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REVIEW

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Targeted therapies for the treatment of non-small-cell lung cancer: Monoclonal antibodies and biological inhibitors

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ABSTRACT

The usual treatments for patients with non-small-cell lung cancer (NSCLC), such as advanced lung adenocarcinoma, are unspecific and aggressive, and include lung resection, radiotherapy and chemotherapy. Recently, treatment with monoclonal antibodies and biological inhibitors has emerged as an effective alternative, generating effective results with few side effects. In recent years, several clinical trials using monoclonal antibodies presented potential benefits to NSCLC, and 4 of them are already approved for the treatment of NSCLC, such as cetuximab, bevacizumab, nivolumab and pembrolizumab. Also, biological inhibitors are attractive tolls for biological applications. Among the approved inhibitors are crizotinib, erlotinib, afatinib and gefitinib, and side effects are usually mild to intense. Nevertheless, biological molecule treatments are under development, and several new monoclonal antibodies and biological inhibitors are in trial to treat NSCLC. Also under trial study are as follows: anti-epidermal growth factor receptor (EGFR) antibodies (nimotuzumab and ficlatuzumab), anti-IGF 1 receptor (IGF-1R) monoclonal antibody (figitumumab), anti-NR-LU-10 monoclonal antibody (nofetumomab) as well as antibodies directly affecting the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) molecule (ipilimumab and tremelimumab), to receptor activator of nuclear factor-kappa B ligand (RANKL) (denosumab) or to polymerase enzyme (veliparib and olaparib). Among new inhibitors under investigation are poly-ADP ribose polymerase (PARP) inhibitors (veliparib and olaparib) and phosphatidylinositol 3-kinase (PI3K) inhibitor (buparlisib). However, the success of immunotherapies still requires extensive research and additional controlled trials to evaluate the long-term benefits and side effects.

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Introduction

Lung tumors are responsible for a large percentage of mortality in the world population. Bronchial carcinoma, also known as bronchial or lung tumor is the most common malignant tumor of the lower respiratory tract. This tumor is classified into 3 main types: non-small-cell lung cancer (NSCLC), small-cell lung cancer (SCLC) and lung carcinoid tumors. Squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma are subtypes of NSCLC. The main symptoms of NSCLC include cough, sputum streaked with blood, pain, voice change, worsening shortness of breath, and pneumonia or bronchitis. Bronchorrhea is a known characteristic of these tumors; however, it is relatively uncommon and appears only in the advanced stages of the disease.[1-3] Pulmonary carcinoma, mainly adenocarcinoma, has a multifactorial profile and could be related to gene mutations, mainly in epidermal growth factor receptor (EGFR) and rearrangements of the anaplastic lymphoma kinase (ALK) genes. Likewise, human epidermal growth factor receptor 2 (HER2), Kirsten rat sarcoma viral oncogene homolog (KRAS), erythropoietin-producing hepatoma (EPH), rat sarcoma gene (RAS), mitogen-activated protein kinase (MAPK), V raf murine sarcoma viral oncogene homolog B1 (BRAF), phosphatidylinositol-4,5-bisphosphate3-kinase, catalytic subunit α isoform (PIK3CA), c-mesenchymal-epithelial transition (c-MET), fibroblast growth factor receptor (FGFR), discoidin domain receptor 2 (DDR2), phosphatase and tensin homolog (PTEN), protein kinase B (PKB), also known as serine/threonine-specific protein kinase (AKT), and reactive oxygen species 1 (ROS1) genes are possible targets under study in the development of effective therapies for lung carcinomas and specifically to adenocarcinoma.[4-9] A selection of these will be further discussed in this review.

