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Short Communication

A REVIEW ON NEWLY APPROVED ANTI CANCER DRUGS

T. M. Suneel Babu[1], Sourav De*[2], Subhasis Banerjee[3]

[1] Seven Hills College of Pharmacy, Tirupati, Andhra Pradesh.
[2]Assistant Professor, Department of Pharmaceutical Chemistry, Seven Hills College of Pharmacy, Tirupati, Andhra Pradesh.
[3] Assistant Professor, Department of Pharmaceutical Chemistry, Gupta College of Technological Sciences, Asansol, West Bengal.

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E-mail: mpharmsourav@rediffmail.com

Abstract
Cancer is most threatening disease posed to mankind. A lot of clinical, experimental research and epidemiological Studies have been carried out in the field of oncology so as to know the possible causes of cancer and mechanisms Involved in transformation of a normal cell into a neoplastic cell. Food and drug authority (U.S.F.D.A) approved several new and combination of anti cancer drugs in recent times. Approved drugs include alkylating agents[1], kinase inhibitors, human monoclonal antibodies[2], immunostimulatory antibodies, nucleoside metabolic inhibitors, epidermal growth factor receptor antagonist, alkylating agents. This review covers drug details that are approved by FDA in therapeutic areas of oncology.

Keywords: Mutations, Alkylating agents, Monoclonal antibodies, FDA, Oncology, Myeloma, Lymphomas, and Neuroblastoma, non-small cell lung cancers (NSCLC)[3]

INTRODUCTION

The discovery of the antineoplastic agents started nearly 50 years ago. Initially researchers triggered into the development of cytotoxic agents. After mustard gas tragedy in world war 2 American pathologist found low levels of wbc in affected bodies due shrinkage of lymph nodes. This created interest in researchers to look in therapeutic applications of such effect. Mustine (modified structure of mustard gas) was found to reduce lymphomas in mice. The mechanism by which mustine damages DNA is referred to as alkylation, a chemical term referring to the way in which the drug attached itself to the DNA, changing the DNA's structure to the point where it could no longer function normally. In the 1950s, this discovery went on to spawn a family of anticancer drugs known as nitrogen mustard alkylating agents[1]. Of these, the drugs chlorambucil (1957), melphalan (1957), cyclophosphamide, (1959) and streptozotocin (1982) are probably the best-known members of this family, and remain in wide use today for the treatment of cancers such as breast cancer, ovarian cancer, bladder cancer and chronic lymphocytic leukemia. And despite its 60-year old age, mustine continues to be used occasionally today, mainly in a combined form with estrogen called estramustine, to treat prostate cancer.

Apart from alkylating agents, there are several other classes of drugs that are used in treatment of cancer like antimetabolites, micro tubule targeted drugs, antibiotics, monoclonal antibodies, hormonal drug, etc... Researches from very longtime in oncology resulted in development of new molecules that are useful in treating cancer. Monoclonal antibody and immunoconjugate therapy are used in treatment of cancer from past 35years. Modern recombinant techniques have made it possible to rapidly produce both chimeric antibodies and humanized antibodies, and totally human antibodies are also being produced. Identification of surface receptors that are integral to proliferation and apoptosis has provided more targets for monoclonal antibodies beyond those originally identified by the murine immune system.

NEW DRUGS

ALECENSA (ALECTINIB) [4-5]

Company: Hoffmann-La Roche

Approval status: Approved December 2016
Specific treatments: Non small cell lung cancer
Therapeutic areas: haematology, oncology. General information:
Alecensa[4] is a kinase inhibitor that targets ALK and RET. Alecensa is specifically indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic non-small cell lung cancers (NSCLC)[3] who have progressed on or are intolerant to crizotinib. Alecensa is supplied as a capsule for oral administration. The recommended dose is 600 mg orally twice daily, taken with food. Administer until disease progression or unacceptable toxicity.

Mechanism of Action
Alecensa (alectinib) is a kinase inhibitor that targets ALK and RET. In nonclinical studies, alectinib inhibited ALK phosphorylation and ALK-mediated activation of the downstream signaling proteins STAT3 and AKT, and decreased tumor cell viability in multiple cell lines harboring ALK fusions, amplifications, or activating mutations. The major active metabolite of alectinib, M4, showed similar in vitro potency and activity.

