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Current Knowledge of Ipilimumab and its use in Treating Non-small Cell Lung cancer

Joseph A. Pinto¹, Luis E. Raez², Helena Oliveres³, Christian C. Rolfo⁴

Affiliations

1, Unidad de Investigación Básica y Traslacional, Oncosalud-AUNA, Lima-Perú

2, Thoracic Oncology Program, Memorial Cancer Institute/Memorial Health Care System, Florida International University.

3, Phase I-Early Clinical Trials Unit, Oncology Department, Antwerp University Hospital, Antwerp, Belgium.

4, Marlene and Stewart Greenebaum Comprehensive Cancer Center, University of Maryland School of Medicine, Baltimore, MD, USA

Corresponding author

Prof. Joseph A. Pinto, MSc.

Unidad de Investigación Básica y Traslacional

Oncosalud-AUNA

Av. Guardia Civil 571, San Borja

Lima 34 – Peru

Email: jpinto@gecoperu.org

Phone: ++51 98432239

Abstract

Introduction: The systemic treatment of non-small cell lung cancer (NSCLC) has changed dramatically with the identification of actionable mutations and the use of targeted agents. Unfortunately, many tumors will acquire resistance and >75% of NSCLC cases lack for an actionable gene aberration. In this setting, immunotherapy rises as effective therapeutic where immune checkpoint inhibitors have entered or are entering the market in many neoplasms, including NSCLC. Ipilimumab is a monoclonal antibody targeting CTLA-4, promoting T-cell activation and its subsequent anti-tumoral immune effect. Ipilimumab might have a very important role in NSCLC as it does in melanoma because of its synergistic effect with PD-1/PDL-1 inhibitors.

Areas covered: We summarize current results of clinical studies of ipilimumab for efficacy and safety in NSCLC and also the current knowledge about potential biomarkers for its efficacy.

Expert Opinion: Combined use of PD-1/PDL-1 and anti-CTL4 inhibitors increases the efficacy against NSCLC and it is a very promising approach not only in NSCLC but also in small cell lung cancer (SCLC) for first or second-line therapy. It's very important to identify biomarkers that can better select the population of patients that benefit the most with these checkpoint inhibitors.

Keywords: Non-small cell lung cancer; CTLA-4; immunotherapy; biomarkers

1.-INTRODUCTION

Lung cancer is a lethal disease producing >1.8 million deaths yearly around the globe (1). Lung cancers are divided in two main histological subtypes with different epidemiology and molecular features: *i*) non-small cell lung cancers (NSCLC) ($\approx 85\%$ of all cases of lung cancer) and *ii*) small-cell lung cancer (SCLC) with a frequency of $\approx 15\%$ (2).

The systemic therapy in advanced NSCLC has evolved quickly since new actionable mutations were discovered and new technologies were incorporating to the clinical routine (3). The therapeutic standard for advanced NSCLC includes platinum doublets or platinum triplets (addition of bevacizumab to platinum based combinations for non-SCC) in cases without treatable driver mutations; targeted therapy in cases bearing EGFR mutations, ALK or ROS1 rearrangement and immunotherapy with pembrolizumab, limited to tumors with PD-L1 > 50%. In the other hand, nivolumab is an option in previously treated with chemotherapy (4).

NSCLC has a high burden of neoantigens due to its mutational features; it makes this cancer suitable for immunotherapy, specifically immune checkpoint inhibitors to overcome the immune tolerance promoted by PD-1, PDL-1 and CTLA-4 (5,6). While nivolumab and pembrolizumab are consolidated immunotherapeutic agents in NSCLC, ipilimumab has showed limited efficacy contrasting to those obtained in melanoma. New ipilimumab combinations with chemotherapeutic agents or radiation are promising. In the other hand, mechanisms underlying anti-CTLA-4 and anti-PD-1 checkpoint blockade are different allowing the opportunity of combining ipilimumab with anti-PD-1 or anti PDL-1 inhibitors (7). A recent meta-analysis by Wu et al., evaluating melanomas, NSCLC and SCLC, showed improved benefits in PFS and overall response rate (ORR) in the addition of nivolumab to ipilimumab (8).