Target therapies with biological molecules

Conventional chemotherapy and/or radiation treatments often fail to eliminate neoplasic cells. One of the reasons is that the required doses for tumor elimination are generally so high that normal tissues suffer irreversible damage due to toxicity.[10,11] Because of this, immunotherapy, also called biologic therapy or biotherapy, is a possible option. These targeted therapies involve immune-based treatments with the intent to control

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tumor growth. New clinical trials using target therapies are underway and test proteins such as biological inhibitors and monoclonal antibodies, cells, vaccines and genetic treatments, among others.[12-21]

Biological molecules approved to treat NSCLC, and specifically adenocarcinoma, include monoclonal antibodies, such as cetuximab, bevacizumab, nivolumab, pembrolizumab (Table 1), and protein kinase inhibitors, such as erlotinib, gefitinib, crizotinib and afatinib (Table 2). Cetuximab and bevacizumab are monoclonal antibodies of EGFR and VEGF, respectively. Nivolumab and pembrolizumab are driven to programmed cell death ligand 1 (PDL-1) molecule. Crizotinib is a kinase inhibitor that has been shown to be effective in treating tumors involving ALK alterations, while gefitinib, erlotinib, and afatinib are applied to patients with tumors related to mutations in EGFR.[5,22-27]

Other relevant molecules are in trial and attempt to regulate immune response and will also be presented here. Among them are anti-epidermal growth factor receptor (EGFR) antibodies (nimotuzumab and ficlatuzumab), anti- insulin-like growth factor 1 receptor (IGF-1R) monoclonal antibody (figitumumab) and anti NR-LU-10 monoclonal antibody (nofetumomab). Besides these listed, important new monoclonal antibodies are under development in order to block the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) molecule (ipilimumab and tremelimumab), to bind with the receptor activator of nuclear factor-kappa b ligand (RANKL) (denosumab) or to inhibit polymerase enzyme (Veliparib and Olaparib).[28-37] Among new promising inhibitors under investigation are poly ADP ribose polymerase (PARP) inhibitors, such as veliparib and olaparib[38-40] and phosphatidylinositol 3-kinase (PI3K) inhibitor such as buparlisib.[41]

Approved monoclonal antibodies for NSCLC

Anti-epidermal growth factor receptor (EGFR) antibodies

Anti-EGFR monoclonal antibodies bind to the extracellular domain of EGFR.[42] EGFR family consists of 4 receptor of tyrosine kinases (ErbB1-4) that are frequently overexpressed in tumors. Ligand binding with the receptor allows receptor dimerization as well as autophosphorylation of tyrosine residues in the tail of the receptors. It provides specific docking sites for cytoplasmic proteins containing Src homology 2 and phosphotyrosine-binding domains. These proteins bind to specific phosphotyrosine residues and initiate intracellular signaling along several pathways.[43] Also, EGFR expression is considered as a predictor of survival.[44]

Cetuximab. Cetuximab is a monoclonal antibody which targets the epidermal growth factor receptor (EGFR), found in 80%-85% of NSLCL patients.[45-50] In patients with advanced lung cancer, cetuximab can be combined with conventional chemotherapy as part of treatment. Previous studies showed an increase in survival rates in clinical trials using this treatment combined with chemotherapy.[51-54] Presently, there are promising studies using cetuximab in combination with other drugs, such as cisplatin and docetaxel, as neoadjuvant treatment of early-stage NSCLC.[55] Although it is a rare, severe allergic reactions during the first infusion can lead to respiratory reactions and elevated blood pressure. In addition, some patients develop skin alterations, such as rashes, acne and infections. Other side effects may include fatigue, headache, fever and diarrhea.[46-50]

Anti-vascular endothelial growth factor antibody (VEGF) antibodies

Vascular endothelial growth factor antibody (VEGF) promotes tumor growth through enhanced endothelial cell proliferation and survival, increased migration and invasion of endothelial cells, increased permeability of vessels, as well as enhanced chemotaxis and homing of bone marrow derived vascular precursor cells. VEGFs signal through 3 tyrosine kinase receptors (VEGFR-1, VEGFR-2 and VEGFR-3) predominantly expressed by endothelial cells.[56,57] VEGF receptor 2 and 3 (VEGFR2/R3) lead to activation of the VEGF pathway. It has been shown recently that when ligand binds with VEGFR, the receptor complex would be internalized.[58]

Bevacizumab. Bevacizumab is an anti-VEGF humanized monoclonal able to reduce tumor expansion by controlling abnormal growth of blood vessels around the tumor. It is the first approved agent against tumor angiogenesis. It was approved by the FDA in 2004 as a first-line treatment in metastasized colorectal cancer, when used in combination with chemotherapy.[59-65] Furthermore, VEGF is linked to intraocular neovascularization in diabetic retinopathy and macular degeneration associated with age. It has been proven that the expression of HER-1/EGFR and VEGF molecules in NSCLC is associated with poor prognosis. Thus, molecules have direct effects on tumor cells, and can be combined with drugs, resulting in an additional clinical benefit in the treatment of

Table 1. Approved monoclonal antibodies to non-small-cell lung cancer: immunotherapeutic molecules in use, mechanisms of action and side effects.

