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# A review Magazine on Infectious Diseases and Cancer

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## A review Magazine on Infectious Diseases and Cancer

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### 1.Introduction:-

Kalpavrksa is one of a kind magazine introduced by us exclusive for the Pharmacy Professionals and other health care professionals mainly focussing on drug and diseases Management which was founded by Doctor of pharmacy students from Seven Hills College of pharmacy and other colleges from India. Pharmacy practice in India is being introduced with interest of making the medication fruitfully to the desired use.

This magazine Kalpavrksa will help the students and other professionals in pharma and other health care professionals to understand the dosage regimen ,treatment, mode of action, therapeutics uses ,side effects etc...,

Presently the current issue is now focused on Guidelines of understanding infectious diseases and Cancer and its therapeutic management and Current update on latest medicaments or medicines introduced into the market as per the guidelines made by USFDA.

### 2.Guidelines Of Antibiotics :-

**A note on infectious diseases on microbes:-** Antibiotics are the agents that are used to treat the bacterial infections. Fleming discovered penicillin antibiotic. Antibiotic prophylaxis is the prescription of antibiotics to minimise the risk of bacterial infection.

#### A list of antibiotics commonly used in India.

**Amino glycoside:** Depend on local susceptibility patterns this is used. Aminoglycosides are among the most rapidly bactericidal drugs available for treatment of aerobic Gram-negative sepsis. All aminoglycosides are potentially ototoxic and nephrotoxic. Renal function, auditory and vestibular function, and therapeutic drug levels should be monitored .Clinically significant adverse effects are more likely in patients of advanced age, and those with renal impairment, hearing loss or vestibular impairment.

**Gentamicin:** Has a broad Gram-negative spectrum, including *Pseudomonas aeruginosa*. Where approximately 95% or more of aerobic Gram-negative isolates remain

susceptible to gentamicin, it is the aminoglycoside of choice.

**Tobramycin:** It is marginally more active *in vitro* than gentamicin against *Pseudomonas aeruginosa* but not other aerobic Gram-negative bacteria, and is inactivated by a similar range of modifying enzymes to gentamicin. Tobramycin should be restricted but may have a role in treatment of proven pseudomonal sepsis.

**Amikacin:** It is the aminoglycoside most resistant to enzymatic inactivation. It must be reserved for treating infections due to microorganisms that are resistant to other aminoglycosides. Amikacin is considerably more expensive than other aminoglycosides.

**Paromomycin:** It has limited use in treating intestinal amoebiasis.

**Framycetin:**It is used topically for superficial eye and ear infections. Short-term use does not appear to be associated with increased ototoxicity; however, long-term use is not recommended.

**Neomycin:** It is used topically and is bactericidal against a range of Gram-negative organisms. It is the most nephrotoxic and ototoxic of the aminoglycosides, which precludes parenteral use. Topical use may induce sensitisation.

**Streptomycin:** Its use is now limited to occasional selected cases of tuberculosis, other mycobacterial infections and enterococcal endocarditis.

### Choice of drugs for suspected or proved microbial pathogens.

Table.1. Drugs of choice for suspected or proved microbial pathogens, 2004.

Suspected or Proved Etiologic Agent	Drug(s) of First Choice	Alternative Drug(s)
<b>Gram-negative cocci</b>		
<i>Neisseria gonorrhoeae</i> (gonococcus)	Ciprofloxacin or ofloxacin	Ceftriaxone, spectinomycin, cefpodoxime proxetil
<i>Neisseria meningitidis</i> (meningococcus)	Penicillin <sup>6</sup>	Cefotaxime, ceftriaxone, ampicillin
<b>Gram-positive cocci</b>		
<i>Streptococcus pneumoniae</i> <sup>8</sup> (pneumococcus)	Penicillin <sup>6</sup>	An erythromycin, <sup>4</sup> a cephalosporin, <sup>7</sup> vancomycin, TMP-SMZ, <sup>2</sup> clindamycin, azithromycin, clarithromycin, a tetracycline, <sup>5</sup> certain fluoroquinolones <sup>3</sup>
<i>Enterococcus faecalis</i>	Ampicillin ± gentamicin <sup>10</sup>	Vancomycin ± gentamicin
<b>Gram-negative rods</b>		
<i>Acinetobacter</i>	Imipenem or meropenem	Tigecycline, minocycline, doxycycline, aminoglycosides, <sup>11</sup> colistin
<i>Bacteroides</i> , gastrointestinal strains	Metronidazole	Clindamycin, ticarcillin-clavulanic acid, ampicillin-sulbactam, piperacillin-tazobactam
<i>Enterobacter</i>	TMP-SMZ, <sup>2</sup> imipenem, meropenem	Aminoglycoside, <sup>a</sup> fluoroquinolone, <sup>3</sup> cefepime
<i>Escherichia coli</i> (sepsis)	Cefotaxime, ceftriaxone,	Imipenem or meropenem, aminoglycosides, <sup>11</sup> a fluoroquinolone <sup>3</sup>

<b>Acid-fast rods</b>		
<i>Mycobacterium tuberculosis</i> <sup>13</sup>	Isoniazid (INH) + rifampin + pyrazinamide ± ethambutol (or streptomycin)	Other antituberculous drugs (see Tables 9–13 and 9–14)
<i>Mycobacterium leprae</i>	Dapsone + rifampin ± clofazimine	Minocycline, ofloxacin, clarithromycin
<b>Spirochetes</b>		
<i>Borrelia burgdorferi</i> (Lyme disease)	Doxycycline, amoxicillin, cefuroxime axetil	Ceftriaxone, cefotaxime, penicillin, azithromycin, clarithromycin
<i>Treponema pallidum</i> (syphilis)	Penicillin <sup>6</sup>	Doxycycline, ceftriaxone
<b>Mycoplasmas</b>	Erythromycin <sup>4</sup> or doxycycline	Clarithromycin, azithromycin, a fluoroquinolone <sup>3</sup>
<b>Chlamydiae</b>		
<i>C. psittaci</i>	Doxycycline	Chloramphenicol
<i>C. pneumoniae</i>	Doxycycline <sup>3</sup>	Erythromycin, <sup>4</sup> clarithromycin, azithromycin, a fluoroquinolone <sup>3,14</sup>
<b>Rickettsiae</b>	Doxycycline <sup>3</sup>	Chloramphenicol, a fluoroquinolone <sup>3</sup>

## Examples of antibiotics for hospitalized pending identification of organism.

Examples of initial antimicrobial therapy for acutely ill, hospitalized adults pending identification of causative organism