2.-OVERVIEW OF THE MARKET

Targeting mutational drivers in genes such as anti-EGFR, ALK, ROS-1 and other genes has created a revolution with marked increase in PFS and OS (9). *EGFR* mutations in NSCLC are present in $\approx 19\%$ of in Western population and $\approx 38\%$ in the Asian population. In contrast to EGFR, ALK and ROS1 alterations have lower frequency (<8% and 2%, respectively). Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) have superior efficacy than chemotherapy in first-line treatment of these patients. Unfortunately, there is a limited improvement in the overall survival. The pooled study of the trials LUX-Lung 3 and LUX-Lung 6

showed an improved overall survival only in patients with del19 EGFR mutations (10).

Despite this progress, there is an unmet need for better therapeutic strategies for NSCLC patients whose tumors are negative for actionable mutations. Nivolumab, pembrolizumab and atezolizumab have demonstrated efficacy and safety in NSCLC. Nivolumab and atezolizumab have the Food Drug Administration (FDA) approval for use in NSCLC whose disease progressed during or after platinum-based chemotherapy, and pembrolizumab has been approved for first-line treatment in patients with metastatic NSCLC without actionable mutations for FDA-approved targeted therapy.

The competition between anti PD-1/PDL-1 inhibitors is strong, conversely to ipilimumab, the only anti-CTLA-4 agent approved by FDA for cancer. Ipilimumab in monotherapy, nowadays, has no demonstrated efficacy in NSCLC; however, combination of ipilimumab in combination with nivolumab in patients with high tumor mutational burden (TMB) is promising in first- or second-line non-oncogene driven advanced NSCLC, regardless the PD-L1 expression.

New ongoing trials are studying the therapeutical strength of the combination between anti PD-1/PDL-1 agents with anti-CTLA-4 inhibitors and combination of immune checkpoint inhibitors with radiotherapy. Ipilimumab have a promising landscape in a near future in the treatment of NSCLC.

3.-IPILIMUMAB DEVELOPMENT

The human *CTLA-4* (Cytotoxic T-Lymphocyte associated protein 4) gene was identified by Dariavach *et al.* by using a DNA probe of mouse *Ctla-4* in a human genomic cDNA library. An overall homology of 76% was predicted between human and murine genes (11,12).

Allison *et al.* described an antagonist effect between CD28 and CTLA-4 on the response to T-cells stimulation (13). They used soluble antibodies anti-CTLA-4 describing that CTLA-4 blockade potentiate T-cell response and proliferation. Ling *et al* performed complete characterizations of these proteins describing high levels of CTLA-4 transcripts in lymphoid tissues (14). Several studies in animal models showed an enhancement in anti-tumor activity reversing CD8+ T-cells tolerance with regression of established tumors by blockade of CTLA-4 (15,16). These promising experiences in animal models encouraged the development of anti-human CTLA-4 antibodies. Thanks to his discoveries and his work in the developing of ipilimumab, Allison was awarded with the Nobel Prize in Physiology or Medicine in the year 2018.

Clinical trials with ipilimumab started in 2000 in melanoma patients' achieving its first FDA approval in 2011(17).

4.-MECHANISM OF ACTION OF IPILIMUMAB

T-cells are key players of immune response and tolerance. Effective activation of naïve T-cells requires two signals delivered by an antigen-presenting cell (APC). The first signal is the recognition of an antigen exposed on the major histocompatibility complex (MHC) by T-cell receptors (TCR). The second signal corresponds to an additional co-stimulatory signal triggered by CD28, which is located on T-cells membrane and activated by CD80/86 (also known as B7-1 and B7-2, respectively), expressed on APCs. This activation produce proliferation, differentiation and the effector function of T-cells (18,19).