Adverse Effects
Adverse effects associated with the use of Alecensa may include, but are not limited to, the following
1. Edema 2. Myalgia

COTELLIC (COBIMETINIB)[6-7]
Company: Genentech
Approval Status: Approved November 2015
Specific Treatments: BRAF V600E or V600K melanoma
Therapeutic Areas Dermatology, Oncology
General Information
Cotellic (cobimetinib) is a kinase inhibitor.
Cotellic is specifically indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib.
Cotellic is supplied as a tablet for oral administration. The recommended dose is 60 mg (three 20 mg tablets) orally taken once daily for the first 21 days of each 28-day cycle until disease progression or unacceptable toxicity. Take Cotellic with or without food. If a dose is missed or if vomiting occurs when the dose is taken, resume dosing with the next scheduled dose.
Mechanism of Action
Cotellic (cobimetinib) is a reversible inhibitor of mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinase 1 (MEK1) and MEK2. MEK proteins are upstream regulators of the extracellular signal related kinase (ERK) pathway, which promotes cellular proliferation. BRAF V600E and K mutations result in constitutive activation of the BRAF pathway which includes MEK1 and MEK2.

Adverse Effects
Adverse effects associated with the use of Cotellic may include, but are not limited to, the following:
1. Sensitivity to ultraviolet light 2. Pyrexia 3. Vomiting

DARZALEX (DARATUMUMAB)[8-9]
Company: Janssen Biotech
Approval Status: Approved November 2015
Specific Treatments: multiple myeloma
Therapeutic Areas Hematology, Oncology
General Information
Darzalex (daratumumab) is a human CD38-directed monoclonal antibody.
Darzalex is specifically indicated for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.
Darzalex is supplied as a solution for intravenous infusion. The recommended dose of Darzalex is 16 mg/kg body weight administered as an intravenous infusion.
Mechanism of Action
CD38 is a transmembrane glycoprotein (48 kDa) expressed on the surface of hematopoietic cells, including multiple myeloma and other cell types and tissues and has multiple functions, such as receptor mediated adhesion, signaling, and modulation of cyclase and hydrolase activity. Daratumumab is an IgG1κ human monoclonal antibody (mAb) that binds to CD38 and inhibits the growth of CD38 expressing tumor cells by inducing apoptosis directly through Fc mediated cross linking as well as by immune-mediated tumor cell lysis through complement dependent cy-

totoxicity (CDC), antibody dependent cell mediated cytotoxicity (ADCC) and antibody dependent cellular phagocytosis (ADCP). Myeloid derived suppressor cells (MDSCs) and a subset of regulatory T cells (CD38+Tregs) expresses CD38 and is susceptible to daratumumab mediated cell lysis.

Side Effects

Adverse effects associated with the use of Darzalex may include, but are not limited to, the following:

1. Infusion reactions 2. Back pain 3. Pyrexia 4. Cough 5. Upper respiratory tract infection

EMPLICITI (ELOTUZUMAB) [10-11]

Company: Bristol-Myers Squibb

Approval Status: Approved November 2015

Specific Treatments: multiple myeloma patients who have received prior therapies

Therapeutic Areas Oncology

General Information

Empliciti (elotuzumab) is a SLAMF7-directed immunostimulatory antibody.

Empliciti is specifically indicated for use in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies.

Empliciti is supplied as a solution for intravenous administration. The recommended dose is 10 mg/kg administered intravenously every week for the first two cycles and every 2 weeks thereafter in conjunction with the recommended dosing of lenalidomide and low-dose dexamethasone. Continue treatment until disease progression or unacceptable toxicity.

