Non-Small-Cell Lung Cancer Signaling Pathways

Subjects: Oncology

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Treatment of advanced (metastatic) non-small-cell lung cancer (NSCLC) is currently mainly based on immunotherapy with antibodies against PD-1 or PD-L1, alone, or in combination with chemotherapy. In locally advanced NSCLC and in early resected stages, immunotherapy is also employed. Tumor PD-L1 expression by immunohistochemistry is considered the standard practice. Response rate is low, with median progression free survival very short in the vast majority of studies reported. Herein, numerous biological facets of NSCLC are described involving driver genetic lesions, mutations ad fusions, PD-L1 glycosylation, ferroptosis and metabolic rewiring in NSCLC and lung adenocarcinoma (LUAD). Novel concepts, such as immune-transmitters and the effect of neurotransmitters in immune evasion and tumor growth, the nascent relevance of necroptosis and pyroptosis, possible new biomarkers, such as gasdermin D and gasdermin E, the conundrum of K-Ras mutations in LUADs, with the growing recognition of liver kinase B1 (LKB1) and metabolic pathways, including others, are also commented.

Keywords: anti-PD-1/PD-L1 monoclonal antibodies ; inflammation-associated cell death pathways ; K-Ras mutations ; LKB1 mutations ; metabolic rewiring

1. Introduction

The programmed death-1 (PD-1) pathway is a key mediator of local immunosuppression in the tumor microenvironment (TME), also modulating T cell priming against tumor antigens and secondary lymph nodes [1]. Blocking PD-1 pathway by inhibiting the PD-1 receptor on immune cells or the PD-L1 ligand on tumor and/or immune cells can inhibit tumor growth and potentially lead to curability. The first study was carried out in 39 patients with metastatic melanoma, colorectal cancer, castrate-resistant prostate cancer, non-small-cell lung cancer (NSCLC) or renal cell cancer who received a single intravenous infusion of anti-PD-1 (MDX-1106, hereafter named nivolumab). One durable complete response, and two partial responses were seen, and two additional patients (with melanoma and NSCLC) showed significant tumor regressions. The serum half-life of anti-PD-1 was 12 to 20 days. Pharmacodynamic assessment indicated a sustained mean occupancy of > 70% of PD-1 molecules on circulating T cells > 2 months following infusion. In nine patients examined, tumor cell surface B7-H1 (PD-L1) expression seems to correlate with the likelihood of response [2]. Currently three monoclonal antibodies that block PD-1 (nivolumab, pembrolizumab and cemiplimab) and three that block PD-L1 (atezolizumab, durvalumab and avelumab) are approved for use by the US Food and Drug Administration (FDA) as first and/or later line treatment for 17 different types of advanced cancers (Table 1) [1]. Cemiplimab (3 mg per kilogram of body weight) every 2 weeks has been used for metastatic cutaneous squamous cell carcinoma with 47% of response. Adverse events include diarrhea, fatigue, nausea, constipation and rash [3]. Cemiplimab alone or in combination with radiotherapy and/or low dose cyclophosphamide have shown a similar safety profile, also the most common treatment-emergent adverse events (TEAEs) were fatigue (45%), nausea (36.7%) and vomiting (25%). The most common immune adverse related events (irAEs) were, arthralgia (10%), hypothyroidism (8.3%) and maculopapular rash (8%). The side effects are comparable with other anti-PD-1 agents. Two complete responses and seven partial responses were observed among 60 patients [4].

Table 1. Anti-PD1/PD-L1 antibodies approved for clnical use.

Anti-PD1/PDL1 Antibody	FDA-Approved Indications
Pembrolizumab	Melanoma, NSCLC, SCLC, HNSCC, cHL, PMBCL, urothelial carcinoma, MSI-H or dMMR cancer, gastric cancer, esophageal cancer, cervical cancer, endometrial carcinoma, RCC, hepatocellular carcinoma and Merkel cell carcinoma

Nivolumab	Melanoma, NSCLC, SCLC, RCC, cHL, HNSCC, urothelial carcinoma, MSI-H or dMMR colorectal cancer and hepatocellular carcinoma.
Atezolizumab	Urothelial carcinoma, NSCLC, TNBC, SCLC
Durvalumab	Urothelial Carcinoma, NSCLC, SCLC
Avelumab	Merkel cell carcinoma, urothelial carcinoma, RCC
Cemiplimab	Cutaneous squamous cell carcinoma

Abbreviations: NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; HNSCC: head and neck squamous cell cancer; cHL: classical Hodgkin lymphoma; PMBCL: primary mediastinal large B-cell lymphoma; MSI-H: microsatellite instability-high; dMMR: mismatch repair deficient; RCC: renal-cell carcinoma; TNBC: triple-negative breast cancer.