Suspected Clinical Diagnosis	Likely Etiologic Diagnosis	Drugs of Choice
(A) Meningitis, bacterial, community-acquired	<i>Pneumococcus</i> , <sup>1</sup> meningococcus	Cefotaxime, <sup>2</sup> 2–3 g IV every 6 hours, or ceftriaxone, 2 g IV every 12 hours plus vancomycin, 10 mg/kg IV every 8 hours
(B) Meningitis, bacterial, age > 50, community-acquired	<i>Pneumococcus</i> , meningococcus, <i>Listeria monocytogenes</i> , <sup>3</sup> gram-negative bacilli	Ampicillin, 2 g IV every 4 hours, plus cefotaxime or ceftriaxone and vancomycin as in (A)
(C) Meningitis, postoperative (or posttraumatic)	<i>S aureus</i> , gram-negative bacilli (meningococcus, in posttraumatic)	Vancomycin, 10 mg/kg IV every 8 hours, plus ceftazidime, 3 g IV every 8 hours
(D) Brain abscess	Mixed anaerobes, pneumococci, streptococci	Penicillin G, 4 million units IV every 4 hours, plus metronidazole, 500 mg orally every 8 hours, or cefotaxime or ceftriaxone as in (A) plus metronidazole, 500 mg orally every 8 hours
(E) Pneumonia, acute, community-acquired, severe	<i>Pneumococci</i> , <i>M pneumoniae</i> , <i>Legionella</i> , <i>C pneumoniae</i>	Doxycycline, 100 mg IV or orally every 12 hours (or azithromycin), plus cefotaxime, 2 g IV every 8 hours (or ceftriaxone, 1 g IV every 24 hours), or a fluoroquinolone <sup>3</sup> alone
(F) Pneumonia, postoperative or nosocomial	<i>S aureus</i> , mixed anaerobes, gram-negative bacilli	Cefepime, 2 g IV every 8 hours, or ceftazidime, 2 g IV every 8 hours, or piperacillin-tazobactam, 4.5 g IV every 6 hours, or imipenem, 500 mg IV every 6 hours, or meropenem, 1 g IV every 8 hours plus tobramycin, 5 mg/kg IV every 24 hours; or ciprofloxacin, 400 mg IV every 12 hours; or levofloxacin, 500 mg IV every 24 hours plus vancomycin, 15 mg/kg IV every 12 hours
(G) Endocarditis, acute (including injection drug user)	<i>S aureus</i> , <i>E faecalis</i> , gram-negative aerobic bacteria, viridans streptococci	Vancomycin, 15 mg/kg IV every 12 hours, plus gentamicin, 1 mg/kg every 8 hours
(H) Septic thrombophlebitis (eg, IV tubing, IV shunts)	<i>S aureus</i> , gram-negative aerobic bacteria	Vancomycin, 15 mg/kg IV every 12 hours plus ciprofloxacin, 400 mg IV every 12 hours; or levofloxacin, 500 mg IV every 24 hours; or ceftriaxone, 1 g IV every 24 hours
(I) Osteomyelitis	<i>S aureus</i>	Naftillin, 2 g IV every 4 hours; or ceftazolin, 2 g IV every 8 hours
(J) Septic arthritis	<i>S aureus</i> , <i>N gonorrhoeae</i>	Ceftriaxone, 1–2 g IV every 24 hours
(K) Pyelonephritis with flank pain and fever (recurrent urinary tract infection)	<i>E coli</i> , <i>Klebsiella</i> , <i>Enterobacter</i> , <i>Pseudomonas</i>	Ceftriaxone, 1 g IV every 24 hours, or ciprofloxacin, 400 mg IV every 12 hours (500 mg orally), or levofloxacin, 500 mg once daily (IV/PO)
(L) Fever in neutropenic patient receiving cancer chemotherapy	<i>S aureus</i> , <i>Pseudomonas</i> , <i>Klebsiella</i> , <i>E coli</i>	Ceftazidime, 2 g IV every 8 hours; or ceftipime, 2 g IV every 8 hours
(M) Intra-abdominal sepsis (eg, postoperative, peritonitis, cholecystitis)	Gram-negative bacteria, <i>Bacteroides</i> , anaerobic bacteria, streptococci, clostridia	Piperacillin-tazobactam as in (F) or ticarcillin-clavulanate, 3.1 g IV every 6 hours; or ertapenem, 1 g every 24 hours; or moxifloxacin, 400 mg IV every 24 hours

## Guidelines of AntiViral:-

An infectious agent having a simple acellular organisation, often just a protein coat and nucleic acid genome; lacking independent metabolism; and reproducing only with the living host cell. The study of viruses is called VIROLOGY. Viruses can exist either intracellularly or extracellularly. Intracellularly viruses exist primarily as replicating nucleic acids that include the host to synthesize viral components. Extracellularly they are inactive because they possess few enzymes and cannot reproduce outside the living cells.

## CLINICAL DIAGNOSIS

Some viral illnesses present with typical syndromes (measles, mumps, and chickenpox). Aseptic meningitis can be caused by the mumps virus, lymphocytic choriomeningitis virus, and several enteroviruses. Symptoms of respiratory disease with many viruses are indistinguishable. Identification of a virus is useful for confirmation of atypical cases, help with outbreak investigation, elucidation of confusing syndromes, and increasingly to support the need for specific antiviral therapy. The frequency with which certain pathogens cause certain diseases eg, respiratory syncytial virus (RSV) for bronchiolitis or parainfluenza virus for croup

## AGENTS FOR VIRAL INFECTIONS

AGENTS FOR VIRAL INFECTIONS. (TABLE-1)