Mechanism of Action

Empliciti (elotuzumab) is a humanized IgG1 monoclonal antibody that specifically targets the SLAMF7 (Signaling Lymphocytic Activation Molecule Family member 7) protein. SLAMF7 is expressed on myeloma cells independent of cytogenetic abnormalities. SLAMF7 is also expressed on Natural Killer cells, plasma cells, and at lower levels on specific immune cell subsets of differentiated cells within the hematopoietic lineage. Elotuzumab directly activates Natural Killer cells through both the SLAMF7 pathway and Fc receptors. Elotuzumab also targets SLAMF7 on myeloma cells and facilitates the interaction with Natural Killer cells to mediate the killing of myeloma cells through antibody-dependent cellular cytotoxicity (ADCC).

Side Effects

Adverse effects associated with the use of Empliciti may include, but are not limited to, the following:

1. Pyrexia 2. Peripheral neuropathy 3. Nasopharyngitis 4. Upper respiratory tract infection 5. Decreased appetite 6. Pneumonia

FARYDAK (PANOBINOSTAT) [12-13]

Company: Novartis

Approval Status: Approved February 2015

Specific Treatments: Multiple myeloma

Therapeutic Areas Hematology, Oncology

General Information

Farydak (panobinostat) is a histone deacetylase inhibitor.

Farydak is specifically indicated for use in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent. This indication is approved under accelerated approval based on progression free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Farydak is supplied as a capsule for oral administration. The recommended dose is 20 mg, taken orally once every other day for three doses per week (on Days 1, 3, 5, 8, 10, and 12) of Weeks 1 and 2 of each 21-day cycle for 8 cycles.

Mechanism of Action

Farydak (panobinostat) is a histone deacetylase (HDAC) inhibitor that inhibits the enzymatic activity of HDACs at nanomolar concentrations. HDACs catalyze the removal of acetyl groups from the lysine residues of histones and some non-histone proteins. Inhibition of HDAC activity results in increased acetylation of histone proteins, an epigenetic alteration that results in a relaxing of chromatin, leading to transcriptional activation. In vitro, panobinostat caused the accumulation of acetylated histones and other proteins, inducing cell cycle arrest and/or apoptosis of some transformed cells. Increased levels of acetylated histones were observed in xenografts from mice that were treated with panobinostat. Panobinostat shows more cytotoxicity towards tumor cells compared to normal cells.

Side Effects

Adverse effects associated with the use of Farydak may include, but are not limited to, the following:

1. Arrhythmias 2. Peripheral edema 3. Decreased appetite 4. Pyrexia 5. Vomiting

Farydak comes with a black box labeled warning. Severe diarrhea occurred in 25% of Farydak treated patients. Monitor for symptoms, institute anti-diarrheal treatment, interrupt Farydak and then reduce dose or discontinue Farydak. Severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes have occurred in patients receiving Farydak. Arrhythmias may be exacerbated by electrolyte abnormalities. Obtain ECG and electrolytes at baseline and periodically during treatment as clinically indicated.

IBRANCE (PALBOCICLIB) [14-15]

Company: Pfizer

Approval Status: Approved February 2015

Specific Treatments: ER-positive, HER2-negative breast cancer

Therapeutic Areas: Obstetrics/Gynecology (Women's Health) Oncology

General Information

Ibrance (palbociclib) is an orally available pyridopyrimidine-derived cyclin-dependent kinase (CDK) inhibitor with antineoplastic activity.

Ibrance is specifically indicated for use in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease. This indication is approved under accelerated approval based on progression-free survival (PFS). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Ibrance is supplied as a capsule for oral administration. The recommended dose of Ibrance is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. Ibrance should be taken with food in combination with letrozole 2.5 mg once daily given continuously throughout the 28-day cycle. The dose should be taken at approximately the same time each day.

If the patient vomits or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time. Ibrance capsules should be swallowed whole (do not chew, crush or open them prior to swallowing). No capsule should be ingested if it is broken, cracked, or otherwise not intact.