NSCLC still has a poor prognosis and immunotherapy (IMT) has become part of the treatment for patients without driver alterations (epidermal growth factor receptor, EGFR, or anaplastic lymphoma kinase, ALK). The ASCO and OH Joint Panel Guideline recommend pembrolizumab for non-squamous cell carcinoma (non-SCC) with high PD-L1 expression (tumor proportion score [TPS] ≥ 50%) [5]. Other recommended options are, the combination of pembrolizumab with carboplatin and pemetrexed, or atezolizumab with carboplatin, paclitaxel and bevacizumab or atezolizumab, carboplatin and nab-paclitaxel. For most patients with non-SCC and negative or low positive PD-L1, the recommendation is pembrolizumab, carboplatin and pemetrexed. However, other combinations are also acceptable. Again, for patients with high PD-L1 expression (TPS ≥ 50%) and SCC, the panel recommends single agent pembrolizumab. However, for patients with SCC and negative or low positive PD-L1, it is also permissible, pembrolizumab, carboplatin and paclitaxel or nab-paclitaxel. The recommendations are based on studies with clear information (Impower 130, KEYNOTE 189, KEYNOTE 142, Impower 150 and KEYNOTE 407) [5]. The review of these studies indicates that the response rate is less than 30%, the median progression-free survival (PFS), not exceeding 6 to 8 months, and median overall survival (OS) of 20 months. Therefore, there is an urgent need to understand the mechanisms of immune evasion and how PD-1 or PD-L1 monoclonal antibodies can be combined with other reagents that can circumvent resistance.

There has been a long debate about the predicted role of PD-L1. PD-L1 immunohistochemistry (IHC) assays estimate the percentage of tumor cells with an intensity of membranous expression (TPS and the percentage of immune cells with similar expression). Currently, four PD-L1 assays are FDA approved in lung cancer. The predictive value of these assays is limited, as benefit is also seen in patients whose tumors do not express PD-L1 and, often, no benefit is observed in patients with PD-L1 expression [6]. Molecular genotyping of NSCLC is becoming more frequently implemented. For instance, KRAS mutations co-occur with other alterations and mutations, particularly in serine/threonine kinase 11 (STK11), also known as liver kinase B1 (LKB1), and Kelch-like ECH-associated protein 1 (KEAP1) (see below). TP53 mutations can co-occur, at different frequencies, with other driver alterations, including EGFR mutations, KRAS mutations, MET exon 14 skipping mutations, but also ALK and ROS1 rearrangements [7]. Multiple endeavors have been performed to find the best way to predict response to anti-PD-1 and anti-PD-L1 monoclonal antibodies, including the correlation with tumor mutation burden (TMB) by whole exome sequencing, considering activating mutations in receptor tyrosine kinase mutations, smoking-related mutational signature and human leukocyte antigen status in order to more accurately predict response [8]. In this complex assessment, differences in PD-L1 expression between responders and non-responders were not identified. The presence of RTK mutations (EGFR mutations) was a negative predictor of response [8].