Drug	Dosing	Spectrum	Toxicities	MOA
Acyclovir	200–800 mg orally five times daily; 250–500 mg <sup>2</sup> intravenously every 8 hours for 7 days	HSV, VZV	Neurotoxic reactions, reversible renal dysfunction, local reactions	Inhibit DNA synthesis and viral infection.
Adefovir	10 mg daily orally	HBV	Gastrointestinal symptoms, transaminitis, lactic acidosis, nephrotoxicity	After entering into the cell it is phosphorylated to the diphosphate which has the high affinity for HBV DNA polymerase compared to host cell DNA polymerase. This enzyme is inhibited and adefovir itself gets incorporated in the viral DNA resulting in termination of the DNA chain.
Amantadine	100 mg orally twice daily (100 mg in elderly) for 10 days	Influenza A, not avian flu	Confusion, gastrointestinal symptoms	It inhibits the replication of influenza A virus. The anti-viral activity for influenza B is not affected. It shows its action in M2 receptors. Resistance to it is developed by mutation causing amino acid substitution in the M2 protein.
Cidofovir	5 mg/kg intravenously weekly for 2 weeks, then every other week	CMV	Neutropenia, renal failure, ocular hypotonia	It inhibits viral DNA polymerase, as well as acts as an alternative substrate.
Entecavir	0.5 mg orally daily, increase to 1 mg orally daily in lamivudine-resistant patients	HBV	Lactic acidosis, rare exacerbation of HBV infection	Inhibit DNA synthesis and viral infection.
Famciclovir	500 mg orally three times daily for 7 days for acute VZV; 250 mg three times daily for 7–10 days for genital or cutaneous HSV-1	HSV, VZV	NA	It inhibits the viral DNA polymerase.
Fomivirsen	165 mg by intravitreal injection once weekly for 3 weeks, then every other week	CMV	Ocular inflammation, retinal detachment	It is an antisense oligonucleotide which binds to mRNA of CMV and interferes with transcription of early proteins in viral replication.
Foscarnet	20 mg/kg intravenous bolus then 120 mg/kg intravenously every 8 hours for 2 weeks; maintain with 60	CMV, HSV resistant to acyclovir, VZV, HIV-1	Nephrotoxicity, genital ulcers, calcium disturbances	It inhibits viral DNA polymerase and reverse transcriptase. It is active against Herpes, CMV, other Herpes
Ganciclovir	5 mg/kg intravenous bolus every 12 hours for 14–21 days, maintain with 3.75 mg/kg intravenously for 5 days each week	CMV	Neutropenia, thrombocytopenia, CNS side effects	It inhibits viral DNA polymerase. It is active against all herpes viruses including Herpes, H. Zoster, EBV and CMV against which it is most active.
Idoxuridine	Topical, 0.1% every 1–2 hours for 3–5 days	HSV keratitis	Local reactions	It gets incorporated in DNA which breaks down DNA easily. Because of low virus selectivity, higher local toxicity and rapid development viral resistance, it is restricted to superficial dendritic keratitis when rapid action is required.
Interferon- $\alpha$ 2b	3–5 million IU subcutaneously 3 times weekly to daily. Intranasally: 1 million IU per 0.1 mL in up to 5 warts three times weekly for 3 weeks	HBV, HCV, HPV	Influenza-like syndrome, myelosuppression, neurotoxicity	PEG-interferon alpha 2b binds to receptor 1 and 2
Interferon- $\alpha$ n3	0.05 mL wart biweekly up to 8 weeks 3 mU intravenously three times per week	HPV ? HCV	Local reactions Influenza-like syndrome, myelosuppression, neurotoxicity	Interferon alpha binds to type 1 interferon receptors (IFNAR1 and IFNAR2)
Lamivudine (3TC)	12 mg/kg/d	HIV-1, HIV-2, HBV	Skin rash, headache, insomnia	It inhibits HIV reverse transcriptase as well as HBV DNA polymerase. Its incorporation into DNA results in chain termination. Most human DNA polymerases are not affected and systemic toxicity of 3TC is low. Point mutation in HIV reverse transcriptase and HBV DNA polymerase gives rise to rapid lamivudine resistance.
Oseltamivir	75 mg twice daily for 5 days beginning 48 hours after onset of symptoms	Influenza A and B	Few	It inhibits influenza virus neuraminidase enzyme which is needed for release of progeny virions from the infected cell.
Penciclovir	Topical, 1% cream every 2 hours for 4 days	HSV	Local reactions	Inhibit DNA synthesis and viral infection.
Palivizumab	15 mg/kg intramuscularly every	RSV	Upper respiratory infection symptoms	NRTI- Nucleoside reverse transcriptase

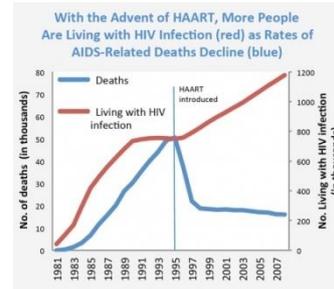
Ribavirin	Aerosol: 1.1 g/d as 20 mg/mL dilution over 12–18 hours for 3–7 days (See text for Lassa fever doses.)	RSV, severe influenza A or B, Lassa fever	Wheezing	It acts against influenza A and B, respiratory syncytial virus and many other DNA and double stranded RNA virus. Its mono and triphosphate derivatives generated intracellularly inhibit GTP and viral RNA synthesis and have other sites of action.
Rimantadine	100 mg orally twice daily	Influenza A	Same as an antitadine, but less severe	It is largely metabolised by hydroxylation followed by glucuronide conjugation. It is similar to an antitadine.
Trifluridine	Topical, 1% drops every 2 hours to 9 drops/d	HSV keratitis	Local reactions	It inhibits HSV-1, HSV-2, CMV and related viruses. Virus selectivity is low and DNA synthesis in host cells is also affected.
Valacyclovir	1 g orally three times daily for 7 days for acute VZV; 1 g twice daily for primary genital HSV-1, HSV-2 infection with 500 mg three times daily for recurrences	VZV, HSV	Thrombotic thrombocytopenic purpura or hemolytic-uremic syndrome in AIDS	It is an ester prodrug of acyclovir with improved oral bioavailability (55–70%) due to active transport by peptide transporters in the intestine and liver, it is completely converted to acyclovir in the first passage by esterases, thus, higher plasma levels of acyclovir are obtained improving clinical efficacy in certain conditions.
Valganciclovir	900 mg orally twice daily for 3 weeks; 900 mg daily as maintenance	CMV	See ganciclovir	Inhibit DNA synthesis and viral infection.
Vidarabine	15 mg/kg/d intravenously for 10 days	HSV, V ZV	Teratogenic, megaloblastosis, neurotoxicity	Inhibit DNA synthesis and viral infection.
Zanamivir	2–5 mg inhalations twice daily for 5 days	Influenza A and B	Few	Influenza B virus neuraminidase inhibitor that is administered by inhalation as a powder due to very low oral bioavailability. It is similar to that of oseltamivir.

#### DIAGNOSTIC FEATURES OF SOME ACUTE EXANTHEMS

DIAGNOSTIC FEATURES OF SOME ACUTE EXANTHEMS (TABLE 2)

DISEASE	PRODROMAL SIGNS AND SYMPTOMS	LABORATORY TESTS
Eczema herpeticum	None.	Herpes simplex virus isolated in cell culture. Multinucleate giant cells in smear of lesion.
Varicella (chickenpox)	0–1 day of fever, anorexia, headache.	Specialized complement fixation and virus neutralization in cell culture. Fluorescent antibody test of smear of lesions.
Infectious mononucleosis (EBV)	Fever, adenopathy, sore throat.	Atypical lymphocytes in blood smears; heterophil agglutination (Monospot test).
Exanthema subitum (HHV-6, 7; roseola)	3–4 days of high fever.	White blood count low.
Measles (rubeola)	3–4 days of fever, coryza, conjunctivitis, and cough.	White blood count low. Virus isolation in cell culture. Antibody tests by hemagglutination inhibition or neutralization.
Atypical measles	Same as measles.	Measles antibody present in past, with titer rise during illness.
Rubella	Little or no prodrome.	White blood count normal or low. Serologic tests for immunity and definitive diagnosis (hemagglutination inhibition).
Erythema infectiosum (parvovirus B19)	None. Usually in epidemics.	White blood count normal.
Enterovirus infections	1–2 days of fever, malaise.	Virus isolation from stool or cerebrospinal fluid; complement fixation titer rise.
Typhus	3–4 days of fever, chills, severe headaches.	Complement fixation.
Rocky Mountain spotted fever	3–4 days of fever, vomiting.	Indirect fluorescent antibody; complement fixation.
Ehrlichiosis	Headache, malaise.	Polymerase chain reaction, immunofluorescent antibody.
Scarlet fever	One-half to 2 days of malaise, sore throat, fever, vomiting.	Group A hemolytic streptococci in cultures from throat; antistreptolysin O titer rise.
Meningococemia	Hours of fever, vomiting.	Cultures of blood, cerebrospinal fluid. High white blood count.
Kawasaki disease	Fever, adenopathy, conjunctivitis.	Thrombocytosis, electrocardiographic changes.
Smallpox (based on prior experience)	Fever, malaise, prostration.	Contact CDC <sup>1</sup> for suspicious rash; EM and gel diffusion assays.