In order to control the immune response, inhibitory signals suppress the T-cell activation. Main signals inhibiting T-cells activation are triggered by CTLA-4 and PD-1 expressed on cell membrane of T lymphocytes. CTLA-4 is tough to regulate T-cell proliferation early in the immune response and primarily in lymph nodes while PD-1 suppresses T-cells later in peripheral tissues.

Regulation by CTLA-4 is produced by ligand competition for B7 between CTLA-4 and CD28. Unlike CD28, CTLA-4 binding to B7 does not produce a stimulatory signal. T-cells will be activated or not depending of the relative amount of CD28:B7 versus CTLA-4:B7. In contrast, inhibitory action of PD-1 is not based in ligand competition but in levels of expression and it is produced under binding to PDL-1, expressed on APCs (18,20). The PD-1 pathway consists in the PD-1 receptor and its ligands PDL-1 and PDL-2. PD-1 and its ligands regulate T-cell tolerance and autoimmunity. PD-L2 expression is restricted only to professional antigen-presenting cells although through microenvironmental stimuli, PD-L2 could be expressed in a wide range of immune cells and some non-immune cells (21,22).

One hallmark of the cancer is the genomic instability, it means great susceptibility to develop new mutation across its entire genome. This phenomenon should lead to the synthesis of neoantigens turning cancer cells into an easy target to the host immune system. However, cancer cells may evolve to diminish its neoantigen presentation and manipulate the mechanisms of immune tolerance to escape from the immune surveillance. Tumor cells express on their surface inhibitory ligands that suppress T-cells and APC activation.

Ramagopal *et al.* described the structure of the complex formed by ipilimumab with its human CTLA-4 target. Ipilimumab binds to CTL4-A on the front β -sheet face and intersects with the CTLA-4:CD28 recognition surface, avoiding the ligand

competition and in consequence promoting the T-cell recognition of tumoral antigens and the further activation of the anti-tumoral immune response (23,24).

5.-PHARMACOKINETICS

Ipilimumab is not metabolized via cytochrome P450 pathway. The mean clearance is 403 mL/day (coefficient of variation: 38%). Clearance of ipilimumab increase in direct relationship with the body weight and serum levels of lactate dehydrogenase (25). Pharmacokinetic volume of distribution calculated by the steady-state method is 6.0L; terminal half-life, 15.4 days (coefficient of variation: 34%) and a time to steady state of 9 weeks of repeated dosing every 4 weeks (26). Absolute lymphocyte count increases significantly after treatment with ipilimumab as single agent or combined with chemotherapy (27).

Several early clinical trials have used ipilimumab in dose ranging from 0.3 to 10 mg/Kg. The dose approved by FDA as adjuvant therapy in melanoma is 10 mg/kg and 3mg/kg for unresectable or metastatic disease.

6.-PHASE I CLINICAL TRIALS

Ipilimumab has been evaluated in phased combination with paclitaxel (175mg/m²) and carboplatin (area under the curve=6) where 10 mg/kg is the recommended dose with toxicities profiles consistent with the previously predefined profile for these three drugs (28).

The multicohort phase I trial CheckMate 012 evaluated nivolumab in stage IIIB/IV NSCLC in several arms of combination with ipilimumab or gemcitabine/cisplatin or pemetrexed/cisplatin or carboplatin/paclitaxel or bevacizumab maintenance or erlotinib, or as monotherapy. On May 2014, Antonia *et al* published the interim results of the combination arm of nivolumab-ipilimumab. This combination was administrated in 46 NSCLC patients in four cohorts (two squamous and two non-squamous cohorts) receiving nivolumab 3 mg/kg plus ipilimumab 1 mg/kg or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg combination dose intravenously every 3 weeks for 4 cycles followed by nivolumab 3 mg/kg intravenously every 2 weeks until progression or unacceptable treatment related adverse effects.