Related Molecule	Target	Mechanism of action	Potentials adverse effects	Reference
Cetuximab	EGF receptor	Inhibition of cell proliferation, enhanced apoptosis, and reduced angiogenesis, invasiveness and metastasis.	Rash on face and chest, diarrhea, loss of appetite and fatigue	54-59
Bevacizumab	VEGF	Selectively binds to VEGF and prevents interaction with its receptor. Anti-angiogenic agent, which prevents the abnormal growth of blood vessels around tumor.	High pressure, fatigue, leukocyte reduction, headache, sore mouth, loss of appetite and diarrhea	66-74,76
Nivolumab	PD-1 molecule	Induces programmed tumor cell death by biding PD-1 molecule	Tiredness, loss of appetite and nausea related side effects the activity of the immune system	42-44,77,78
Pembrolizumab	PD-1 molecule	Induces programmed tumor cell death by biding PD-1 molecule	body pain, chills, constipation, cough, fever, headache, loss of voice, rapid weight gain and bleeding	45,79-81

Table 2. Approved biological inhibitors to non-small-cell lung cancer: immunotherapeutic molecules in use, mechanisms of action and side effects.

Related Molecule	Receptor	Mechanism of action	Potentials adverse effects	Reference
Crizotinib	ALK protein	Blocks the abnormal ALK protein that causes cell growth.	Nausea, vomiting, diarrhea, constipation, bloating, fatigue, edema and eye alterations	10,11,36,84-86,125,126
Erlotinib	VEGF	Inhibit cell proliferation, differentiation, motility, and survival.	Rash on the face and chest, diarrhea, loss of appetite and fatigue	10,40,66,89,92,124,147,148
Afatinib	EGFR/HER2 blocker and TK protein inhibitor	Inhibition of the EGFR, HER2 and HER 4. Also inhibits transphosphorylation of HER3. Treatment with this molecule inhibits cell growth, angiogenesis, metastasis, and tissue invasion.	Diarrhea, rash, stomatitis, decreased appetite, bleeding, itchiness, dry skin	1,10,41,94-97
Gefitinib	EGFR	Inhibits EGRF. Reduces cell proliferation	Diarrhea, nausea, vomiting, anorexia, stomatitis, dehydration, skin reactions, asthenia, conjunctivitis, blepharitis	71,94,100,105,112,113.

advanced NSCLC.[59-65] In addition, some studies indicate its use as a first-line treatment for metastasis occurring in lung adenocarcinoma.[66,67] A biomarker study indicates that bevacizumab also improved tumor vasculature and blood perfusion in NSCLC patients.[68] However, Bevacizumab can cause bleeding, which limits its use over long periods. Other severe but rare side effects include blood clots, bowel problems, heart disease, and delayed healing. Common side effects include high blood pressure, fatigue, reduction of leukocyte count, headache, mouth sores, loss of appetite and diarrhea.[59-65,69]

Anti-programmed cell death ligand 1 (PD-1) antibodies

The PD-1 pathway is an important regulator in the induction and maintenance of peripheral tolerance.[70] PD-1 (CD279) is a member of the B7-CD28 family present on the cell surface as a co-inhibitory receptor expressed in T-cells, B-cells, monocytes, and natural killer T-cells, after activation.[71] PD-L1 (B7-H1) and PD-L2 (B7-DC) are expressed on professional presenting cell such as dendritic cells (DCs). Binding of PD-L1 or PD-L2 to PD-1 inhibits T-cell receptor signaling and down-regulates the expression of anti-apoptotic molecules. PD-1 suppresses T-cells later in an immune response, primarily in peripheral tissues.[70]