Mechanism of Action

Ibrance (palbociclib) is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of signaling pathways which lead to cellular proliferation. In vitro, palbociclib reduced cellular proliferation of estrogen receptor (ER)-positive breast cancer cell lines by blocking progression of the cell from G1 into S phase of the cell cycle. Treatment of breast cancer cell lines with the combination of palbociclib and antiestrogens leads to decreased retinoblastoma protein (Rb) phosphorylation resulting in reduced E2F expression and signaling and increased growth arrest compared to treatment with each drug alone. In vitro treatment of ER-positive breast cancer cell lines with the combination of palbociclib and antiestrogens leads to increased cell senescence, which was sustained for up to 6 days following drug removal. In vivo studies using a patient-derived ER-positive breast cancer xenograft model demonstrated that the combination of palbociclib and letrozole increased the inhibition of Rb phosphorylation, downstream signaling and tumor growth compared to each drug alone.

Side Effects

Adverse effects associated with the use if Ibrance may include, but are not limited to, the following:

1. Neutropenia 2. Leucopenia 3. Anemia 4.Upper respiratory infection 5. Stomatitis 6. Alopecia 7. Thrombocytopenia 8. Asthenia 9. Peripheral neuropathy
10. Epistaxis

IMLYGIC (TALIMOGENE LAHERPAREPVEC) [16-17]

Company: Amgen

Approval Status: Approved October 2015

Specific Treatments: unresectable recurrent melanoma

Therapeutic Areas: Dermatology, Oncology

General Information

Imlygic (talimogene laherparepvec) is a genetically modified oncolytic viral therapy.

Imlygic is specifically indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.

Imlygic is supplied as a suspension for intralesional injection. Imlygic should be administered by injection into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound guidance.

Imlygic is provided in single-use vials of 1 mL each in two different dose strengths: 10*6 (1 million) plaque-forming units (PFU) per mL (light green cap) – for initial dose only and 10*8 (100 million) PFU per mL (royal blue cap) – for all subsequent doses. The initial recommended dose is up to 4 mL at a concentration of 10*6 (1 million) PFU per mL. The recommended dose for subsequent administrations is up to 4 mL at a concentration of 10*8 (100 million) PFU per mL.

Mechanism of Action

Imlygic (talimogene laherparepvec) is a genetically modified oncolytic viral therapy. It was designed to replicate within tumors and to produce the immune stimulatory protein GM-CSF. Imlygic causes lysis of tumors, followed by release of tumor-derived antigens, which together with virally derived GM-CSF may promote an antitumor immune response.

Side Effects

Adverse effects associated with the use of Imlygic may include, but are not limited to, the following:

1. Chills 2. Pyrexia 3. Influenza-like illness 4. Injection site pain

IMBRUVICA (IBRUTINIB) [18]

Company: Pharmacyclics

Approval Status: Approved February 2014

Specific Treatments: chronic lymphocytic leukemia

Therapeutic Areas: Hematology, Oncology

General Information

Imbruvica (ibrutinib) is an orally available, selective inhibitor of Bruton's tyrosine kinase (Btk), a gene that is disrupted in the human disease X-linked agammaglobulenemia (XLA). BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways.

Imbruvica is specifically approved for chronic lymphocytic leukemia in patients who have received at least one prior therapy.

Imbruvica is supplied as a capsule for oral administration. The recommended dose is 420 mg taken orally once daily (three 140 mg capsules once daily). Capsules should be taken orally with a glass of water. Do not open, break, or chew the capsules.

Mechanism of Action

Imbruvica (ibrutinib) is an orally available, selective inhibitor of Bruton's tyrosine kinase (Btk). Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. BTK's crole in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion.

Side Effects

Adverse events associated with the use of Imbruvica for chronic lymphocytic leukemia may include, but are not limited to, the following:

1. Thrombocytopenia 2. Diarrhea 3. Bruising 4. Neutropenia 5. Anemia 6. Upper respiratory tract infection 7. Musculoskeletal pain 8. Rash 9. Pyrexia 10. Constipation 11. Peripheral edema 12. Arthralgia 13. Stomatitis 14. Sinusitis 15. Dizziness

LENVIMA (LENVATINIB) [19]

Company: Eisai

Approval Status: Approved February 2015

Specific Treatments: thyroid cancer

Therapeutic Areas: Oncology

General Information

Lenvima (lenvatinib) is a receptor tyrosine kinase (RTK) inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1, as well as other RTKs that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions.