Grade 3-4 events were present in 48% of patients; treatment related deaths were reported in 3 patients (respiratory failure, bronchopulmonary hemorrhage and toxic epidermal necrolysis). ORR in the four cohorts was 22% (29). Hellmann MD et al. published the results of the other arms: nivolumab 1 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks, nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 12 weeks, or nivolumab 3 mg/kg every 2 weeks plus

ipilimumab 1 mg/kg every 6 weeks intravenously. Data from the latter two cohorts were considered more important for their impact in future clinical trials. In the every 12 weeks cohort, 37% of patients had grade 3-4 and 33% in the every 6 week cohort (30).

Ipilimumab has also been evaluated in combination with pembrolizumab in a phase I/II study in unresectable or metastatic NSCLC and with one or more prior regimen of treatment. In the first phase, ipilimumab was given in either 1 or 3mg/kg every 3 weeks for 4 cycles and the dose of pembrolizumab was 2 mg/kg, and then, based in the toxicity profile reported for the combination, dose of ipilimumab was reduced to 1mg/kg and this dose was used in the second phase. Unfortunately, the ORR (24%) was similar than obtained for pembrolizumab alone with a significant toxicity profile. 67% of patients experienced treatment-related adverse events where 24% experienced grade 3-5 treatment-related AEs. Nine percent of patients discontinued treatment because of side effect and one treatment-related death by pancreatitis was reported (31).

Ipilimumab has also been evaluated in combination with radiotherapy. A phase I of ipilimumab (3 mg/kg every 3 weeks for 4 doses) in combination with stereotatic ablative radiation therapy (SABR) given concurrently (one day after the first ipilimumab dose) or sequentially (one week after the second ipilimumab dose) showed response in tumors out of the radiation fields with 23% of patients with clinical benefit (partial response (PR) or stable disease (SD) ≥ 6 months) (32).

7.-PHASE II/III CLINICAL TRIALS

Ipilimumab has been evaluated as single immunotherapeutic agent in phase II and III trials. A phase II study in first-line treatment in stage IIIB/IV NSCLC compared two combinations of ipilimumab (10 mg/kg intravenously every 3 weeks) with concurrent or sequential paclitaxel (175 mg/m²) plus carboplatin (area under the curve (AUC) of 6) every 3 weeks versus carboplatin plus paclitaxel (175 mg/m² and AUC=6, every 3 weeks). Sequential ipilimumab plus paclitaxel/carboplatin had an improved immune-related progression-free survival (PFS) (HR=0.72; 95%CI:0.50-1.06; P=0.05) compared to the control group but not for concurrent ipilimumab plus paclitaxel/carboplatin group (HR=0.81; 95%CI:0.55-1.17; P=0.13) while no improvement in PFS or overall survival (OS) was observed (33).

In the other hand, the phase III study of the sequential combination of ipilimumab/carboplatin /paclitaxel vs. carboplatin/paclitaxel plus placebo in patients with stage IV or recurrent chemotherapy-naive squamous NSCLC failed to prove an improvement in the primary endpoint, the overall survival (HR=0.91;

95%CI:0.77-1.07; P=0.25) while there was a slightly benefit (not statistically significant) in PFS (HR=0.87; 95%CI:0.75-1.01) (34).

Trials evaluating the combination of ipilimumab and nivolumab had better results, mainly because the inclusion of TMB of biomarker of patient selection. The analysis of the single-arm phase II study CheckMate 568 (nivolumab 3 mg/kg every two weeks plus ipilimumab 1 mg/kg every 6 weeks) showed that a TMB ≥ 10 mutations per megabase is an effective cutoff to select patients most likely to have a response to this combination (ORR>40%), regardless of tumor PD-L1 expression level (35). Due to these results, the phase 3 study CheckMate 227 (originally designed to compare nivolumab plus ipilimumab, nivolumab monotherapy, or chemotherapy in cases PD-L1 $\geq 1\%$ and nivolumab plus ipilimumab, nivolumab plus chemotherapy, or chemotherapy in cases PD-L1 <1%) was amended to add a coprimary endpoint to evaluate PFS among patients with a TMB ≥ 10 mutation per megabase, irrespective of the PD-L1 status. The 1-year PFS rate was 42.6% vs 13.2% for nivolumab plus ipilimumab versus chemotherapy, respectively (HR for disease progression or death, 0.58; 97.5%CI:0.41-0.81; P<0.001) (36).