2. Anti-PD-1 and Anti-PD-L1 Antibodies and Driver Alterations in NSCLC

Many attempts have been made with anti-PD-1 and anti-PD-L1 antibodies to improve the response and PFS in NSCLC patients with driver alterations. A study was carried out in 551 patients treated in 24 centers from 10 countries. Most patients received nivolumab (466) pembrolizumab (48), atezolizumab (19), durvalumab (11) and the rest, other drugs. Most patients received anti-PD-1 anti-PD-L1 antibodies as second or third-line therapies. The molecular alterations included KRAS (2071), EGFR (125), BRAF (43), MET (36), HER2 (29), ALK (23), RET (16) and ROS1 (7). The median PFS was very short for each of these categories, ranging from 2.1 months to 3.2 months. The reasons for the lack of activity are not well-known [9]. Intriguingly, it has been seen that driver fusions in lung adenocarcinomas co-occur with SETD2 mutations (16% of cases) in contrast with lung adenocarcinomas with EGFR, KRAS, BRAF and MET mutations,

where the frequency of SETD2 mutations is only 2% [10]. SETD2 is a histone and microtubule methyltransferase and is considered a tumor suppressor gene playing a critical function in DNA damage repair and remodeling of mitotic spindles. SETD2 mutations partly explain the resistance to PD-1 and PD-L1 antibodies in lung adenocarcinomas driven by fusions, making the screening for SETD2 mutations advisable. SETD2 directly methylates signal- transducer and activator of transcription 1 (STAT1) on K525, that is warranted for the activation of STAT1 and the interferon signaling pathway [11]. These findings warrant further research in the subclasses of NSCLC driven by ALK, ROS, RET and other fusions. Moreover, the interferon signaling hyperactivation can also result in resistance to anti-PD-1 and anti-PD-L1 antibodies, as well as involving auto-immune disease, such as, systemic lupus erythematosus [12]. Reduction in circular RNAs in peripheral blood mononuclear cells (PBMCs) is observed in patients with systemic lupus erythematosus that is accompanied by increased RNase L activity and enhanced protein kinase R (PKR) activation and expression of interferon (IFN)-induced genes. These findings could be relevant for further assessment of the participation of circular RNAs in immune response, knowing that circular RNAs retain PKR. The release of PKR could have a role in the control of viral infections. In normal cells, circular RNAs sequester PKR while viral infections activate RNase L and RNase L cleavage of circular RNA releases PKR[13][14]. Of interest is the fact that stimulator of interferon genes (STING) activates IFN and double stranded RNAs (dsRNAs), with increased sensor levels of MDA5, RIG-1 and PKR [15].

New hints break the paradigm that EGFR tyrosine kinase inhibitors (TKIs) negate the effects of anti-PD-1 and anti-PD-L1 monoclonal antibodies. Recent observations have shown that HypoTKI (hypofractionated EGFR TKI: high doses with low frequency treatment) appears to be more effective than the standard treatment of HyperTKI (hyperfractionated EGFR TKI: low doses with daily treatment). Mice bearing TUBO tumors treated with afatinib with HypoTKI regimen were more effective in reducing tumor burden than HyperTKI. Similar to afatinib, HypoTKI, gefitinib and osimertinib, were more potent than, Hyper TKI, gefitinib or osimertinib, in reducing tumor burden and limiting tumor relapse. It was noted that HypoTKI, but not HyperTKI, increases CD3+, CD8+ and CD4 + T and B cells in the TME. Hypo EGFR TKI can induce hypoptosis in tumor cells, releasing tumor-derived danger-associated molecular patterns (DAMPs), that can activate cGAS-STING and Toll-like receptors (TLR)-Myd88, that are essential for type I interferon production. It is inferred from these findings that hypo-fractionated regimens can be applied to other driver alterations, such as, ALK, opening a new opportunity to re-visit the therapeutic approach of combination of EGFR TKIs with anti-PD-1 and anti-PD-L1 antibodies [16].

3. Anti-PD-1 and Anti-PD-L1 Antibodies and Endocytosis

Another strategy to enhance the efficacy of anti-PD-1 and/or anti-PD-L1 monoclonal antibodies could be the inhibition of endocytosis. Endocytosis is crucial in regulating cell-surface expression of a large number of membrane molecules, including signaling receptors involved in anti-tumor immune responses. Clathrin-mediated endocytosis (CME) and clathrin-independent endocytosis (CIE) are responsible for receptor internalization [17]. In the CME, the binding of adaptor protein 2 (AP2) complex to the activated receptor on the cell membrane surface, permits the recruitment of clathrin, which creates a coat around the vesicle in formation. Dynamin GTPase is involved in detaching vesicles from the membrane, and the receptors finally internalized, can be recycled through recycling endosomes and come back to the membrane external surface, or be destroyed by lysosomes. The CIE does not involve clathrin, however, dynamin may be involved [18]. These mechanisms make most receptors, such as, as EGFR and PD-L1, unavailable to be targetable by monoclonal antibody (mAb) and, in cancer cells, they represent escaping mechanisms [19]. The external portion of mAb, called fragment crystallizable region (Fc), interacts with effector cells, such as, NK cells, neutrophils, macrophages, monocytes, eosinophils, and dendritic cells (DCs) to activate the antibody-dependent cellular cytotoxicity (ADCC). The main mechanism of cell death utilized in ADCC is though the release of granzymes and perforine, instead of Fas signaling and the release of reactive oxygen species (ROS) [20].

