

Review

PD1 – PDL1 Blockade Immunotherapy Applied as a Lung Cancer Treatment: Main Results, Proven Impact and Recent Knowledge Extensions

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The ability of lung cancer to evade immunosurveillance is ensured by an “immune deficiency state” leading to a tolerance towards tumoral cell’s antigens. Then, a theory that supports the anti-tumoral role of the immune system, made its strong proof, by individualization of a pathway to suppress this immune tolerance. Tumor cells utilize and, in some cases, are dependent upon some specific signals, “Immune check points” to escape immune-mediated destruction. So, blockade of these IC, such as programmed cell death Ligand-1 (PD-L1) and programmed cell death 1 (PD-1), can reactivate an adaptative immune response against tumoral cells. Rapidly growing data reflected the safety of anti PD-L1 antibodies, and then studies proved a distinguished gain in treatment response, overall survival in patients put on immunotherapy in the second or in the first line treatment compared to conventional chemotherapy recommended for advanced lung cancer. Meta-analyses and reviews tried to define the clinical, histological phenotype and the immunostaining showing the best outcome for this treatment. Ongoing trials have the objective of assessing the safety and the benefit of combined anti PD-L1 immunotherapy and chemotherapy. Regarding these results, the widening of the field of studying, anti PD-1/ PD-L1 immunotherapy was a real update of lung cancer management, followed by a total revision of the standard recommendations.

Keywords: Immunotherapy; Programmed Cell Death Ligand 1; Programmed Cell Death 1; Monoclonal Antibody

Background

The ability of lung cancer to evade immune surveillance is ensured by an “immune deficiency state” leading to a tolerance towards tumor antigens. Several molecular substratums inducing this immune tolerance were described. Inhibitory or down regulating receptors which interfere with T cell activation are expressed by dendritic cells or by tumor cells themselves.

Then, a new theory suggests restoring the immune anti-tumor role as a treatment of all immunogenic cancers. This theory made its strong proof, by individualization of a pathway to suppress this immune tolerance. In fact, one approach to trigger antitumor immune response has been termed “immune checkpoint blockade”, referring to the blockade of immune-inhibitory pathways activated by cancer cells [1].

PD-1 / PD-L1 blockade immunotherapy restore a secondary immune reaction, mediated by CD8+ lymphocytes, targeting tumor cells. Currently, there is sufficient data about safety, efficacy, global survival and response of the metastatic non small cells lung cancer to these antibodies.

Principles of Immunotherapy

Human tumors arise out of a mixture of genetic mutations and modifications that provides cellular immortality, aggressiveness, metastatic potential but also creates “neo-antigens”. Considered as foreign proteins, they would render neoplastic cells detectable and targeted by the immune system. Nevertheless, a tumor had the ability to evade the immune system. The human adaptive immune system fights cancer cells through the activation of T lymphocytes. These latters, already activated

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by Antigen Presenting Cells (APC) and differentiated into CD8+ or CD4+, infiltrate tumor tissue and induce cellular apoptosis. Regulatory T lymphocytes and APC preserve this cycle, after its onset, to deviate towards an auto-immune reaction. Using the Immune Checkpoints (IC), the APC modulate the activation of T lymphocytes, inhibit their proliferation, decrease cytokine release, and stop cytotoxicity. Tumor cells also utilize and, in some cases, are dependent upon these signals to escape immune-mediated destruction [2]. So, blockade of these IC, such as cytotoxic T-lymphocyte associated protein 4 (CTLA-4), programmed cell death Ligand-1 (PD-L1) and programmed cell death 1 (PD-1), can restore the adaptative cellular immune response against a tumor and enable T lymphocytes to target it. This fact is proven in vitro, then, tried for several solid tumors. This additional “molecularly targeted agents” have been evaluated in clinical trials with limited success, and efforts are currently focusing on identifying biomarkers in tumor or blood to predict benefit from such therapies. Phase I and II trials were performed in patients with melanoma, renal cell carcinoma, non-Hodgkin lymphoma esophageal cancer, colorectal cancer and lung cancer [2,3].

For NSCLC, three antibodies targeting this specific IC had reached clinical phase studies: Nivolumab, Pembrolizumab and Atezolizumab.

Anti PD-1 Immunotherapy Used in NSCLC and its Main Results

Nivolumab

Nivolumab is an IgG4, non-killer isotype, fully human monoclonal Antibody targeting membranous PD-1.