## ONE OF THE PICTORIAL REPRESENTATION FOR HAART THERAPY IN HIV PATIENTS FROM 1981 TO 2007:



HAART—highly active antiretroviral therapy—is a customized combination of different classes of medications that a physician prescribes to treat HIV. Although it cannot rid the body of the virus, HAART can control the amount of virus in the bloodstream (viral load), helping to delay the onset of symptoms and progression to AIDS, prolonging survival in people with HIV.

### Guidelines of anti-neoplastics :

#### INTRODUCTION:

##### Neoplasia:

Means new growth produced is called neoplasia or tumour .

##### Definition:

A mass of tissue formed as a result of abnormal, excessive, uncoordinated, autonomous, purposeless, proliferation of cells even after cessation of stimulus for growth which caused it.

ANTICANCER DRUGS: Anticancer drugs either kill cancer cells or modify their growth.

##### Etiology

Cancer is the second most common cause of death in the United States. The American Cancer Society estimates that almost 1.4 million new cases of invasive cancer will be diagnosed in the year 2006, with over 570,000 deaths. Some type of invasive cancer will develop in slightly less than one of every two men and slightly more than one of every three women in the United States during their lifetime. Based on the SEER 2005 database, the lifetime probability of developing cancer is about 46% for men and 38% for women

Cancer	Risk of Diagnosis (%)	Risk of Death (%)
Prostate	17.9 (1 in 6)	3.0
Breast (women)	13.2 (1 in 8)	3.0
Lung		
(men)	7.6	7.43
(women)	5.7	4.8
Colorectal		
(men)	5.8	2.4
(women)	5.5	2.3
Bladder (men)	3.6	0.7
Uterus <sup>1</sup>	3.4	0.8
Any cancer		
(men)	45.8 (1 in 2)	23.6
(women)	38.1 (1 in 3)	20.0

#### Hereditary Factors:

Hereditary predisposition to some cancers has been linked to genetic events and is manifested by a family history of a common cancer or cancers occurring frequently—in a younger than expected age group—or any history of a relatively rare cancer. Examples include familial retinoblastoma, familial adenomatous polyposis (FAP), multiple endocrine neoplasia (MEN) syndromes, and the hereditary breast and ovarian cancer syndromes.

### Risk Factors :

Carriers of *BRCA* mutations who have children appear to be at higher risk for developing breast cancer by age 40 years than carriers who are nulliparous—in contrast to the usual risk factors for sporadic breast cancer. Interestingly—and despite the association of *BRCA1* with an increased risk of hormone receptor-negative breast tumors—recent data confirm that oophorectomy in women with either mutation before the age of 40 years significantly reduces the risk of breast cancer (up to 75%) and ovarian cancer, presumably by decreasing exposure of breast tissue to estrogen.

**Screening for Genetic Risk Factors:** Many cancer centers now have genetic screening and counseling programs. Patients with a strong family history of cancer should be referred to such programs before testing is performed. Early and regular cancer screening is recommended for affected members of the family.

### Staging of Cancer:

Standardized staging for tumor burden at the time of diagnosis is important both for determining prognosis and for making decisions about treatment. The untreated primary tumor (T) will gradually increase in size, leading to regional lymph node involvement (N) and, finally, distant metastases (M).

### Surgery & Radiation Therapy:

Most cancers present initially as localized tumor nodules and cause local symptoms. Depending on the type of cancer, initial therapy may be directed locally in the form of surgery or radiation therapy. Surgical excision or local radiation (or both) is the treatment of choice for a variety of potentially curable cancers, including most gastrointestinal and genitourinary cancers, central nervous system tumors, and cancers arising from the breast, thyroid, or skin as well as most sarcomas.

Surgery at presentation has both diagnostic and therapeutic effectiveness, since it permits pathologic staging of the extent of local and regional invasion as well as an opportunity for removal of the primary neoplasia. Radiation therapy is usually delivered as brachytherapy or teletherapy. In **brachytherapy**, the radiation source is placed close to the tumor. This intracavitary approach is used for many gynecologic or oral neoplasms and occasionally for breast cancer. In **teletherapy**, supervoltage radiotherapy is usually delivered with a linear accelerator, as this instrument permits more precise beam localization and avoids the complication of skin radiation toxicity. A small percentage of these patients may require chemotherapy later for disease recurrence.

### Treatment choices for cancers responsive to systemic agents.

Carcinoma of the adrenal gland <sup>2</sup>	Mitotane.	Doxorubicin, suramin <sup>2</sup>
Carcinoid <sup>2</sup>	Fluorouracil plus streptozocin with or without interferon- $\alpha$ .	Doxorubicin, cyclophosphamide, octreotide, cyproheptadine, <sup>1</sup> methysergide <sup>2</sup>
Osteogenic sarcoma <sup>2</sup>	High-dose methotrexate, doxorubicin, vincristine.	Cyclophosphamide, ifosfamide, bleomycin, dacarbazine, cisplatin, dactinomycin
Soft tissue sarcoma <sup>2</sup>	Doxorubicin, dacarbazine.	Ifosfamide, cyclophosphamide, etoposide, cisplatin, high-dose methotrexate, vincristine
Melanoma <sup>2</sup>	Dacarbazine, interferon- $\alpha$ , interleukin-2.	Carbimazole, lomustine, melphalan, thiopeta, cisplatin, paclitaxel, tamoxifen, vincristine vaccine therapy (Melacine) <sup>2</sup>
Kaposi's sarcoma	Doxorubicin, vincristine alternating with vinblastine or vincristine alone. Palliative radiation therapy.	Interferon- $\alpha$ , bleomycin, etoposide, doxorubicin
Neuroblastoma <sup>2</sup>	<b>Combination chemotherapy:</b> variations of cyclophosphamide, cisplatin, vincristine, doxorubicin, dacarbazine.	Melphalan, ifosfamide, autologous or allogeneic bone marrow transplantation

### Newer Anticancer Drugs:

Molecular techniques have allowed insight into the biologic events resulting in cancer, and these same techniques have resulted in identification of just the beginning of a cascade of biologic therapies directed toward specific molecular or cellular factors critical to the pathogenesis of cancer growth and survival. Rather than the traditional cytotoxic therapy, two biologic therapies, imatinib mesylate and alemtuzumab, were rapidly approved for use based on marked efficacy with low toxicity for the treatment of two different hematologic malignancies. In 2003 through the first quarter of 2004, seven new agents were approved by the FDA for the treatment of a variety of cancers, including novel cytotoxics, biologic therapy, and radioimmunoconjugates. Two agents to reduce chemotherapy-associated nausea and vomiting were also released for use. The first nanoparticle taxane, nab-paclitaxel was approved for the treatment of metastatic breast cancer. .