Based on these assumptions, endocytosis inhibitors can be used to move tumor cell antigens targeted by therapeutic monoclonal antibodies to the cell surface, in order to improve the ADCC and clinical responses to these agents. An ex vivo human tumor assay has shown distinct patterns of EGFR trafficking in SCC, correlating with therapeutic outcomes [21]. The study shows that tumors can be classified into those where EGF was, or was not, able to be endocytosed. Patients in whom tumor EGFR escapes endocytosis respond better to EGFR monoclonal antibody therapy [22]. For decades, the blockage mechanisms of the different patterns involved in endocytosis were investigated without successful results [23]. In this review the author explored the activity of many inhibitors, including those of the CME, such as, potassium depletion, hypertonic sucrose, cytosolic acidification, monodansylcadaverine andphenylarsine oxide (PAO). However, due to side effects of each of these compounds, they are not applicable in vivo.

Dynamin is involved in EGFR- and PD-L1 endocytosis. A reversible small molecular weight inhibitor of dynamin, dyngo4A, shows its efficacy if added to anti-EGFR mAb. The drug combination increases EGFR expression on the cell surface and, at the same time, ADCC is both responsive and refractory in EGFR SCC lines. Dyngo4a also increases the expression of

p-Akt, which is involved in mTOR phosphorylation of PRAS40, a powerful inhibitor of mTORC1 complex. This inhibition translates into a blockage of cell transcription [24]. Despite promising results in preclinical studies, the agent has not yet been tested in clinical trials.

In addition to dyngo4a, prochlorperazine (an antiemetic and anti-psychotic drug) is also a dynamin inhibitor that concentrates in cell membranes and can bind to multiple cellular targets [25]. In addition, prochlorperazine increases the interaction between NK cells and cancer cells with a “zippering” effect. Besides blocking CME, prochlorperazine also has a blocking effect in another way, by internalizing receptors, such as, EGFR, HGFR, VEGFR and PDGFR, called fast endophiline-mediated endocytosis (FEME) [24], a fast-acting tubulovesicular endocytic pathway independent from AP2 and clathrin [26].

Prochlorperazine (PCZ) alone, and in combination with anti-EGFR in sensitive and resistant EGFR cells lines, decreases the expression of p-ERK and p-Akt. The lack of phosphorylation of Akt reduces the activity of Bcl-2/Bcl-X complex and NF-kB via apoptosis and gene transcription, respectively. In NSG mice models with the addition of an HLA-II mediated immunity, the combination of PCZ and Cetuximab in EGFR resistant tumors has a statistically significant tumor regression with durable response. This model was reproduced adding avelumab (an anti-PD-1 monoclonal antibody with low ADCC activity) to PCZ in mouse colon carcinoma, showing a significant improvement in inhibition of primary tumor growth compared to PCZ-or avelumab-only treatment. Unfortunately, due to a loss of PD-L1 expression and a reduction of MCH-I molecule expression, the same activity was not shown when the combination is applied to renal cancer cells in the same mice model. A pilot clinical study with five patients shows an increased expression of EGFR on cell surface after 30 min of PCZ infusion without any significant changes in vital signs [24].

Prochlorperazine could be repurposed to enhance the efficacy of anti-tumor mAbs. It is tempting to speculate that FAK inhibitors, or drugs inhibiting FAK, like dihydroartemisinin (DHA) [27], could also be used as dynamin inhibitors (Table 2). Of note, a phase 1/2 study (NCT02758587) is ongoing to assess safety, tolerability and preliminary activity of defactinib (a FAK inhibitor) combined with pembrolizumab in patients with advanced solid tumors, including NSCLC, pancreatic cancer, and mesothelioma. In addition, other markers involved in Src pathway endocytosis control could play an important role, such as the ubiquitin ligase Hakai [22].