Ongoing phase III studies are focusing in the combination with a PD-1 inhibitor (table 1).

8.-SAFETY

Ipilimumab has a well-established safety profile product of the broad experience in clinical trials. Expected immune related adverse events in any grade include rash and pruritus (47-68%), liver toxicity (3-9%), diarrhea and colitis (44% of patients receiving ipilimumab 10mg/kg), and hypophysitis (1-6%). Less frequent immune-related adverse events included pancreatitis (<1.5%) and in <1% of patients, episcleritis/uveitis, lymphadenopathy/sarcoid-like syndrome and neuropathies (37). Rheumatological events are rare and have been described for ipilimumab as monotherapy or combined with anti-PD-1 antibodies (38).

The phase 1 study CheckMate 012 evaluating the combination of Nivolumab 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 12 weeks or 1 mg/kg every 6 weeks, found a similar toxicity profile in both combinations (39). Results of the CheckMate 012 and the phase 3 study CheckMate 227 showed a tolerable safety of this combination. Frequency of any adverse event in the CheckMate 227 scheme (ipilimumab 1 mg/kg every 6 weeks) of any grade was 75.2% (31.2% of events in grade 3 or 4). Frequency of serious events of any grade was 24% (17.7% of grade 3 or 4 events). In total 17.4% of patients presented any treatment-related event leading to discontinuation. More frequent adverse event (any grade) were rash (16.7%), diarrhea (16.3%), pruritus (14.1%) and fatigue (13.2%). More

qfrequent grade 3-4 events were rash (1.6%), diarrhea (1.6%), anemia (1.6%) and fatigue (1.4%) (36).

Immune-related adverse event in the central nervous system are rare. Encephalitis cases have been reported with the combination of nivolumab and ipilimumab (40,41).

Incidence of fatal adverse events related with ipilimumab was 0.99% (95%CI:0.48-1.69) in a meta-analysis evaluating data from 5466 patients from 10 randomized clinical trials (42). Cases of fulminant myocarditis were observed in patients with melanoma treated with the combination ipilimumab and nivolumab. The autopsy showed a pattern of lymphocytic infiltration of the myocardium by T-cells, mainly CD8+ (43).

9.-BIOMARKERS OF EFFICACY

The Food and Drug Administration (FDA) approved PDL-1 immunohistochemistry as a predictive biomarker for PD-1 inhibitory treatment. In contrast there is no a clinically useful biomarker to select candidate patients to be treated with ipilimumab while immune cell composition and genomic biomarkers are strong candidates and need to be validated. Potential biomarkers for ipilimumab have been drawn from several works evaluating diverse cancer types, mainly melanoma.

Tumoral mutational burden (TMB) detected by whole exome sequencing has become nowadays the most promising biomarker for CTLA-4 blockade (44–46) whereas tumors with chromosome instability were less likely to respond to ipilimumab (46). In the other hand, using the CRISPR-Cas9 technology, functional loss of the Apelin Receptor gene (*APLNR*) has been mechanistically related to resistance to anti-CTLA-4 and anti-PD-1 antibodies by lack of activation of JAK-STAT pathway and subsequent IFN γ signaling in tumor cells (47).

In addition to genomic data, blood immune parameters were also evaluated. Jacquelot et al. observed in a cohort of unresectable stage III and IV melanoma that PDL-1 expression was associated with resistance to CTLA-4 blockade while CD137 expression on CD8+ T-cells is associated with a lack of relapse (48). When ipilimumab is combined with radiotherapy, clinical benefit is associated with increase of peripheral CD8+ T cells, CD8+/CD4+ T-cell ratio and proportion of 4-1BB and PD-1 expressed in CD8+ T-cells (32).