This molecule was tried as a treatment of NSCLC, in a phase I dose escalation cohort expansion trial [4]. The aim was to evaluate safety, clinical activity of nivolumab in patients with advanced NSCLC, kidney, melanoma, colorectal, and castration-resistant prostate cancer. During cohort expansion, patients with NSCLC were stratified for squamous versus nonsquamous cell histology and randomly assigned to receive 1-, 3-, or 10-mg/kg doses of Nivolumab. Patients continued treatment for up to 96 weeks (12 cycles) or until unacceptable toxicity, confirmed complete response, confirmed disease progression, or withdrawal of consent. Based on pharmacokinetic exposure, safety, and efficacy data from all patients enrolled onto this study (ORR, OS), the dose of Nivolumab 3 mg/kg administered intravenously every 2 weeks was retained as the most convenient, and chosen for later phase III trials. In phase I trial, researchers underlined an encouraging response in squamous NSCLC (ORR= 17%, OS= 9.2 months, survival rates of 41% at 1 year and 19% at 3 years). Phase II trials of Nivolumab monotherapy [5] confirmed that fact in second line treatment of squamous NSCLC (ORR= 15%, OS= 8.2 months). So, phase III trials were performed first in patients with squamous NSCLC. In CHECKMATE17 [6], publishers randomly assigned 272 patients with advanced, previously treated squamous-cell NSCLC, to receive Nivolumab, at a dose of 3 mg/kg every 2 weeks, or Docetaxel, at a

dose of 75 mg per square meter of body-surface area every 3 weeks. The primary end point was overall survival. Regardless of PD-L1 expression level, overall survival (median OS = 9.2 months with Nivolumab vs 6 months with Docetaxel, OS rate at one year = 42% with Nivolumab vs 24% with Docetaxel), response rate (20% vs 9%, P=0.008), and progression-free survival (3.5 months vs 2.8 months) were significantly better with Nivolumab than with Docetaxel. Across the prespecified expression levels (1%, 5%, and 10%), PD-L1 expression was neither prognostic nor predictive of any of the efficacy end points. The rates of objective response, OS and PFS in the PD-L1 subgroups favored Nivolumab and were similar to those in the primary population. In CHECKMATE57 trial [7,8], targeted population was advanced, previously treated, non-squamous NSCLC. The objective was to compare Nivolumab to Docetaxel. The primary end point was the OS. Data after two years follow-up showed a significant benefit for patients put on Nivolumab (two years OS rate = 51% Nivolumab vs 39% Docetaxel). Differing to squamous population in CHECKMATE17, in this trial, at the time of the interim analysis, a test for interaction suggested a strong predictive association between PD-L1 expression and clinical outcome at all expression levels for all efficacy end points, especially survival benefit. Using PD-L1 expression cutoffs as $\geq 1\%$, $\geq 5\%$, and $\geq 10\%$, the best survival improvement was reported for the subgroup with PD-L1 $\geq 10\%$ (median OS = 19 months with Nivolumab vs 8 months with Docetaxel).

Efficacy of Nivolumab in first line treatment of NSCLC is less obvious and still unproven. Phase I multicohort studies using Nivolumab in chemo-naïve stage IIIB or IV NSCLC demonstrated a tolerable safety profile and durable responses [9,10]. In Gettinger study (9), Among the 20 patients with a PD-L1 expression level of 5% or more, the objective response rate was 31% and the rate of PFS at 24 weeks was 40%. On the basis of this preliminary data set, this population was thought to be more likely to show a progression-free survival benefit with Nivolumab than patients with a lower (<5%) PD-L1 expression level. CHECKMATE 026, a Phase III trial, was performed on 541 patients with untreated stage IV or recurrent NSCLC and a PD-L1 tumor-expression level of 1% or more to receive Nivolumab or platinum-based chemotherapy [11]. The primary end point was progression-free survival among patients with a PD-L1 expression level of 5% or more. Among the 423 patients with a PD-L1 expression level of 5% or more, the median PFS was 4.2 months with Nivolumab vs 5.9 months with chemotherapy, and the median OS was 14.4 months versus 13.2 months respectively. Similar results regarding PFS and OS were found in the analyses including all the patients (PD-L1>1%) who had undergone randomization. Researchers underlined some observations worth noting about CHECKMATE 026: A high percentage of patients in this trial who had received palliative radiotherapy previously, up to 2 weeks before randomization, and a median time from diagnosis to randomization of approximately 2 months. Those two factors may have selected for

patients who had a poorer prognosis because of a high tumor burden and advanced disease. According to study design, patients in Chemotherapy group have got Nivolumab as a second line after progression. Given that Nivolumab therapy prolongs survival among previously treated patients with advanced NSCLC [7,8], the high frequency of subsequent Nivolumab treatment may have contributed to the favorable OS in the chemotherapy group.