### Prevention of Cancer:

#### Primary Prevention

#### Lifestyle Modifications

Population studies suggest that lifestyle—including tobacco use, diet, obesity, and alcohol consumption—accounts for a majority of avoidable cancer deaths in the United States. Other factors, including obesity, parity, and length of lactation, have also been associated with increased cancer risk.

The molecular targets for carcinogens such as alcohol and tobacco have not yet been identified. However, an evaluation of tumor samples from over 100 patients with squamous cell carcinoma of the head and neck found an association between smokers and genetic mutations in the *p53* gene, thought to result in the initiation or progression of this cancer. This supports epidemiologic evidence that abstinence from smoking is important in preventing head and neck cancer. Cigarette smoking has been linked to cancers of the lung, mouth, pharynx, esophagus, pancreas, kidney, and bladder. The risk decreased each year after quitting smoking, indicating that change in this major lifestyle factor can still reduce risk of death from cancer. Phytoestrogens are plant estrogenic substances including isoflavones, coumestans, and lignans. There has been interest in the role of phytoestrogens in the prevention of breast cancer, due to the lower rates of breast cancer observed in women with a high consumption of phytoestrogens. Various lifestyle and dietary factors have been associated with a reduced risk of breast cancer. Increased duration of lactation, particularly for at least 1 year and with more than one pregnancy, reduced the subsequent risk of breast cancer in one large meta-analysis.

The Women's Intervention Nutrition Study (WINS) is a large, phase III trial that randomized over 2400 postmenopausal women

Diagnosis	Current Treatment of Choice	Other Valuable Agents and Procedures
Acute lymphocytic leukemia	<b>Induction:</b> combination chemotherapy: Adriamycin, prednisone, daunorubicin, and asparaginase (DVP, Asp). <b>Consolidation:</b> multiagent alternating chemotherapy. Allogeneic bone marrow transplant for young adults or high-risk disease or second remission. Central nervous system prophylaxis with intrathecal methotrexate with or without whole brain radiation. <b>Remission:</b> thioguanine, maintenance: methotrexate.	Doxorubicin, cytarabine, cyclophosphamide, etoposide, leuprolide, chlorambucil, interferon- $\alpha$ , autologous bone marrow transplantation on T cell disease. Nelarabine (relapsed or refractory)
Acute myelocytic and myelomonocytic leukemia	<b>Induction:</b> combination chemotherapy with cytarabine and an anthracycline (daunorubicin, idarubicin). Treating with idarubicin for acute promyelocytic leukemia. <b>Consolidation:</b> high-dose cytarabine. Autologous (with or without purging) or allogeneic bone marrow transplantation for high-risk disease or second remission.	Gemtuzumab, azotamycin (Myotarg), mitoxantrone, idarubicin, etoposide, mercaptopurine, thioguanine, azacitidine, <sup>2</sup> arsenic, <sup>2</sup> methotrexate, doxorubicin, tretinoin, <sup>2</sup> allopurinol, <sup>1</sup> leukapheresis, prednisone, arsenic trioxide for acute promyelocytic leukemia
Chronic myelocytic leukemia	Imatinib mesylate (Gleevec), hydroxyurea, interferon- $\alpha$ . Allogeneic bone marrow transplantation for younger patients.	Busulfan, mercaptopurine, thioguanine, cytarabine, plicamycin, melphalan, autologous bone marrow transplantation, <sup>2</sup> allopurinol <sup>1</sup>
Chronic lymphocytic leukemia	Fludarabine, chlorambucil, and prednisone (if treatment is indicated). Rituximab with fludarabine or cyclophosphamide. Second-line therapy: alemtuzumab (Campath-1H).	Rituximab, vincristine, cyclophosphamide, doxorubicin, cladribine, 2-chlorodeoxyadenosine, CdA, allogeneic bone marrow transplantation, androgens, <sup>2</sup> allopurinol <sup>1</sup>
Multiple myeloma	<b>Combination chemotherapy:</b> vincristine, doxorubicin, dexamethasone, melphalan and prednisone; melphalan, cyclophosphamide, carbimazole, vincristine, doxorubicin, prednisone, thalidomide. Autologous transplantation in first complete or partial remission. Miniallogeneic transplant for poor-prognosis disease. Bortezomib for relapsed or refractory disease.	Clarithromycin, etoposide, cytarabine, interferon- $\alpha$ , dexamethasone autologous bone marrow transplantation
	Hydroxyurea, phlebotomy for polycythemia. Anagrelide for thrombocytosis.	Busulfan, chlorambucil, cyclophosphamide, interferon- $\alpha$ , radiophosphorus <sup>32</sup> P
Choriocarcinoma trophoblastic neoplasms <sup>2</sup>	Methotrexate or dactinomycin (or both) plus chlorambucil.	Vinblastine, cisplatin, mercaptopurine, doxorubicin, bleomycin, etoposide
Carcinoma of the thyroid gland <sup>2</sup>	Radioiodine ( <sup>131</sup> I).	Doxorubicin, cisplatin, bleomycin, melphalan

within 1 year of a diagnosis of early-stage breast cancer to an intensive dietary fat reduction (15% of dietary calories from fat) or no dietary intervention. During the course of the trial, from 1994 to 2001, approximately 56% of the dietary calories in the control group, and 35% in the treatment group were from fat. At 60 months of follow-up, there was a significant 24% relative improvement in relapse-free survival in the low-fat diet group. On multivariate analysis, this benefit was only seen in women with hormone receptor negative cancers. The treatment group had a 5 lb average weight loss compared with a 2 lb weight gain in the control group, raising the question of whether the observed reduction in relapse was due to the weight loss or to the dietary fat content. Other ongoing intervention trials include the Women's Healthy Eating and Living (WHEL) study, which targets women 1–3 years following a diagnosis of breast cancer to assess the effects of a low-fat, high-fiber diet on recurrence and death from cancer

### Secondary Prevention:

Screening is used for early detection of cancer in otherwise asymptomatic populations. Detection of cancer may be achieved through observation (eg, skin, mouth, external genitalia, cervix), palpation (eg, breast, mouth, thyroid, rectum and anus, prostate, testes, ovaries and uterus, lymph nodes), and laboratory tests and procedures (eg, Papanicolaou smear, sigmoidoscopy or colonoscopy, mammography). Effective screening requires a test that will specifically detect early cancers or premalignancies, be cost effective, and result in improved therapeutic outcomes. For most cancers, stage at presentation is related to curability, with the highest cure rates reported when the tumor is small and there is no evidence of metastasis

### Chemoprevention:

Chemoprevention focuses on the prevention of cancer by administering chemical compounds that interfere with the multistaged carcinogenic process. Chemicals used in chemoprevention must be nontoxic and well tolerated by otherwise asymptomatic individuals. Because of the long natural history of carcinogenesis, there must also be a method of evaluating the efficacy of chemopreventive agents other than waiting for the development of tumours. Biomarkers, including the premalignant markers such as colonic polyps, and aberrant crypt formation in the colon, are currently in clinical use. Other less specific surrogate markers for cancer risk such as breast density are also in use as primary end points in prevention studies. Molecular susceptibility markers may become useful; nuclear leukoplasia, retinoic acid receptor agonists are under investigation in chemoprevention studies of patients with head and neck cancer.