Lenvima is specifically indicated for the treatment of locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer.

Lenvima is supplied as a capsule for oral administration. The recommended daily dose of Lenvima is 24 mg (two 10 mg capsules and one 4 mg capsule) orally taken once daily with or without food. Lenvima should be taken at the same time each

day. If a dose is missed and cannot be taken within 12 hours, skip that dose and take the next dose at the usual time of administration. For dose modifications in specific patients, please see drug label. Lenvima should be administered until disease progression or until unacceptable toxicity occurs.

Mechanism of Action

Lenvima (lenvatinib) is a receptor tyrosine kinase (RTK) inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib also inhibits other RTKs that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; the platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET

Side Effects

Adverse effects associated with the use of Lenvima may include, but are not limited to, the following:

1. Hypertension 2. Arthralgia/myalgia 3. Nausea 4. Stomatitis 5. Vomiting 6. Proteinuria 7.Palmar-plantar 8. Erythro dysesthesia syndrome 9. Dysphonia

LONSURF (TRIFLURIDINE AND TIPIRACIL) [20]

Company: Taiho Oncology

Approval Status: Approved September 2015

Specific Treatments: metastatic colorectal cancer

Therapeutic Areas: Gastroenterology, Oncology

General Information

Lonsurf is a combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor.

Lonsurf is specifically indicated for patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

Lonsurf is supplied as tablet for oral administration. The recommended dose is 35 mg/m2 /dose orally twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. Lonsurf should be administered within 1 hour after completion of morning and evening meals.

Mechanism of Action

Lonsurf is a combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor. Following uptake into cancer cells, trifluridine is incorporated into DNA, interferes with DNA synthesis and inhibits cell proliferation.

Side Effects

Adverse effects associated with the use of Lonsurf may include, but are not limited to, the following:

1. Anemia 2. Neutropenia 3. Asthenia/fatigue 4.Thrombocytopenia 5. Diarrhea 6. Abdominal pain 7. Pyrexia

NINLARO (IXAZOMIB) [21]

Company: Millennium Pharmaceuticals

Approval Status: Approved November 2015

Specific Treatments: Multiple myeloma

Therapeutic Areas: Oncology

General Information

Ninlaro (ixazomib) is a proteasome inhibitor.

Ninlaro is specifically indicated for use in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Ninlaro is supplied as a capsule for oral administration. The recommended starting dose of Ninlaro is 4 mg administered orally once a week on Days 1, 8, and 15 of a 28-day treatment cycle. The recommended starting dose of lenalidomide is 25 mg administered daily on Days 1 through 21 of a 28-day treatment cycle. The recommended starting dose of dexamethasone is 40 mg administered on Days 1, 8, 15, and 22 of a 28-day treatment cycle. Ninlaro should be taken once a week on the same day and at approximately the same time for the first three weeks of a four week cycle. Ninlaro should be taken at least one hour before or at least two hours after food. The whole capsule should be swallowed with water. The capsule should not be crushed, chewed or opened. If a dose is delayed or missed, the dose should be taken only if the next scheduled dose is ≥ 72 hours away. A missed dose should not be taken within 72 hours of the next scheduled dose. A double dose should not be taken to make up for the missed dose. If vomiting occurs after taking a dose, the patient should not repeat the dose. The patient should resume dosing at the time of the next scheduled dose.

Mechanism of Action

Ninlaro (ixazomib) is a proteasome inhibitor. Ixazomib preferentially binds and inhibits the

chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome. Ixazomib induced apoptosis of multiple myeloma cell lines in vitro. Ixazomib demonstrated in vitro cytotoxicity against myeloma cells from patients who had relapsed after multiple prior therapies, including bortezomib, lenalidomide, and dexamethasone. The combination of ixazomib and lenalidomide demonstrated synergistic cytotoxic effects in multiple myeloma cell lines. In vivo, ixazomib demonstrated antitumor activity in a mouse multiple myeloma tumor xenograft model.