Nivolumab. Nivolumab is a monoclonal antibody of the IgG4 isotype, which inhibits PD-1 molecule and causes the programmed death of the tumor cells. Recently, assays have been performed to test nivolumab as a kind of maintenance therapy, or in combination with chemotherapy or other targeted agents (bevacizumab and erlotinib or ipilimumab) in patients in advanced stages. The FDA approved nivolumab for the treatment of patients with metastatic squamous NSCLC after prior therapy. In 2015, nivolumab was approved for use against non-squamous NSCLC patients that had stopped responding to chemotherapy. More common side effects include back pain, blisters, chills, constipation, cough, diarrhea, headache, fever and weight gain.[31,72-76]

Pembrolizumab. Pembrolizumab is an anti-PD-1 antibody that generated good results in phase I clinical trials, and the treatment shrank tumors in 18 percent of patients with advanced NSCLC that were no longer responding to chemotherapy. Pembrolizumab was premarket-approved for the treatment of both squamous and non-squamous NSCLC.[31,33,76,77] In 2015, the FDA approved pembrolizumab as a second-line treatment for patients with lung cancer.[78] However, confirmatory trials are required to verify the benefit of pembrolizumab for patients with metastatic NSCLC. Among the more common side effects are body pain, chills, constipation, cough, fever, headache, loss of voice, rapid weight gain and bleeding.[33,77-79]

Approved protein kinase inhibitors

Crizotinib, gefitinib, erlotinib, and afatinib are considered small-molecule protein kinase inhibitors, specifically tyrosine kinase inhibitors (TKI). Tyrosine kinases (TK) are enzymes that catalyze phosphorylation of select tyrosine residues in target proteins. TK are responsible for the activation of proteins through a signal transduction cascade. However, phosphorylation can be inhibited by TKI.[80] These molecules prevent tyrosine kinase phosphorylation and the activation of signal transduction pathways through targeted action on the receptor.[5] TKIs can operate by different mechanisms: competition with adenosine triphosphate (ATP), phosphorylation or induction of conformational change on TK.[80] The specific response of each protein kinase inhibitor is described below.

Anaplastic Lymphoma Kinase (ALK) inhibitors

Anaplastic Lymphoma Kinase (ALK) is a member of the insulin receptor super-family of receptor tyrosine kinases. The inhibitors of ALK are able to block the ALK kinase activity and promote tumor reduction. About five percent of NSCLC have a mutation in ALK gene that produces an abnormal protein causing tumor growth.[6,81]

Crizotinib. Crizotinib is a molecule approved by FDA that blocks the ALK protein. This biological molecule reduced the tumor size by about 50% to 60% of patients with alterations in the ALK protein, although most of them had been previously treated with chemotherapy. The most common side effects of the treatment are nausea, vomiting, diarrhea, constipation, bloating, fatigue, edema and eye problems. Some side effects can be serious, such as decreased leukocyte count and lung and heart alterations.[22,81-84] Recent studies comparing crizotinib and chemotherapy showed that this molecule generated a

reduction in symptoms on ALK-positive nonsquamous NSCLC.[85] Recent clinical studies showed that the association of EGFR tyrosine kinase inhibitors and crizotinib were strongly effective targeted therapies in metastatic NSCLC, mainly in lung adenocarcinoma.[5,6,22]

EGFR-targeting tyrosine kinase inhibitors

The EGFR is a receptor found on the surface of the cells, and is a member of the epidermal growth factor family (EGF-family) of extracellular protein ligands, with diverse cellular functions, including cell proliferation, differentiation, motility, and survival. Some lung cancer cells have an altered expression of this protein. EGFR activation stimulates several intracellular signaling pathways. The MAPK pathway and the PI3K–AKT pathway play very important roles in tumorigenesis by induction of self-sufficient growth, insensitivity to antigrowth signals, as well as escape from apoptosis, sustained angiogenesis, metastasis, and tissue invasion.[1,5,27,86-91]

Erlotinib. Erlotinib is a molecule that blocks EGFR. It is used primarily for advanced lung cancer, and may also be used in patients with mutations in the EGFR gene, frequent in 10 to 15% of NSCLC. This inhibitor is administered orally, and side effects are usually lessor than those of conventional chemotherapeutics. The most troubling side effects are rashes, skin infections, diarrhea, loss of appetite and fatigue.[45,59,92-95] It was approved by the FDA in 2010 for the treatment of advanced non-small cell lung cancer (NSCLC) and in Europe as a monotherapy for the maintenance treatment of patients with stable disease after chemotherapy.[5,25,26,45,92,96-98]

