 11.1 months in untreated patients. In this study, the response rate was 36.3% (30). The second generation of ALK TKIs was found to be more effective in the central nervous system. The ASCEND-3 study also reported 58.8% central nervous system response rates of ceritinib (30).

In a study evaluating the efficacy and safety of alectinib, the systemic response rate was 50.8% and the central nervous system response rate was 58.8%. 20.6% of this response rate was composed of complete response patients (31). Likewise, in the North American study, the central nervous system response rate was

75% in a patient population with a 25% complete response in the central nervous system (31).

ALEX and J-ALEX studies compared the efficacy of crizotinib with alectinib in the first-line treatment of ALK-positive patients (32). The main difference between these two studies was that the patient population was different and alectinib was used at different doses such as 300 mg and 600 mg. Alectinib was superior to crizotinib in both two studies. PFS, which was about 11 months with crizotinib, was over 25 months in the alectinib arm. Therefore, alectinib was approved by FDA for the first line treatment of m NSCLC with ALK mutation (32).

In patients treated with an ALK inhibitor, the drug resistance and the associated progression are a considerable concern. There are 3 different resistance mutations in patients who develop treatment resistance. These are classified as ALK amplification, on-target genetic mutations (35%) such as ALK mutations, or the occurrence of by-pass pathways (EGFR, IGF1R, c-KIT, SRC) (35%). The cause of resistance at 30% probability is not known (33).

Other Mutations

ROS1 is a receptor tyrosine kinase with homology to the insulin receptor superfamily (7). Its frequency is approximately 1-2%. It tends to be more common in young, women and never or mild smokers. ROS1 rearrangements are typically mutually exclusive with EGFR, ALK, or KRAS alterations. In PROFILE 1001 study, crizotinib demonstrated 56% response rate in ROS1 positive tumors (34).

Activating BRAF mutations occur in 1-3% of mNSCLC cases. Adenocarcinoma subtype and smokers have a higher frequency. V600E mutation is more frequent than other mutations but less frequent in melanoma patients. Response rates were found to be 42% with BRAF inhibitors alone and 63% with combinations of BRAF and MEK inhibitors (6).

The mesenchymal-epidermal transition (MET) proto-oncogene codes for a transmembrane tyrosine kinase heterodimer receptor. Binding of MET to its ligand, the hepatocyte growth factor (HGF) activates multiple signaling pathways leading to cancer cell migration, invasion, proliferation, metastases, and neoangiogenesis (35). Several pathways can lead to dysregulation of the MET/HGF pathway in a variety of tumors including NSCLC. These include rare MET mutations; high MET gene copy number seen in 1-11% of cases, which is associated with high MET protein expression and poor prognosis; and MET amplifications seen in about 20% cases which are linked to secondary resistance to EGFR TKIs in patients with EGFR mutated NSCLC (7).

RET is a receptor tyrosine kinase coded by a gene on chromosome 10 (10q11). It is involved in cell proliferation, migration, differentiation and neuronal migration. These fusion genes have been identified in about 1.7% of adenocarcinomas with young non-smokers having solid subtype pathology (7). In these patients, it may be beneficial to use cabozantinib, vandetanib, sunitinib and alectinib. Response rates range from 16 to 53% (6).

KRAS mutations are detected on chromosome 12 in approximately 20% of NSCLC. They are more frequently in adenocarcinoma, smokers with Caucasian ethnicity (35).These mutations are mutually exclusive with EGFR, HER2, or BRAF mutations and ALK rearrangements. KRAS-mutated tumors are intrinsically resistant to EGFR-directed therapies (36). The inhibition of effector protein of the MAPK pathway (MEK1 and MEK2 kinases) is a potential strategy. Selumetinib is a selective inhibitor of the MEK1/MEK2 kinase. In the second line treatment, a significant improvement is observed in PFS (5.3 vs 2.1 months, p=0.014), though OS was not different (9.4 vs 5.2 months, p=0.21) (37).

HER-2 gene mutation is also seen in 1-3% of NSCLC. It is more common in non-smokers with adenocarcinoma. The studies with neratinib, trastuzumab and temsirolimus are continuing. However, response rates are quite low and range from 10-20% (7).