Side Effects

Adverse effects associated with the use of Ninlaro may include, but are not limited to, the following:

1. Constipation 2.Thrombocytopenia 3. Peripheral neuropathy 4.Peripheral edema 5. Vomiting 6. Back pain

ODOMZO (SONIDEGIB) [22]

Company: Novartis

Approval Status: July 2015

Specific Treatments: locally advanced basal cell carcinoma

Therapeutic Areas: Dermatology, Oncology

General Information

Odomzo (sonidegib) is a hedgehog pathway inhibitor.

Odomzo is specifically indicated for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy.

Odomzo is supplied as a capsule for oral administration. The recommended dose is 200 mg orally once daily taken on an empty stomach, at least 1 hour before or 2 hours after a meal.

Mechanism of Action

Odomzo (sonidegib) is a hedgehog pathway inhibitor. Sonidegib binds to and inhibits Smoothened, a transmembrane protein involved in Hedgehog signal transduction.

Side Effects

Adverse effects associated with the use of Odomzo may include, but are not limited to, the following:

1. Muscle spasms 2. Alopecia 3. Musculoskeletal pain 4. Myalgia 5. Pruritus

ONIVYDE (IRINOTECAN LIPOSOME INJECTION) [23]

Company: Merrimack

Approval Status: Approved October 2015

Specific Treatments: metastatic pancreatic cancer

Therapeutic Areas: Gastroenterology, Oncology

General Information

Onivyde (irinotecan liposome injection) is a topoisomerase inhibitor.

Onivyde is specifically indicated in combination with fluorouracil and leucovorin, for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

Onivyde is supplied as an injection for intravenous infusion. Administer Onivyde prior to leucovorin and fluorouracil. The recommended dose of Onivyde is 70 mg/m2 administered by intravenous infusion over 90 minutes every 2 weeks. Increase the dose of Onivyde to 70 mg/m2 as tolerated in subsequent cycles.

Mechanism of Action

Onivyde (irinotecan liposome injection) is a topoisomerase inhibitor encapsulated in a lipid bilayer vesicle or liposome. Topoisomerase 1 relieves torsional strain in DNA by inducing single-strand breaks. Irinotecan and its active metabolite SN-38 bind reversibly to the topoisomerase 1-DNA complex and prevent re-ligation of the single-strand breaks, leading to exposure time-dependent double-strand DNA damage and cell death. In mice bearing human tumor xenografts, irinotecan liposome administered at irinotecan HCl-equivalent doses 5-fold lower than irinotecan HCl achieved similar intratumoral exposure of SN-38.

Side Effects

Adverse effects associated with the use of Onivyde may include, but are not limited to, the following:

1.Diarrhea 2. Stomatitis 3.Pyrexia 4. Lympho penia 5. Neutropenia Onivyde comes with a black box warning of the potential for severe neutropenia and severe diarrhea with the use of Onivyde.

OPDIVO (NIVOLUMAB) [24]

Company: Bristol-Myers Squibb

Approval Status: Approved March 2015

Specific Treatments: metastatic squamous non-small cell lung cancer

Therapeutic Areas: Oncology, Pulmonary/Respiratory Diseases

General Information

Opdivo (nivolumab) is a human monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production.

Opdivo is specifically indicated for the treatment of patients with metastatic squamous nonsmall cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy.

Opdivo is supplied as a solution for intravenous infusion. The recommended dose is 3 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity. Please see the drug label for specific dose modifications.

Mechanism of Action

Opdivo (nivolumab) is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Up regulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors.

Side Effects

Adverse effects associated with the use of Opdivo for advanced squamous non-small cell lung cancer may include, but are not limited to, the following:

1. Fatigue 2. Dyspnea 3. Musculoskeletal pain 4. Constipation

PORTRAZZA (NECITUMUMAB) [25]

Company: Eli Lilly

Approval Status: Approved November 2015

Specific Treatments: metastatic squamous non-small cell lung cancer

Therapeutic Areas: Oncology, Pulmonary/Respiratory Diseases

General Information

Portrazza (necitumumab) is an epidermal growth factor receptor (EGFR) antagonist.