Gefitinib. Gefitinib is also an inhibitor of EGFR tyrosine kinase that has shown antitumor activities in NSCLC. Gefinib also induces differentiation in acute myeloid leukemia cell lines and in patient samples lacking EGFR by an unknown mechanism.[99] In 2015, gefitinib was approved by the FDA for the treatment of patients with metastatic EGFR mutation-positive NSCLC. However, the treatment is associated with the detection of EGFR exon 19 deletions or exon 21 (L858R) substitution mutations by an FDA-approved test.[100,101]

Afatinib. Although EGFR-mutant NSCLC predicts a high sensitivity to the reversible EGFR-tyrosine kinase inhibitors (TKI), such as gefitinib or erlotinib, resistance to these agents remains a clinical challenge. Afatinib is a novel dual irreversible blocker of EGFR/HER2 and HER4 and inhibitor of TK. It also inhibits transphosphorylation of HER3 protein. Based on these findings, afatinib has been tested in advanced NSCLC patients, showing that the treatment with this biological molecule significantly increased progression-free survival in pretreated patients resistant to gefitinib or erlotinib.[1,5,27,86-91] Afatinib is usually administered to patients with advanced NSCLC not treated with another growth blocker. Adverse effects of this inhibitor include diarrhea, rash, stomatitis, decreased appetite, bleeding, itchiness, dry skin.[1,5,27,86-89]

New monoclonal antibodies under evaluation: Candidates for NSCLC treatment

Anti-IGF 1 receptor (IGF-1R) monoclonal antibodies

The membrane-bound insulin-like growth factor 1 (IGF1) receptor is a tyrosine kinase receptor that mediates the effects of IGF-1. IGF-1 is a polypeptide protein hormone similar in molecular structure to insulin. IGF-1 plays an important role in growth and has anabolic effects. The membrane-bound insulin-like growth factor 1 (IGF1) receptors play a relevant role in IGF1 signaling, acting as biomarkers for anti-IGF1R antibody.[102,103] Several studies tried to identify predictive biomarkers with relevance for monitoring the efficacy of IGF1R targeted therapy.

Figitumumab. Figitumumab is a fully human anti-IGF 1 receptor (IGF-1R) monoclonal antibody. Figitumumab has a high affinity for IGF1R/IR heterodimeric receptors as well as IGF1 homodimer receptors and inhibits the IGF/IGF1R signaling axis.[104,105] Combination studies mainly using NSCLC patients showed that figitumumab was promising when associated with carboplatin and paclitaxel in phase I trial and randomized phase II study. However, a phase III study of carboplatin, paclitaxel, with or without figitumumab in first-line for metastatic NSCLC was stopped in 2009.[64,106,107]

Anti NR-LU-10 monoclonal antibodies. NR-LU-10 is an anti-pan carcinoma monoclonal antibody. This is a murine antibody that detects an antigen found in normal colons, livers, lungs, breasts, prostates, and kidneys, and in tumors of the lungs, pancreas, colon, kidney, ovaries, and breasts. The target antigen and mechanisms of action have not yet been fully characterized.[108]

Nofetumomab. Nofetumomab is a Fab fragment of murine monoclonal antibody NR-LU-10, IgG2b subclass.[109,110] Nofetumomab is directed against a 40 kDa antigen, glycoprotein expressed on the surface of many tumors, including NSCLC. It is usually indicated in the detection of extensive stage disease in patients with biopsy-confirmed, previously untreated, small-cell lung cancer.[109,110] There is no clinical trial under development.