Pembrolizumab

Pembrolizumab is a type IgG4, non-killer isotype, humanized monoclonal antibody, targeting PD-1 expressed in tumoral cells.

The open-label phase II/III KEYNOTE-010 trial [12] showed a significant improvement in term of OS for both doses tested (at 2 mg/kg biweekly: HR 0.71, $P=0.0008$; at 10 mg/kg biweekly: HR 0.61, $P<0.0001$) compared to Docetaxel in patients with previously treated PD-L1-positive ($\geq 1\%$) advanced NSCLC. The median OS was 8.5 months versus 10.4 months versus 12.7 months for Docetaxel, Pembrolizumab 2 mg/kg, and Pembrolizumab 10 mg/kg, respectively. No difference for PFS was reported in the total population, with a median time of 4 months for all three cohorts. In the subgroup of patients with PD-L1 expression $\geq 50\%$ of tumor cells, there was an improving of both OS (at 2 mg/kg biweekly: HR 0.54, $P=0.0002$; at 10 mg/kg biweekly: HR 0.50, $P<0.0001$) and PFS (HR: 0.59 for both doses, $P=0.0001$ and $P<0.0001$ for 2 and 10 mg/kg, respectively). These results highlighted the relationship between PD-L1 status and Pembrolizumab efficacy beyond the first-line treatment.

KEYNOTE-024 was one of the largest phase III trials using Pembrolizumab as a first line treatment for NSCLC [13]. Researchers randomly assigned 305 patients who had previously untreated advanced NSCLC with PD-L1 expression over 50% of tumor cells and no sensitizing mutation of the epidermal growth factor receptor gene “EGFR” or translocation of the anaplastic lymphoma kinase “ALK” gene to receive either Pembrolizumab (at a fixed dose of 200 mg every 3 weeks) or the investigator’s choice of platinum-based chemotherapy. Progression free survival (PFS) was significantly improved by approximately four months with immunotherapy (10.3 vs. 6.0 months). The hazard ratios favored Pembrolizumab in all subgroups examined, with lower benefit in never smokers. After the superior efficacy of Pembrolizumab at second interim analysis (at 6 months OS rate: 80.2% vs. 72.4%; HR: 0.60, $P=0.005$), the trial was stopped early by the external data and safety monitoring committee, with patients in the chemotherapy group given the opportunity to receive Pembrolizumab. This significantly prolonged OS data was remarkable (70% alive at one year compared to 54% on chemotherapy), more than 40% of patients were switched from the control arm to Pembrolizumab after progression of the disease. The response rate to Pembrolizumab treatment was higher (45% vs. 28%) and the median duration of response was longer (not reached vs. 6.3 months). Patients enrollment in KEYNOTE-042 [14] is ongoing.

This trial is examining efficacy of Pembrolizumab in patients with NSCLC having 1% or more PD-L1 positivity in their tumors, comparing it to a control group receiving a doublet of platinum based chemotherapy plus Paclitaxel or Pemetrexed.

Anti PD-L1 Immunotherapy Used in NSCLC and its Main Results

Atezolizumab

PD-L1 is a trans-membranous protein that negatively regulates immune responses through its interactions with PD-1. Several monoclonal antibodies were developed, such as Atezolizumab at the head of the group, to block the PD-1/PD-L1 interaction.

Phase II trials, POPLAR and BIRCH, made clear the efficiency of Atezolizumab immunotherapy in NSCLC. BIRCH was an open-label, multicenter, single-arm trial which brought together 667 advanced NSCLC patients without brain metastases, with PD-1 expression $> 1\%$ of tumor cells [15]. Cohorts of patients were established according to their characteristics. EGFR and KRAS mutations were identified in 327 and 177 patients overall, respectively. Three cohorts of patients were characterized: 142 chemo-naïve patients (Cohort 1), 271 patients who had progressed after one prior platinum therapy (Cohort 2) and 254 patients who had undergone two or more prior chemotherapy regimens (Cohort 3). Overall response rate, which was the primary endpoint, was 19%, 17% and 17% in the three cohorts respectively. Six-month PFS rates were 46%, 29%, and 31% for the three cohorts. Efficiency was significantly correlated to PD-L1 expression and to non-previously treated status.