Fibroblast growth factor receptor 1 (FGFR1) is a member of the FGFR family. Its activation leads to downstream signaling through PI3K/AKT, RAS/MAPK pathways, leading to tumor growth, migration and angiogenesis (38). FGFR1 amplification is seen more commonly in SCC (21%) than adenocarcinoma (3%). Several small molecule FGFR TKIs such as ponatinib and dovitinib are currently under clinical development in Phase I/II studies (35).

Biological Agents and Angiogenesis İnhibitors

The vascular endothelial growth factor (VEGF) pathway is one of the best characterized proangiogenic pathways. It comprises six growth factor ligands (VEGF A-E and placental growth factor) and three receptors (VEGFR 1-3). The prominent role of VEGF signaling pathway has prompted the development of antiangiogenic strategies that include Mabs that block the function of the ligand or the receptor and small molecule TKIs that directly inhibit VEGFRs and their signaling pathways (7). Bevacizumab, an antibody against VEGF ligand A, is the only approved agent in the first-line treatment of advanced nonsquamous histology of NSCLC. Since squamous cell histology, tumor necrosis and cavitation were associated with major hemoptysis in patients in a phase 2 study, squamous mNSCLC patients were not included in the subsequent phase 3 trials (39).

In the ECOG 4599 study, nonsquamous NSCLC were randomized to receive paclitaxel and carboplatin with or without bevacizumab (15 mg/kg). Bevacizumab was associated with significant prolongation of both OS (12.3 vs. 10.3 months; $P = 0.0003$) and PFS (6.2 vs 4.5 months; $P < 0.001$). In the AVAiL study, 1043 patients with nonsquamous NSCLC were randomized to receive gemcitabine and cisplatin with or without bevacizumab (7.5 or 15 mg/kg). PFS was significantly prolonged with both doses of bevacizumab (6.7 vs. 6.1 months for 7.5 mg/kg, P= 0.003 and 6.5 vs. 6.1 months for 15 mg/kg for 15 mg/kg, $P = 0.03$). OS was however not prolonged (40).

Ramucirumab, which is also used in recurrent stomach cancer, was used in combination with docetaxel in second treatment in mNSCLC. When combined with docetaxel in the phase 3 REVEL study, it was shown that the response rate, PFS, and OS were statistically significant compared to chemotherapy (6).

Table 4. PD and PDL–1 antibodies in the first and second line treatment of mNSCLC

Study	Drugs	Response Rate (%)	PFS (Month)	OS (Month)
CheckMate 017	Nivolumab 2 mg/kg vs Docetaxel 75 mg/m^2	20 vs 9	3.5 vs 2.8	9.2 vs 6.0
CheckMate 057	Nivolumab 2 mg/kg vs Docetaxel 75 mg/m^2	19 vs 12	2.3 vs 4.2	12.2 vs 9.4
KeyNote–010	Pembrolizumab 2 mg/kg vs Pembrolizumab 10 mg/kg vs Docetaxel 75 mg/m^2	18 vs 9 18 vs 9	3.9 vs 4.0 4.0 vs 4.0	10.4 vs 8.5 12.7 vs 8.5
POPLAR	Atezolizumab 1200 mg vs Docetaxel 75 mg/m^2	15 vs 15	2.7 vs 3.0	12.6 vs 9.7
OAK	Atezolizumab 1200 mg vs Docetaxel 75 mg/m^2	14 vs 13	2.8 vs 4.0	13.8 vs 9.6
KeyNote–024	Pembrolizumab 200 mg vs Platinum–based chemotherapy	45 vs 28	10.3 vs 6.0	Unreached vs Unreached
CheckMate 026	Nivolumab 3 mg/kg vs Chemotherapy	26 vs 33	4.2 vs 5.9	14.4 vs 13.2

In LUME-Lung studies 1 and 2, in the second line treatment, docetaxel and pemetrexed versus nintedanib were used in combination but the response rates were found to be low. While PFS was favored for combination in both trials, OS advantage was not shown (6). Antiangiogenic agents are associated with class-specific adverse events, including hypertension, hemorrhage and venous thromboembolism, which may preclude treatment in some patients.