Anti-epidermal growth factor receptor (EGFR) antibodies

Since EGFR is a therapeutic target for NSCLC, several therapeutic agents targeting this receptor including antibodies of this receptor. Some monoclonal antibodies, such as Nimotuzumab and ficlatuzumab, have shown efficacy in combination with chemotherapy and radiotherapy.[112-117]

Nimotuzumab. Nimotuzumab (h-R3) is a humanized monoclonal antibody to EGFR, which binds to this receptor and inhibits binding of EGFR to cancer cells. It has several indications, among them: head and neck cancer, nasopharyngeal carcinoma, and esophageal cancer.[111,112] It is in clinical trials for several tumor types, including NSCLC, as well as colorectal, pancreatic, cervical and breast. Serious adverse events were observed mainly consisting of tremors, fever, vomiting, nausea, dry mouth, asthenia, hypertension and flushing. The typical serious dermatological toxicities

associated with other monoclonal antibodies to EGFR were observed with nimotuzumab.[112-117]

Ficlatuzumab. In recent years, several biomarkers of lung cancer have been found and recognized as possible targets for treatment of this disease; among them is the growth factor of transition/hepatocyte mesenchymal intraepithelial (c-MET / HGF). Changes in gene c-MET and MET and HGF aberrations are involved in resistance to inhibitors of the EGFR in NSCLC patients with EGFR mutations.[118] Ficlatuzumab is a monoclonal antibody (IgG1) humanized and directed to HGF and is currently under study for NSCLC. Its mechanism of action is due to its high affinity and specificity for binding to the HGF receptor, thus inhibiting gene c-MET / HGF and its biological activities. The most common adverse reactions observed in immunotherapy were fatigue, peripheral edema, headache and diarrhea.[118-121]

Anti- receptor activator of nuclear factor-kappa B ligand (RANKL) antibodies

Receptor activator of nuclear factor-kappa B ligand (RANKL) is a mediator of the formation, function and survival of osteoclast. Blocking of RANKL has been demonstrated to prevent tumor-induced osteolysis and skeletal complications.[122]

Denosumab. Denosumab is a fully human anti-receptor activator of nuclear factor-kappa B ligand (RANKL) monoclonal antibody. It is a novel agent that inhibits osteoclastic-medicated bone reabsorption by binding to osteoblast-produced RANKL. Denosumab reduces the incidence of skeletal-related events in patients with bone metastases from solid tumors. It is under evaluation for patients with lung cancer, in the phase 3 trial versus zoledronic acid (ZA). In an exploratory study, denosumab was associated with increased overall survival compared with ZA, in patients with metastatic lung cancer.[123,124]

Anti-Cytotoxic T-Lymphocyte-Associated Antigen 4 (CTLA-4) monoclonal antibodies

Cytotoxic T-Lymphocyte-Associated Antigen (CTLA-4) molecule is known to regulate T-cell proliferation in early Stages of T-cell response, primarily in lymph nodes. CTLA-4 prevents the down-regulation of cytotoxic T-cells in the early stages of T-cell activation.[125] Antibodies to CTLA-4 inhibit critical negative T-cell regulators, since they inhibit the costimulatory signaling for T-cells.[126-128]

Ipilimumab. Ipilimumab is a fully human monoclonal IgG1 antibody that binds with the CTLA-4 molecule. In patients with metastatic melanoma treated previously with chemotherapy, this therapy can improve the treatment with ipilimumab. The activity of ipilimumab in combination with chemotherapeutic agents such as paclitaxel and carboplatin has been evaluated in patients with advanced chemotherapy, inducing a better treatment outcome. Ipilimumab is associated with inflammatory adverse reactions resulting from increased or excessive immune activity. Possible adverse immune reactions are gastrointestinal, liver, skin, nervous system, endocrine system or other organ systems. Although most adverse immune reactions occur during the induction period, some were also reported during the onset months after the last dose of ipilimumab.[28-30,32]

Tremelimumab. Tremelimumab (CP-675,206, anti-CTLA-4) is a fully humanized monoclonal IgG2 antibody that binds with the CTLA-4 molecule, usually used for metastatic melanoma and other cancers. CTLA-4 (CD152) is a homolog of the coactivation receptor CD28.[126-128] This molecule is in phase I clinical trial and associated with durvalumab. They showed tolerability and were selected for phase 3 studies, which are ongoing.[34]

New biologic inhibitors under evaluation: Candidates to NSCLC treatment

Poly ADP ribose polymerase (PARP) inhibitors

Poly ADP Ribose Polymerase (PARP) inhibitors block the poly ADP ribose polymerase (PARP) which is thought to repair damage to DNA. Since many tumors are dependent on PARP, this protein can be an attractive target for therapy. They act against tumors in people with hereditary BRCA1 or BRCA2 (breast cancer 1, early onset) mutations.[38]