In the phase II POPLAR trial [16], researchers randomized 287 patients with previously treated NSCLC to Atezolizumab monotherapy (144 patients) or Docetaxel (143 patients) chemotherapy. The median OS in POPLAR was 12.6 months (95% CI: 9.7–16.0) and 9.7 months (95% CI: 8.6–12.0), with HR=0.73 (95% CI: 0.53–0.99; $p=0.04$) for the Atezolizumab and Docetaxel arms, respectively.

After the gain in survival of 2.9 months with Atezolizumab in a phase II trial [16], the open-label, randomized phase III OAK trial was conducted [17], including patients with advanced NSCLC (squamous or non-squamous cell carcinomas) who had progressive disease after one to two previous cytotoxic chemotherapy regimens, comparing Atezolizumab with Docetaxel. Its preliminary analysis of data confirmed a significant improvement in survival of the anti-PD-L1 agent compared to docetaxel, in previously treated NSCLC patients, regardless of PD-L1 expression status or levels (median OS: 13.8 vs. 9.6 months in the Atezolizumab and Docetaxel arms, respectively; HR: 0.73; $P=0.0003$). Regarding histologic subgroups, patients with both non-squamous (HR: 0.73; $P=0.0383$) and squamous (HR: 0.73; $P=0.0015$) derived benefit from Atezolizumab whatever was the PD-L1 expression status [17].

Toxicity profile in Use of PD1/PDL1 Antagonists

Immunotherapy has a different toxicity profile compared to third generation chemotherapy [6,8,18]. Outstanding side effects related to immunotherapy use are immuno-allergic manifestations of the skin, lung, thyroid or gastro-intestinal tract (table 1).

Initial approval and evaluation studies showed treatment-related adverse events (TrAE) in approximately 41% to 70.9% of all patients [4,13,19,20]. Most of side effects were benign and mild. Grade 3 to 5 TrAE were noted in 5 to 9% of patients put on PD1/PDL1 antagonists. In phase III studies, severe TrAE were more frequent in chemotherapy than immunotherapy [6,7,19]. Usual systemic TrAE caused by PD1/PDL1 antagonists were fatigue (10 - 19.4%), pruritus (2 - 10.7%), decreased appetite (8 - 10.5%) and joint's pain (2 - 9.1%).

Table 1: Most frequent treatment-related adverse events of PD1/PDL1 antagonists used in advanced NSCLC

	Reck (13)		Garon (19)		Gettinger (4)	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Treatment-Related AEs occurring in ≥ 5% of Patients put on PD1/PDL1 antagonists monotherapy						
anemia	5.2	1.4	4.2	0		
fatigue	10.4	1.3	19.4	0.8		
diarrhea	14.3	3.9	8.1	0.6	11.6	0.8
constipation	3.9	0	2	0.4		
nausea	9.7	0	7.5	0.8		
Decreased appetite	9.1	0	10.5	1		
Hypothyroidism	9.1	0	6.9	0.2	6.2	0
pneumonitis	5.8	2.6	3.6	1.8	7	2.3
asthenia			4.8	1		
pyrexia	10.4	0	4.2	0.6		
Immune related AEs of PD1/PDL1 antagonists						
Skin reaction	3.9	3.9	9.7	0.2	15.5	0
nausea	9.7	0	7.5	0.8		
Hypothyroidism	9.1	0	6.9	0.2	6.2	0
pneumonitis	5.8	2.6	3.6	1.8	7	2.3
Infusion reaction	4.5	0	3	0.2	3.9	0.8
pruritus			10.7	0		
thyroiditis	2.6	0				

Note: The table shows frequency of each side effect in the corresponding trial

The most common immune-mediated side effects included cutaneous, thyroid, gastro-intestinal, and pulmonary events occurring for 16%, 16.9%, 12%, and 7% of patients respectively. Grade 3 to 5 TrAE were: pulmonary (1.8 - 2.3%), gastro-intestinal (0.8 - 1.4%), infusion reactions (0.2 - 0.8%) and hepatic (0.8 - 1%) events.

Immuno-allergic TrAE were generally low grade, and those at higher grades were manageable in most cases with drug discontinuation, immune suppressive agents (steroids) or hormonal substitution (thyroxin therapy).

Considering the limited use of anti PD1/PDL1, the recent recognition as a certified treatment for cancer, there is an evident lack of knowledge concerning long-term or delayed side effects. So, data of follow-up after treatment is still growing.