## Drugs of Infections and Infectious Diseases update 2015

Avycaz (ceftazidime-avibactam)

### Company:

Actavis

### Approval Status:

Approved February 2015

### Specific Treatments:

complicated intra-abdominal and urinary tract infections

### Therapeutic Areas

Gastroenterology

Urology

Bacterial Infections

Urinary Tract Infections

### General Information

Avycaz (ceftazidime-avibactam) is a combination of a cephalosporin and a beta-lactamase inhibitor.

Avycaz in combination with metronidazole, is indicated for the treatment of complicated intra-abdominal infections (cIAI) caused by the following susceptible microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Providencia stuartii*,

*Enterobacter cloacae*, *Klebsiella oxytoca*, and *Pseudomonas aeruginosa* in patients 18 years or older.

Avycaz is also indicated for the treatment of complicated urinary tract infections (cUTI) including pyelonephritis caused by the following susceptible microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter koseri*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Citrobacter freundii*, *Proteus spp.*, and *Pseudomonas aeruginosa* in patients 18 years or older.

Avycaz is supplied as a solution for intravenous infusion. The recommended dosage of Avycaz is 2.5 grams (2 grams ceftazidime and 0.5 grams avibactam) administered every 8 hours by intravenous (IV) infusion over 2 hours. For treatment of cIAI, metronidazole should be given concurrently.

### Clinical Results

#### FDA Approval

The FDA approval of Avycaz was supported in part by the previous findings of the efficacy and safety of ceftazidime for the treatment of cIAI and cUTI. The contribution of avibactam to Avycaz was primarily established in vitro and in animal models of infection. Avycaz was studied in two phase II randomized, blinded, active-controlled, multicenter trials, one each in cIAI and cUTI, including pyelonephritis. These trials were not designed with any formal hypotheses for inferential testing against the active comparators.

### Side Effects

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

- vomiting
- nausea
- constipation
- anxiety

### Mechanism of Action

The ceftazidime component of Avycaz is a cephalosporin antibacterial drug with in vitro activity against certain gram-negative and gram-positive bacteria. The bactericidal action of ceftazidime is mediated through binding to essential penicillin-binding proteins (PBPs). The avibactam component of Avycaz is a non-beta-lactam beta-lactamase inhibitor that inactivates some beta-lactamases and protects ceftazidime from degradation by certain beta-lactamases. Avibactam does not decrease the activity of ceftazidime against ceftazidime-susceptible organisms.

### Additional Information

For additional information regarding Avycaz or complicated intra-abdominal and urinary tract infections, please visit <https://www.avycaz.com/>

## Bexsero (Meningococcal Group B Vaccine)

### Company:

Novartis

**Approval Status:** Approved January 2015

### Specific Treatments:

invasive meningococcal disease caused by serogroup B

### Therapeutic Areas

Pediatrics/Neonatology

Vaccines

Meningitis

Pediatric Health

Vaccines

### General Information

Bexsero is a multicomponent Meningococcal Serogroup B vaccine.

Bexsero is specifically indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B. Bexsero is approved for use in individuals 10 through 25 years of age.

Bexsero is supplied as a solution for intramuscular administration. Bexsero should be administered in two doses (0.5 mL each) at least 1 month apart.

### Clinical Results

#### FDA Approval

The FDA approval of Bexsero was based on three studies conducted in Canada, Australia, Chile, and the United Kingdom in

approximately 2,600 adolescents and young adults. Among subjects who received two doses of Bexsero, after vaccination, 62 to 88% had antibodies in their blood that killed three different *N. meningitidis* serogroup B strains in tests carried out in a laboratory, compared with 0 to 23% before vaccination. These three strains are representative of strains that cause serogroup B meningococcal disease in the U.S.

#### Side Effects

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

- pain at the injection site
- myalgia
- erythema
- fatigue
- headache
- induration
- nausea
- arthralgia

#### Mechanism of Action

Bexsero is a multicomponent Meningococcal Serogroup B vaccine. NHBA, NadA, fHbp, and PorA are proteins found on the surface of meningococci and contribute to the ability of the bacterium to cause disease. Vaccination with Bexsero leads to the production of antibodies directed against NHBA, NadA, fHbp, and PorA P1.4. The susceptibility of serogroup B meningococci to complement-mediated antibody-dependent killing following vaccination with Bexsero is dependent on both the antigenic similarity of the bacterial and vaccine antigens, as well as the amount of antigen expressed on the surface of the invading meningococci.

#### Additional Information

For additional information regarding Bexsero or invasive meningococcal disease caused by serogroup B, please visit <http://www.bexsero.com/>

#### **Cresemba (isavuconazonium sulfate)**

##### **Company:**

Astellas

##### **Approval Status:**

Approved March 2015

##### **Specific Treatments:**

invasive aspergillosis and invasive mucormycosis

##### **Therapeutic Areas**

FamilyMedicine

Aspergillosis

FungalInfections

Mycosis Fungoides

##### General Information

Cresemba (isavuconazonium sulfate) is an azole antifungal.

Cresemba is specifically indicated for patients 18 years of age and older for the treatment of invasive aspergillosis and invasive mucormycosis.

Cresemba is supplied as a solution for intravenous infusion and as a capsule for oral administration. The recommended dose is as follows:

Cresemba injection:

Loading dose: 1 reconstituted vial (372 mg) intravenously every 8 hours for 6 doses (48 hours)

Maintenance dose: 1 reconstituted vial (372 mg) intravenously once daily

Cresemba capsules:

Loading dose: 2 capsules (372 mg) orally every 8 hours for 6 doses (48 hours)

Maintenance dose: 2 capsules (372 mg) orally once daily

##### Clinical Results

##### **FDA Approval**

The FDA approval of Cresemba was based on the following trials:

##### Invasive Aspergillus

Trial 1 was a randomized, double-blind, non-inferiority active controlled trial which evaluated the safety and efficacy of Cresemba versus voriconazole for primary treatment of invasive fungal disease caused by Aspergillus species or other filamentous fungi. Patients randomized to receive Cresemba treatment were administered a loading dose intravenously of 372 mg of

isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) every 8 hours for the first 48 hours. Beginning on day 3, patients received intravenous or oral therapy of 372 mg of isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) once daily. Patients randomized to receive voriconazole treatment were administered voriconazole intravenously with a loading dose of 6 mg/kg every 12 hours for the first 24 hours followed by 4 mg/kg intravenously every 12 hours for the following 24 hours. Therapy could then be switched to an oral formulation of voriconazole at a dose of 200 mg every 12 hours. In this trial, the protocol-defined maximum treatment duration was 84 days. Mean treatment duration was 47 days for both treatment groups, of which 8 to 9 days was by an intravenous route of administration. All-cause mortality through Day 42 in the overall population (ITT) was 18.6% in the Cresemba treatment group and 20.2% in the voriconazole treatment group for an adjusted treatment difference of -1.0% with 95% confidence interval of -8.0% to 5.9%. Similar results were seen in patients with proven or probable invasive aspergillosis confirmed by serology, culture or histology.