In non-randomized trials, some hematological parameters such as high leukocyte, lymphocyte, eosinophil counts have been related to an improved OS while low neutrophil and monocyte counts are related with a better outcome in terms of

response, OS and PFS (49–52). Low serum levels of lactate dehydrogenase and C-reactive proteins have been related to an improved outcome (53,54). In addition, some clinical parameters seem to be related with the outcome. Early immune-related adverse events and a less number of involved organs were related to a better outcome (54,55).

A list of potential biomarkers is provided in **table 2**.

10.-CONCLUDING REMARKS

Currently, immunotherapy represents the most attractive therapeutic approach in NSCLC patients without actionable mutations that represent the larger fraction of these patients. Although ipilimumab is approved in melanoma, in NSCLC single use of immunotherapeutic agents (nivolumab, pembrolizumab and atezolizumab) have limited efficacy while combination of ipilimumab with PD-1 inhibitors such as nivolumab or pembrolizumab are showing encouraging results. Using radiation therapy before ipilimumab administration offers new therapeutic opportunities for this drug. The safety profile of ipilimumab is manageable while combination with other immunotherapeutic agents increases the frequency of grade 3/4 treatment-related adverse events. New predictive biomarkers should help to improve the selection of patients who will benefit from ipilimumab especially in combination with PD-1 inhibitors for its toxicity profile.

11.-EXPERT OPINION

Immunotherapy has a very important role in NSCLC. It is an effective and well developed therapeutic strategy with the benefit of the *know-how* acquired in treatment of melanoma. However we are just in the infancy in this field. When we talk about immunotherapy in NSCLC we are only talking about checkpoint inhibition, no other types of immunotherapy. The immunotherapeutic agents currently approved in NSCLC only include anti-PD1/PDL-1 inhibitors, despite, paradoxically; trials evaluating ipilimumab were conducted before approval of these drugs. Ipilimumab and other anti-CTLA-4 inhibitors like tremelimumab are bringing to the plate another mechanism of action to synergize with anti-PD1/PDL-1 inhibitors. Anti-CTLA-4 agents like ipilimumab might have a very important role in NSCLC as they play in melanoma because of its synergistic effect with PD-1/PDL-1 inhibitors. Ipilimumab as single agent failed to prove benefit in NSCLC; however the combination with nivolumab increases the efficacy and antitumoral effects against NSCLC and it's a very promising combination to be considered.

At the same time it's very important to try to find a biomarker for immunotherapy to select the population of patients that will obtain benefit from these checkpoint inhibitors, because the overall response rates to immunotherapy (ORR) are

achieved in <50% of the patients. Numerous potential biomarkers are in development while TMB have shown to be adequate to select patients that will obtain benefit from ipilimumab plus nivolumab and to protect from the toxic effects of immunotherapy to patients who will not obtain benefit from these drugs.

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Drug summary box

Drug name: Ipilimumab

Phase: III

Indication: Non-small cell lung cancer

Pharmacology description: Fully human IgG1 monoclonal antibody directed against CTLA-4

Route of administration Intravenous in 90 minutes infusion

Pivotal Trials: Phase III Trial of Ipilimumab Combined With Paclitaxel and Carboplatin in Advanced Squamous Non-Small-Cell Lung Cancer (NCT01285609). An Open-Label, Randomized Phase 3 Trial of Nivolumab, or Nivolumab Plus

Ipilimumab, or Nivolumab Plus Platinum Doublet Chemotherapy Versus Platinum Doublet Chemotherapy in Subjects With Chemotherapy-Naïve Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC) (NCT02477826).