Combined Immunotherapy and Chemotherapy: A Worthy Tendency?

Conventional chemotherapy directly targets tumor cell mitotic process. Besides, several clinical evidences suggest that antitumor effects of cytotoxic chemotherapy also occur through enhancement of the adaptative immune reaction [21-23]. Indeed, cytokine secretion, induction of a pro-inflammatory anti-tumor profile and activation of pathways able to promote recognition of the tumor antigens by immune effector cells were described in vivo after chemotherapy. Based on this data, the association of chemotherapy and immunotherapy was suggested to be synergic. The objective was to strengthen the impact of immune checkpoints blockade, especially for tumors which express in low degrees those receptors.

Combining platin-based doublet chemotherapy to PD1/PD-L1 antagonists was tried. Potential benefits of combining Pembrolizumab with chemotherapy were reported in KEYNOTE-021 study [24]. In this phase II trial, Pembrolizumab was given with standard first-line chemotherapy (carboplatin/pemetrexed) for untreated stage IIIB or IV non-squamous NSCLC patients with no targetable EGFR or ALK genetic mutations, whatever was the PD-L1 expression level. The primary endpoint was the proportion of patients who achieved an objective response, defined as the percentage of patients with radiologically confirmed complete or partial response according to RECIST 1.1. Results showed an objective response after treatment in 55% of patients put on Pembrolizumab plus chemotherapy, and in 29% of patients put on chemotherapy alone. In the group of patients given Pembrolizumab, there was an improved overall response rate (ORR: 55% vs. 29%, $P=0.0016$) and median PFS (13.0 vs. 8.9 months; HR: 0.53; $P=0.0102$). Response after this combination was noted regardless of PD-L1 expression, although those with the highest expression have higher response rates (ORR: 80% for PD-L1 $\geq 50\%$). This encouraging finding needs further exploration. An ongoing international, randomized, double-blind, phase III study, KEYNOTE-189, is performed to assess the addition of Pembrolizumab to chemotherapy in NSCLC chemo-naïve patients [24].

In another multi-cohort study, researchers set the objective of exploring the safety and efficacy of Nivolumab monotherapy versus Nivolumab combined with platinum-based doublet chemotherapy as a first line treatment of advanced NSCLC patients [25]. Nivolumab was evaluated with cisplatin-gemcitabine for squamous or cisplatin-pemetrexed for nonsquamous cell tumors or carboplatin-paclitaxel for both histologies. ORR was 33% for Nivolumab plus cisplatin-gemcitabine, 47% for Nivolumab plus cisplatin-pemetrexed, 47% for Nivolumab 10 mg/kg plus carboplatin-paclitaxel, and 43% for Nivolumab 5 mg/kg plus carboplatin-paclitaxel. In addition, 2-year OS rates were 25, 33, 27 and 62%. This small study suggested that a combination of chemotherapy with immunotherapy may be feasible and improve response rates, especially considering the association Nivolumab-Carboplatin-Paclitaxel.

Combined Immunotherapy and Radiotherapy: Mutual Potentiating Effects

PD-1/PD-L1 antibodies serve to lift the restraint on the secondary cell-mediated anti-tumoral immune response. High-dose ionizing irradiation may enhance the immunogenicity of the tumor, making it more targetable [26] through: release of pro-inflammatory cytokines (such as interferon- γ), increased production and variety of tumoral antigens due to DNA damage, expression of molecules on tumor cells that make them susceptible to T-cell-mediated apoptosis, increasing the ratio of T-effector cells compared to T-reg cells, and direct vascular damage that allows dendritic cells to access tumor microenvironment and to mature into antigen presenting cells [27]. This "Abscopal phenomenon" was reported in mice [28] which had shrinkage of the tumors inside or far from the radiated zone. It has been also proven that fractionated radiotherapy can induce PD-L1 expression in tumor cells and strengthen their immune cover-up [29]. This escape could be neutralized by PD-L1 antagonists. So, radio-immunotherapy potentially could tip the balance in the tumor environment from immunosuppression to immune activation. Several ongoing trials have set protocols of concurrently combined immunotherapy and irradiation, or also chemoradiation followed by immunotherapy. Those studies concerned NSCLC, breast cancer, melanomas and glioblastomas [30-33], aiming to assess tumoral progression in and outside the radiation field and toxicity of such combination.

Response-Predicting Biomarkers?