Table 2. Selected biomarkers for novel potential therapeutic strategies to improve PD-1/PD-L1 inibitor efficacy.[28][29][30][31][32][33][34][35][36][37][38][39][40][41][42][43][44][45][46][47][48][49][50][51][52][53]

Biomarker	Proposed Function	Targeted Agent	Status in Solid Tumors	Reference
Dynamin	Regulation of endocytosis (e.g., EGFR, PD-L1) through Src-FAK signaling	-Dyngo compounds	-Preclinical	[24–28]
		-Prochlorperazine		
		-FAK inhibitors (e.g., defactinib)	-Phase 1-2 studies	

	-Regulation of cancer stem cells and tumour aggressiveness;	-Gefitinib		
ID1 (Inhibitor of DNA binding I)	-Regulation of pathways related to inflammation-associated cell death: activation of necroptosis by triggering activation of RIP1/RIP3/MLKL pathway and minimal effect in inducing pyroptosis; -ID1 overexpression can be correlated with KRAS and LKB1 mutations.	-ID1 Inhibitors (e.g., AGX-51, pimozide)	-Preclinical	[29,30]
β2-adrenergic receptor (β2-AR)	Activation of β2-AR by neurotransmitters, such as norepinephrine, inactivates LKB1, with upregulation of cAMP response element-binding protein (CREB) and interleukin-6 (IL6)	Propranolol	-Phase 1-2 studies	[31]
STAT3	Mediator of tumor-induced immunosuppression	STAT inhibitors (e.g., niclosamide, dihydroartemisinin)	-Phase 1–2 studies	[28,32]
IL-1β	Regulation of tumorigenesis and mediator of immunosuppression through myeloid-derived suppressor cells (MDSCs)	IL-1β inhibitors (e.g., canakinumab, rilonacept, anakinra)	-Phase 1–3 studies	[33–37]
SHP2 (Src homology 2 domain containing phosphatase 2)	Regulation of signaling pathways, in cancer and immune cells, involved in inflammation and tumorigenesis (e.g., RTK, RAS and PD1)	SHP2 inhibitors (e.g., TNO155, RMC-4630, JAB-3068)	-Phase 1–2 studies	[38]
xCT (glutamate-cystine antiporter system)	Glutathione (GSH) synthesis, antioxidant response and ferroptosis	Inhibitors of xCT-GSH pathway (e.g., erastin, iImidazole ketone erastin [IKE], sulfasalazine, dihydroartemisinin [DHA], sorafenib, buthionine sulfoximine [BSO])	-Preclinical (Erastin, IKE); -Phase 1–3 (phase 3 for Sorafenib)	[28,39–44]
Acetyl-CoA acetyltransferase (ACAT1)	Cholesterol esterification in T cells	ACAT1 inhibitor (e.g., avasimibe)	-Preclinical	[45]

STING	cGAS-STING pathway: key role in bridging cGAS-STcGAS-STING pathway: key role in cGAS-STING pathway: key role in bridging innate and adaptive anticancer immunity	STING agonists (e.g., ADU-S100, MK-1454, STING agonists (e.g. ADU-S100, MK-1454, GSK3745417)	-Phase 1–2 studies	[46–48]
YAP	Master transcriptional regulator involved in multiple cellular functions (activated by NTRK1/NTRK2) and immunosuppression	NTRK or YAP inhibitors (e.g., entrectinib, larotrectinib, repotrectinib, or dihydroartemisinin)	-Phase 1–3 (phase 3 for Entrectinib)	[28,49]
NLRP3	NLRP3 inflammasome: key role in immune response	NLPR3 inhibitors (e.g., OLT1177-dapansutrile, CY-09, tranilast)	-Preclinical	[50,51]
LAG-3	Immune checkpoint receptor modulating T-cell proliferation and activation	LAG-3 inhibitors (e.g., relatlimab)	Phase 1–2 studies	[52,53]

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