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Table 1.- Ongoing phase III clinical trials combining ipilimumab with anti-PD-1 inhibitors (Updated November 2017)

NCT Number	Study Arms	Status	Conditions	Outcome Measures
NCT02477826	Nivolumab Nivolumab + ipilimumab Nivolumab + Platinum doublet CT Platinum doublet CT	Recruiting	Stage IV NSCLC	OS; PFS; ORR; Disease related symptom improvement
NCT03351361	Nivolumab + Ipilimumab Platinum doublet CT	Not yet recruiting	Advanced NSCLC (First Line treatment of performance status 2 or elderly patients)	OS, Survival rate, ORR, PFS, safety, tolerability
NCT02864251	Nivolumab+Platinum doublet CT Nivolumab + Ipilimumab Platinum doublet CT	Recruiting	EGFR Mutation, T790M Negative NSCLC Who Have Failed 1L EGFR TKI Therapy	PFS; OS; ORR; DOR; PFS rate
NCT02998528	Nivolumab + Ipilimumab Platinum doublet CT	Recruiting	Early Stage Non Small Cell Lung Cancer	EFS; pCR; OS; Major pathological response
NCT03215706	Nivolumab + Ipilimumab in Combination With CT CT Combination	Recruiting	First Line NSCLC	OS; PFS; ORR
NCT03469960	6 months of nivolumab + ipilimumab then nivolumab + ipilimumab then in case of progression platinum-based doublet 6 months of nivolumab + ipilimumab then observation then in case of progression nivolumab + ipilimumab then in case of progression platinum-based doublet	Recruiting	Stage IV NSCLC	PFS, QOL, OS
NCT03515629	Pembrolizumab REGN2810 + ipilimumab REGN2810 + CT + IPILIMUMAB	Recruiting	First Line NSCLC	PFS, OS, ORR, Treatment-related adverse events, Dose-limiting toxicities
NCT03391869	Ipilimumab + Nivolumab Local Consolidative Therapy + Ipilimumab + Nivolumab	Recruiting	Immunotherapy-naïve metastatic NSCLC	OS, PFS, Time to Appearance of New Metastases, QOL

NCT03302234	Pembrolizumab + ipilimumab Pembrolizumab + placebo	Not yet recruiting	Untreated Metastatic NSCLC	OS; PFS; ORR; DOR; Time to True Deterioration in Cough, Pain in Chest, and Shortness of Breath; Incidence of Aes; Incidence of Discontinuations
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Abbreviations: CT, chemotherapy; NSCLC, Non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; ORR, overall response rate; DOR, duration of response; QOL, quality of life

Table 2.- Potential biomarkers for ipilimumab efficacy

Type of biomarker	Biomarker	Indicator	Outcome	Reference
Genomic	Tumor mutational burden	High mutational load	Response to CTLA-4 blockade	[40,41,42]
	Chromosomal alterations	Chromosome instability	Resistance to CTLA-4 blockade	[42]
	APLNR gene	APLNR mutated	Resistance to CTLA-4 blockade	[43]
Blood immune	PDL-1	PDL-1 expression in T-cells	Resistance to CTLA-4 blockade	[44]
	CD137	CD137 expression on CD8+ T-cells	Response to dual CTLA-4/PD-1 blockade	[44]
	CD8+ T-cells	increased peripheral CD8+ T-cells	Clinical benefit in combination with RT	[29]
Hematological	Lymphocyte count	Increased compared to baseline	Improved response or OS	[45]
	Eosinophil count	Increased at baseline or 3-6 weeks	Improved response or OS	[45,47]
	Neutrophil count	Decreased at baseline or at week 3-6	Increased response, PFS and OS	[46]
	Monocyte count	Decreased at baseline	Improved OS	[48]
Biochemical	Lactate dehydrogenase	Normal or Decreased at baseline or week 12	Improved response and OS	[49,50]
	C-reactive protein	Decreased at week 12	Improved OS	[49,50]
Clinical	immune-related AE	Early immune-related AE	Increased response	[51]
	Affected organs	Increased number of affected organs	Improved OS	[50]

Abbreviations: OS, overall survival; PFS, progression-free survival.

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