Portrazza is specifically indicated for use in combination with gemcitabine and cisplatin, for first-line treatment of patients with metastatic squamous non-small cell lung cancer.

Portrazza is supplied as a solution for intravenous administration. The recommended dose is 800 mg administered as an intravenous infusion over 60 minutes on Days 1 and 8 of each 3-week cycle prior to gemcitabine and cisplatin infusion. Continue until disease progression or unacceptable toxicity.

Mechanism of Action

Portrazza (necitumumab) is a recombinant human lgG1 monoclonal antibody that binds to the human epidermal growth factor receptor (EGFR) and blocks the binding of EGFR to its ligands. Expression and activation of EGFR has been correlated with malignant progression, induction of angiogenesis, and inhibition of apoptosis. Binding of necitumumab induces EGFR internalization and degradation in vitro. In vitro, binding of necitumumab also led to antibody-dependent cellular cytotoxicity (ADCC) in EGFR-expressing cells.

Side Effects

Adverse effects associated with the use of Portrazza may include, but are not limited to, the following:

1. Rash 2. Hypomagnesaemia

Portrazza comes with a boxed warning regarding the risk of cardiopulmonary arrest and hypomagnesaemia.

TAGRISSO (OSIMERTINIB) [26]

Company: AstraZeneca

Approval Status: Approved November 2015

Specific Treatments: EGFR T790M mutation positive non-small cell lung cancer

Therapeutic Areas: Oncology, Pulmonary/Respiratory Diseases

General Information

Tagrisso (osimertinib) is an EGFR-TKI, a targeted cancer therapy, designed to inhibit both the activating, sensitizing mutations (EGFRm), and T790M, a genetic mutation responsible to EGFR-TKI treatment resistance.

Tagrisso is specifically indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer, as detected by an FDA-approved test, who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy.

Tagrisso is supplied as a tablet for oral administration. The recommended dose is 80 mg tablet once a day until disease progression or unacceptable toxicity. Tagrisso can be taken with or without food. If a dose is missed, do not make up the missed dose and take the next dose as scheduled.

Mechanism of Action

Tagrisso (osimertinib) is kinase inhibitor of the epidermal growth factor receptor (EGFR), which binds irreversibly to certain mutant forms of EGFR (T790M, L858R, and exon 19 deletion) at approximately 9-fold lower concentrations than wild-type.

Side Effects

Adverse effects associated with the use of Tagrisso may include, but are not limited to, the following:

1. Diarrhea 2. Rash 3. Dry skin 4. Nail toxicity

UNITUXIN (DINUTUXIMAB) [27]

Company: United Therapeutics

Approval Status: Approved March 2015

Specific Treatments: pediatrics with high-risk Neuroblastoma

Therapeutic Areas: Oncology, Pediatrics/Neonatology, Neuroblastoma, Pediatric Health

General Information

Unituxin (dinutuximab) is a chimeric monoclonal antibody.

Unituxin is specifically indicated for use in combination with granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin-2 (IL-2) and 13-cis-retinoic acid (RA), for the treatment of pediatric patients with high-risk Neuroblastoma who achieve at least a partial response to prior first-line multiagent, multimodality therapy.

Unituxin is supplied as a solution for intravenous infusion. The recommended dose of Unituxin is 17.5 mg/m2 /day administered as an intravenous infusion over 10 to 20 hours for 4 consecutive days for a maximum of 5 cycles. Unituxin should be initiated at an infusion rate of 0.875 mg/m2 /hour for 30 minutes. The infusion rate can be gradually increased as tolerated to a maximum rate of 1.75 mg/m2 /hour

Mechanism of Action

Unituxin (dinutuximab) binds to the glycolipid GD2. This glycolipid is expressed on Neuroblastoma cells and on normal cells of neuroectodermal origin, including the central nervous system and peripheral nerves. Dinutuximab binds to cell surface GD2 and induces cell lysis of GD2 expressing cells through antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

Side Effects

Adverse effects associated with the use of Unituxin may include, but are not limited to, the following:

1. Thrombocytopenia 2. Lymphopenia 3. Infusion reactions 4. Hypotension 5. Hyponatremia 6. Aminotransferase anemia 7. Hypokalemia 8. Capillary leak syndrome 9. Urticaria 10. Hypo albuminemia 11.Increased aspartate aminotransferase 12. Hypocalcemia

Unituxin carries a Boxed Warning alerting patients and health care professionals that Unituxin irritates nerve cells, causing severe pain that requires treatment with intravenous narcotics and can also cause nerve damage and life-threatening infusion reactions, including upper airway swelling, difficulty breathing, and low blood pressure, during or shortly following completion of the infusion. Unituxin may also cause other serious side effects including infections, eye problems, electrolyte abnormalities and bone marrow suppression.

VENCLEXTA (VENETOCLAX) [28-29]

Company: Abbvie

Approval Status: Approved April 2016

Specific Treatments: chronic lymphocytic leukemia with 17p deletion

Therapeutic Areas: Hematology Oncology

General Information

Venclexta (venetoclax) is a BCL-2 inhibitor, an antiapoptotic protein.

Venclexta is specifically indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion, as detected by an FDA approved test, who have received at least one prior therapy.

Venclexta is supplied as tablets for oral administration. Initiate therapy with Venclexta at 20 mg once daily for 7 days, followed by a weekly ramp-up dosing schedule to the recommended daily dose of 400 mg. Venclexta tablets should be taken orally once daily with a meal and water. Do not chew, crush, or break tablets.

Mechanism of Action

Venclexta (venetoclax) is a selective and orally bio-available small-molecule inhibitor of BCL-2, an antiapoptotic protein. Overexpression of BCL-2 has been demonstrated in CLL cells where it mediates tumor cell survival and has been associated with resistance to chemotherapeutics. Venetoclax helps restore the process of apoptosis by binding directly to the BCL-2 protein, displacing pro-apoptotic proteins like BIM, triggering mitochondrial outer membrane permeabilization and the activation of caspases.

Adverse effects

Adverse effects associated with the use of Venclexta may include, but are not limited to, the following:

1. Neutropenia 2. Anemia 3. Upper respiratory tract infection 4. Thrombocytopenia

YONDELIS (TRABECTEDIN) [30-31]

Company: Janssen

Approval Status: Approved October 2015

Specific Treatments: liposarcoma or leiomyosarcoma

Therapeutic Areas Oncology

General Information

Yondelis (trabectedin) is an alkylating agent.

Yondelis is specifically indicated for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen.

Yondelis is supplied as an injection for intravenous administration. The recommended dose is 1.5 mg/m2 administered as an intravenous infusion over 24 hours through a central venous line every 21 days (3 weeks), until disease progression or unacceptable toxicity, in patients with normal bilirubin and AST or ALT less than or equal to 2.5 times the upper limit of normal. There is no recommended dose of Yondelis in patients with serum bilirubin levels above the institutional upper limit of normal.

Mechanism of Action

Yondelis (trabectedin) is an alkylating drug that binds guanine residues in the minor groove of DNA, forming adducts and resulting in a bending of the DNA helix towards the major groove. Adduct formation triggers a cascade of events that can affect the subsequent activity of DNA binding proteins, including some transcription factors, and DNA repair pathways, resulting in perturbation of the cell cycle and eventual cell death.

Side Effects

Adverse effects associated with the use of Yondelis may include, but are not limited to, the following:

1. Peripheral edema 2. Dyspnea 3. Neutropenia 4. Increased alt 5. Thrombocytopenia 6. Anemia 7. Increased ast 8. Increased creatine phosphokinase

Conclusion

The US food and drug administration accelerated approval of drugs for earlier approval of drugs that treat serious conditions like cancer. From all research achievements immunotherapy area clearly stands out from the rest. From the success in advanced melanoma, there is now evidence that immunotherapy works against a range of cancers. Even for the patients who have exhausted all traditional treatments immunotherapy is able to halt cancer growth, often with only mild side effects. As fundamental research on cancer immunotherapy intensified, immunotherapy involves unleashing the body's natural immune response to cancer, and the second helps the immune system find and destroy cancer cells.

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