PD-L1 expression rate on viable tumor cells, or also tumor proportion score (TPS) has been suggested as a reliable predictive of efficiency of PD-L1 blockade agents, since it guarantees a site of action. However, it has been shown in several studies that many patients with minor expression of PD-L1 can still respond to PD1 pathway blockade, while some patients with high levels of PD-L1 do not respond so. Regarding histologic subgroups, patients with both non-squamous and squamous cell tumors benefit

from Nivolumab whatever was the PD-L1 expression status [8]. What is also understood is that the response to different immunotherapeutic combinations probably relies on the patient's entire immune status, including PD-L1 status.

In fact, identifying new predictive biomarkers is challenging, knowing the adaptive nature of immunity, the presence of multiple immune checkpoints involved in T-cell regulation, endless mutations within the tumor that could affect its immunogenicity and lead to a molecular heterogeneity.

There are now several commercially available anti-human PD-L1 antibodies, and there has been a large debate over the producibility of staining using different antibodies [34,35] and an over estimation of the TPS. Some authors explained these results by an expression of the PD-L1 by tumor-associated macrophages [36].

New Recommendations Including PD1/PDL1 Blockade Therapy

After publication of the CHECKMATE 017/057 results, efficacy of Nivolumab used for squamous and non squamous advanced NSCLC as a second line therapy is well proved [6-8]. The improved survival in patients with relapsed NSCLC treated with Nivolumab compared with Docetaxel in CHECKMATE 057 establishes a new treatment option for patients who have progressed on platinum-doublet chemotherapy. Food and Drug Administration (FDA) recommendations were first limited to squamous cell lung cancer, then extended to all NSCLC three months later [37]. Nivolumab represents a new treatment option for patients requiring second-line treatment for metastatic non-small cell lung cancer. The role of Nivolumab in patients with sensitizing EGFR and ALK alterations is less clear. Until dedicated studies are performed, patients with EGFR or ALK alterations should have progressed on appropriate targeted therapy before initiating PD-1 inhibitor therapy. Even patients whose tumors lack programmed cell death ligand 1 (PD-L1) expression also appear to have durable responses, so this expression is a nonessential complementary diagnostic for Nivolumab use.

As a phase I trial, KEYNOTE 001 was conducted to prove efficacy (reflected by objective response rate ORR) and safety of use of Pembrolizumab in patients with NSCLC. The FDA considered the ORR of 41% in 61 patients with metastatic NSCLC treated with Pembrolizumab, whose tumors staining for PD-L1 \geq 50% determined by an FDA-approved test, as evidence of a clinically meaningful magnitude of response. This ORR exceeded the reported ORR for any of the approved drugs for second-line treatment of patients with NSCLC until 2015 [38]. In October 2015, Pembrolizumab was approved by the FDA for use in patients with metastatic NSCLC whose tumors express PDL1 and who have disease progression on or after platinum-containing chemotherapy or targeted

therapy against ALK or EGFR, if appropriate. The dose approved for use is 2 mg/kg every 3 weeks. This dose was then used in KEYNOTE 010 phase II trial [12].

In October 2016, the first U.S. FDA approval of a checkpoint inhibitor for first-line treatment of lung cancer took place [39].

Conclusion

Immunotherapy using PD-L1 blockade was a real update of the lung cancer management. After some large scale trials on metastatic and /or locally advanced tumors, the field of application has been widened. Interestingly, researchers suggest a benefit in the association to radiation therapy or even to classic chemotherapy doublets. This emerging paradigm of cancer immunotherapy may have obvious implications in further updated recommendations.

List of Abbreviations

PD-L1= programmed cell death Ligand-1

PD-1= programmed cell death 1

APC= Antigen Presenting Cells

IC= immune checkpoints

CTLA 4= cytotoxic T-lymphocyte associated protein 4

IgG= immunoglobulin G

NSCLC= non-small-cell lung cancer

ORR= overall response rate

OS= overall survival

PFS= progression-free survival

EGFR= epidermal growth factor receptor

ALK= anaplastic lymphoma kinase

KRAS= Kirsten rat sarcoma

HR= hazard rate

Tr AE= treatment-related adverse events

TPS= tumor proportion score

FDA= food and drug administration

Declarations

- Consent for publication
- Availability of data and material : not applicable
- Competing interests : all authors declare having no conflict of interest in relation to the main topic of the manuscript

Authors' contributions: writing of the manuscript, bibliography recruiting and discussion were ensured by NB. Revision and more bibliography selection were done by Pr SF.

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