##### Invasive Mucormycosis

This open-label non-comparative trial evaluated the safety and efficacy of a subset of patients with invasive mucormycosis. Thirty-seven (37) patients had proven or probable mucormycosis. Patients were treated with Cresemba intravenously or via oral administration at the recommended doses. Median treatment duration was 102 days for patients classified as primary, 33 days for refractory, and 85 days for intolerant. The trial compared treatment with Cresemba with the natural disease progression associated with untreated mucormycosis. Cresemba was safe and effective. However, the efficacy of Cresemba for the treatment for invasive mucormycosis has not been evaluated in concurrent, controlled clinical trials.

##### Side Effects

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

- nausea
- vomiting
- diarrhea
- headache
- abnormal liver blood tests
- hypokalemia
- constipation
- dyspnea
- coughing
- peripheral edema

Cresemba may also cause serious side effects including liver problems, infusion reactions and severe allergic and skin reactions.

##### Mechanism of Action

Cresemba (isavuconazonium sulfate) is the prodrug of isavuconazole, an azole antifungal drug. Isavuconazole inhibits the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14- $\alpha$ -demethylase. This enzyme is responsible for the conversion of lanosterol to ergosterol. An accumulation of methylated sterol precursors and a depletion of ergosterol within the fungal cell membrane weakens the membrane structure and function. Mammalian cell demethylation is less sensitive to isavuconazole inhibition.

##### Additional Information

For additional information regarding Cresemba or invasive aspergillosis and invasive mucormycosis, please visit <https://www.cresemba.com/>

#### **Evotaz (atazanavir and cobicistat)**

##### **Company:**

Bristol-Myers Squibb

##### **Approval Status:**

Approved January 2015

##### **Specific Treatments:**

HIV-1 infection

##### **Therapeutic Areas**

Immunology

## HIV/AIDS

### General Information

Evotaz is a fixed-dose combination of the HIV-1 antiretroviral drug, atazanavir and the CYP3A inhibitor, cobicistat.

Evotaz is specifically indicated for use in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in adults.

Evotaz is supplied as a tablet for oral administration. In treatment-naïve and -experienced adults, the recommended dosage of Evotaz is one tablet taken once daily orally with food. Administer Evotaz in conjunction with other antiretroviral agents.

### Clinical Results

#### **FDA Approval**

The FDA approval of Evotaz was based on comparative Phase III trial data (Gilead Sciences, Inc.'s Study 114). The randomized, double-blind clinical trial (N=692) evaluated the efficacy and safety of Reyataz 300 mg with cobicistat 150 mg (the components of Evotaz) (n=344) versus Reyataz 300 mg with ritonavir 100 mg (Reyataz/ritonavir) (n=348), another pharmacokinetic enhancing agent, in combination with emtricitabine/tenofovir disoproxil fumarate in treatment-naïve adults. Patients had a baseline estimated CrCL >70mL/min, a mean baseline plasma HIV-1 RNA of 4.8 log<sub>10</sub> copies/mL, and a mean baseline CD4+ cell count of 352 cells/mm<sup>3</sup>. At 48 weeks, 85% of patients in the Evotaz arm achieved HIV-1 RNA levels of <50 copies/mL compared to 87% of patients in the Reyataz/ritonavir arm. Low rates of virologic failure (HIV-1 RNA >50 copies/mL: 6% Evotaz arm; 4% Reyataz/ritonavir arm) were observed at 48 weeks, making Evotaz the only protease inhibitor pharmacoenhanced with cobicistat with virologic failure rates as low as 6%.

### Side Effects

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

- jaundice
- ocular icterus
- nausea

### Mechanism of Action

Evotaz is a fixed-dose combination of atazanavir and cobicistat. Atazanavir is an HIV-1 protease inhibitor. Cobicistat is a mechanism-based inhibitor of cytochrome P450 (CYP) enzymes of the CYP3A family.

### Additional Information

For additional information regarding Evotaz or HIV-1 infection, please visit <http://www.bms.com/>

## **Prezcobix (darunavir and cobicistat)**

### **Company:**

Janssen

### **Approval Status:**

Approved January 2015

### **Specific Treatments:**

HIV-1 infection

### **Therapeutic Areas**

#### Immunology

#### HIV

#### HIV/AIDS

### General Information

Prezcobix is a once-daily, fixed-dose combination containing darunavir, a protease inhibitor, and the pharmacokinetic enhancing or boosting agent cobicistat.

Prezcobix is specifically indicated for use in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in treatment-naïve and treatment-experienced adults with no darunavir resistance-associated substitutions (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, L89V).

Prezcobix is supplied as a tablet (800 mg of darunavir and 150 mg of cobicistat) for oral administration. The recommended dose is one tablet taken once daily with food.

### Clinical Results

#### **FDA Approval**

The FDA approval of Prezcobix was based on a bioequivalence study evaluating the use of a darunavir and cobicistat fixed-dose combination tablet versus single agents and a clinical study evaluating the safety and efficacy of cobicistat-boosted darunavir

for the treatment of HIV-1 in adults with no darunavir resistance-associated mutations. The tolerability profile of the fixed dose-combination is similar to that of the two agents taken separately. The efficacy of Prezcobix is based on efficacy demonstrated in clinical trials of darunavir co-administered with ritonavir and pharmacokinetic trials showing similar exposures of darunavir when boosted with cobicistat compared to darunavir boosted with ritonavir.

### Side Effects

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

- diarrhea
- nausea
- rash
- headache
- abdominal pain
- vomiting

### Mechanism of Action

Prezcobix is a once-daily, fixed-dose combination tablet containing darunavir, a protease inhibitor, and the pharmacokinetic enhancing or boosting agent cobicistat.

### Additional Information

For additional information regarding the use of Prezcobix or HIV-1, please visit <http://www.prezcobix.com/>

## **New Drugs regimens for Oncology approved in 2015**

### **Farydak (panobinostat)**

#### **Company:**Novartis

#### **Approval Status:**Approved February 2015

#### **Specific Treatments:**Multiple myeloma

#### **Therapeutic Areas**

#### Hematology

#### Oncology

#### Multiple Myeloma

#### **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.

#### **Clinical Results**

#### **FDA Approval**

The FDA approval of Farydak was based on a randomized, double-blind, placebo-controlled, multicenter study in patients

with relapsed multiple myeloma who had received 1 to 3 prior lines of therapy. A total of 768 subjects received bortezomib (1.3 mg/m<sup>2</sup> injected intravenously) with dexamethasone (20 mg) in addition to Farydak 20 mg (or placebo), taken orally every other day, for 3 doses per week in Weeks 1 and 2 of each 21-day cycle. Treatment was administered for a maximum of 16 cycles (48 weeks). The primary endpoint was progression-free survival (PFS), using modified European Bone Marrow Transplant Group (EBMT) criteria, as assessed by the investigators. In the overall trial population, the median PFS was 12 months in the Farydak, bortezomib, dexamethasone arm and 8.1 months in the placebo, bortezomib, dexamethasone arm. At the time of interim analysis, overall survival was not statistically different between arms. The approval of Farydak was based upon the efficacy and safety in a prespecified subgroup analysis of 193 patients who had received prior treatment with both bortezomib and an immunomodulatory agent and a median of 2 prior therapies as the benefit:risk appeared to be greater in this more heavily pretreated population than in the overall trial population. Of these 193 patients, 76% of them had received  $\geq 2$  prior lines of therapy. The median PFS was 10.6 months in the Farydak, bortezomib, and dexamethasone arm and 5.8 months in the placebo, bortezomib, and dexamethasone arm.