Veliparib and olaparib. Clinical trials for lung cancer are looking for new biological therapy drugs. Because of this, Veliparib (ABT-888) and olaparib (AZD-2281) are new biological therapies under development, called a PARP inhibitors. These inhibitors are in clinical trials to be administrated after chemotherapy to delay or prevent NSCLC remission, on maintenance therapy.[38-40]

Phosphatidylinositol 3-kinase (PI3K) inhibitor

Phosphatidylinositol 3-kinase (PI3K) enzymes, are associated with PI3K/AKT/mTOR pathway, an important signaling pathway that regulates growth control, metabolism and translation initiation. Activation of the Phosphatidylinositol 3-kinase (PI3K) signaling pathway is frequently associated with tumorigenesis in NSCLC. Phosphatidylinositol 3-kinase (PI3K) inhibitors act by inhibiting one or more PI3K enzymes.[41,129-139]

Buparlisib. Phosphatidylinositol 3-kinase (PI3K) inhibitors include buparlisib (BKM120), a pan inhibitor of PI3K and alpelisib (BYL719), a PI3Kα-selective inhibitor.[41,129-139] However, buparlisib did not meet its primary objective in stage 1 clinical trial, since PI3K pathway activation were detected in NSCLC.[129] To try and solve this problem, there are new studies attempting to maximize its benefits by using buparlisib and alpelisib stratification according to PI3K pathway activation status or selective enrollment of patients and chemotherapy combination.[41]

Final considerations

Immunotherapy with biological inhibitors and monoclonal antibodies are treatments recently applied to tumors, since they cause less damage to normal cells. This technology represents enormous contributions in the treatment of lung cancer. Monoclonal antibodies are highly specific and require that tumor cells express the target antigen, since they can only activate various mechanisms involved in the immune response,

such as induction of apoptosis as well as the blockage of cell growth and transcription factors.

The increased efficacy of anticancer conventional therapy through additional treatment with biological molecules against NSCLC, especially with lung adenocarcinoma, may have significant clinical implications, constituting a new approach in cancer treatment. However, the successful development of immunotherapies requires extensive research and randomized controlled trials, to detail the proper use of these molecules, and the benefits and side effects in the long term. In several cases, many important questions such as heterogeneity of stage, timing and type of administration of these molecules are still unanswered.

Abbreviations

AIS	adenocarcinoma in situ
AKT	serine/threonine-specific protein kinase
ALK	anaplastic lymphoma kinase
ATS	American Thoracic Society
BRAF	V-raf murine sarcoma viral oncogene homolog B1
BRCA	breast cancer, early onset
c-MET/HGF	growth factor of transition / hepatocyte mesenchymal intraepithelial
c-MET	c-mesenchymal-epithelial transition
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
DDR2	discoidin domain receptor 2
EGFR	epidermal growth factor receptor
EGFR	epidermal growth factor receptor
ER2	human epidermal growth factor receptor 2
ERS	European Respiratory Society
FDA	Food and Drug Administration
FGFR	fibroblast growth factor receptor
IASLC	International Association for the Study of Lung Cancer
IGF-1	insulin-like growth factor 1
IGF-1R	human anti-IGF 1 receptor
KRAS	Kirsten rat sarcoma viral oncogene homolog
MAPK	mitogen-activated protein kinase
MIA	minimally invasive adenocarcinoma
NSCLC	non-small-cell lung cancer
PARP	poly ADP ribose polymerase
PD-L1	ligand of programmed cell death ligand 1
PI3K	phosphatidylinositol 3-kinase
PIK3CA	phosphatidylinositol-4,5-bisphosphate3-kinase, catalytic subunit α
PTEN	phosphatase and tensin homolog
RANKL	receptor activator of nuclear factor-kappa B ligand
RAS	erythropoietin-producing hepatoma (EPH), rat sarcoma gene
PKB	protein kinase B
ROS1	reactive oxygen species 1
SCLC	small cells lung cancer
TK	tyrosine kinase
TKI	tyrosine kinase inhibitor
VEGF	vascular endothelial growth factor
WHO	World Health Organization

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