Immunotherapy

Responses obtained from acceptable and controllable toxicities in phase 1 trials in previously treated patients have led to the majority of investigations with immunotherapy. Until recently, immunotherapy in cancer treatment has been limited to the treatment of immunogenic tumors such as melanoma and renal cell tumors, while immunotherapeutic approaches in lung cancer are becoming increasingly popular. A large number of phase 1 to 3 studies involving in particular against programmed cell death protein-1 and its ligands against monoclonal antibodies, cytotoxic T lymphocyte-associated protein 4 (CTLA-4), and their combinations, continue throughout the world.

Various PD-1/PD-L1 antibodies (immune check point inhibitors) are already approved for the first- and second-line setting, with manageable toxicity profiles, improved efficacy and longer duration of response compared to standard chemotherapy. Numerous studies have also been conducted on activating or inhibitory receptors that play a role in T cell activation and inhibition. PD-1 and PD-L1 antibodies in the first and second line treatment of mNSCLC are shown in Table 4. The PACIFIC study is a phase 3 study in which immunotherapy was used in the treatment of locally advanced NSCLC. Patients treated with chemoradiotherapy were randomized to placebo and 10 mg/kg durvalumab every 2 weeks for 12 months after treatment. PFS was 16.8 months in the durvalumab arm while 5.6 months in the placebo arm. The objective response rate was 28% in the durvalumab arm while this rate was 16% in the placebo arm (41).

A key Note-24 study comparing pembrolizumab (200 mg/day, 3 weeks) with chemotherapy in primary mNSCLC showed that patients with PD-L1 levels of 50% and over provided PFS (10.3 months, 6.0 months) and OS (unreachable) advantages (42). In the direction of this data, pembrolizumab has been approved by the FDA for first-line treatment in advanced stage NSCLC. In this study objective response rate (ORR) was 45% with pembrolizumab and 28% with chemotherapy. However, in cases with a PD-L1 level> 50%, the ORR was found 80%.

Another study in first-line treatment was KeyNote-21 study. In this study, Pembrolizumab was compared with pemetrexet/carboplatin combination chemotherapy. The patient who developed progression on the chemotherapy arm was continued with pembrolizumab. Overall survival in this study has not yet been reached. PFS was significantly higher in the pembrolizumab arm (13.0 versus 8.9 months) (43).

Check Mate 026 study was another study evaluating the efficacy of chemotherapy with nivolumab in first-line treatment. The ORR in this study was 26% with nivolumab, while 33% with chemotherapy. PFS was found higher in the chemotherapy arm (4.2 versus 5.9 months). OS was found similar in both treatment arms (14.4 vs. 13.2 months) (44). In the squamous cell lung can-

cer, nivolumab, a PD-1 antibody efficiency was compared with docetaxel in Checkmate 017. In this study, the median OS was 9.2 months in nivolumab group and 6.0 months chemotherapy group. Approximately 41% reduction in risk of death was observed. However, in this study, PS was found similar. Treatment-related grade 3 side effects were lower in the immunotherapy arm (7% to 55%).

Following the demonstration that treatment efficacy is independent of PD-L1 level in this study, FDA approved nivolumab on progressed squamous cell lung cancer after platinum-based treatment (45). Another PD-1 antibody, pembrolizumab activity has been evaluated in many studies in the treatment of metastatic NSCLC. In one of these studies, Keynote-010, patients with a PD-L1 level of at least 1% were taken. Survival was significantly superior for the PD-L1 ≥ 50% according to stratification of <1%, 1-49%, and ≥ 50% levels. Atezolizumab is a PDL-1 antibody, unlike the other two drugs. The drug efficacy was shown in POPLAR (phase 2) and OAK (phase 3) studies. OS benefit was demonstrated in the atezolizumab arm in both studies (46).

The patient population in which immunotherapy agents are most effective has not yet been identified. PD-L1 level other determinants that may predict treatment response research continues. One of these was the tumor mutation load. Treatment efficacy was significantly higher in patients with high tumor burden. Another determinant was the immunomodulatory adverse events seen in patients. Both PFS and OS were higher in this group (46).

CONCLUSION

In recent years, the progression-free survival and overall survival in patients with non-small cell lung cancer have improved because of the use of new therapeutic agents. Targeted therapies, immunotherapeutic agents and biological agents developed by the discovery of novel tumor pathways and mutations are used alone or in combination.

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