**Side Effects**

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

- diarrhea
- fatigue
- nausea
- peripheral edema
- decreased appetite
- pyrexia
- vomiting

Fardak 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.

**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.

**Additional Information**

For additional information regarding Farydak or multiple myeloma, please visit <http://www.farydak.com/>

**Brance (palbociclib)**

**Company:**Pfizer

**Approval Status:**Approved February 2015

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

**Therapeutic Areas**

Obstetrics/Gynecology (Women's Health)

Oncology

Breast Cancer

**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.

Please see the drug label for recommended dose modifications based on adverse events.  
Clinical Results

#### **FDA Approval**

The FDA approval of Ibrance was based on a randomized, open-label, multicenter study of Ibrance plus letrozole versus letrozole alone conducted in 165 postmenopausal women with ER-positive, HER2-negative advanced breast cancer who had not received previous systemic treatment for their advanced disease. Randomization was stratified by disease site (visceral versus bone only versus other) and by disease-free interval (>12 months from the end of adjuvant treatment to disease recurrence versus ≤12 months from the end of adjuvant treatment to disease recurrence or de novo advanced disease). Ibrance was given orally at a dose of 125 mg daily for 21 consecutive days followed by 7 days off treatment. Subjects received study treatment until progressive disease, unmanageable toxicity, or consent withdrawal. For subjects treated with the combination of Ibrance plus letrozole, the median PFS was 20.2 months compared to the 10.2 months of PFS in subjects who received letrozole alone. Overall response rate in subjects with measurable disease as assessed by the investigator was higher in the Ibrance plus letrozole compared to the letrozole alone arm (55.4% versus 39.4%).

#### **Side Effects**

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

- neutropenia
- leukopenia
- fatigue
- anemia
- upper respiratory infection
- nausea
- stomatitis
- alopecia
- diarrhea
- thrombocytopenia
- decreased appetite
- vomiting
- asthenia
- peripheral neuropathy
- epistaxis

#### **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.

#### **Additional Information**

For additional information regarding Ibrance or ER-positive, HER2-negative breast cancer, please visit <http://www.ibrance.com/>

#### **Lenvima (lenvatinib)**

**Company:**Eisai

**Approval Status:**Approved February 2015

**Specific Treatments:**thyroid cancer

#### **Therapeutic Areas**

Oncology

Thyroid Cancer

#### **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.

#### **Clinical Results**

#### **FDA Approval**

The FDA approval of Lenvima was based on a multicenter, randomized, double-blind, placebo-controlled trial in 392 subjects with locally recurrent or metastatic radioactive iodine-refractory differentiated thyroid cancer and radiographic evidence of disease progression within 12 months prior to randomization, confirmed by independent radiologic review. The subjects received Lenvima 24 mg once daily (n=261) or placebo (n=131) until disease progression. Study results showed Lenvima-treated subjects lived a median of 18.3 months without their disease progressing (progression-free survival), compared to a median of 3.6 months for subjects who received placebo. Additionally, 65% of subjects treated with Lenvima saw a reduction in tumor size, compared to 2% of subjects who received a placebo.

#### **Side Effects**

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

- hypertension
- fatigue
- diarrhea
- arthralgia/myalgia
- decreased appetite
- weight decreased
- nausea
- stomatitis
- headache
- vomiting
- proteinuria
- palmar-plantar erythrodysesthesia syndrome
- abdominal pain
- dysphonia

#### **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 (PDGFR $\alpha$ ), KIT, and RET.

#### **Additional Information**

For additional information regarding Lenvima or thyroid cancer, please visit <http://lenvima.com/>

#### **Opdivo (nivolumab)**

**Company:**Bristol-Myers Squibb

**Approval Status:**Approved March 2015

**Specific Treatments:**metastatic squamous non-small cell lung cancer

#### **Therapeutic Areas**

Oncology

Pulmonary/Respiratory Diseases

Lung

Cancer

Non-Small Cell Lung Cancer

#### **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.

#### **Clinical Results**

#### **FDA Approval**

The FDA approved of Opdivo for metastatic squamous nonsmall cell lung cancer was based on a randomized, open-label study enrolling 272 patients with metastatic squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. Patients received Opdivo administered intravenously at 3 mg/kg every 2 weeks or docetaxel administered intravenously at 75 mg/m<sup>2</sup> every 3 weeks. This study included patients regardless of their PD-L1 status. The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was overall survival (OS). The trial demonstrated a statistically significant improvement in OS for patients randomized to Opdivo as compared with docetaxel at the prespecified interim

analysis when 199 events were observed (86% of the planned number of events for final analysis). The median survival was 9.2 months versus 6.0 months for the Opdivo versus docetaxel arms, respectively.

#### **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:

- fatigue
- dyspnea
- musculoskeletal pain
- decreased appetite
- cough
- nausea
- constipation

#### **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. Upregulation 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.

#### **Additional Information**

For additional information regarding Opdivo or metastatic cell non-small cell lung cancer, please visit <http://www.opdivo.bmscustomerconnect.com/>

#### **Unituxin (dinutuximab)**

**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 colonystimulating 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/m<sup>2</sup> /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/m<sup>2</sup> /hour for 30 minutes. The infusion rate can be gradually increased as tolerated to a maximum rate of 1.75 mg/m<sup>2</sup> /hour. Follow dose modification instructions (see drug label) for adverse reactions.

#### **Clinical Results**

#### **FDA Approval**

The FDA approval of Unituxin was based on a randomized, open-label, multicenter trial of 226 pediatrics with high-risk neuroblastoma whose tumors shrunk or disappeared after treatment with multiple-drug chemotherapy and surgery followed by additional intensive chemotherapy and who subsequently received bone marrow transplantation support and radiation therapy. Subjects were randomly assigned to receive either an oral retinoid drug, isotretinoin (RA), or Unituxin in combination with interleukin-2 and granulocyte-macrophage colony-stimulating factor, which are thought to enhance the activity of Unituxin by stimulating the immune system, and RA. Three years after treatment, 63% of subjects receiving the Unituxin combination were alive and free of tumor growth or recurrence, compared to 46% of subjects treated with RA alone. In an updated analysis of survival, 73% of subjects who received the Unituxin combination were alive compared with 58% of those receiving RA alone.

#### **Side Effects**

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

- pain
- pyrexia
- thrombocytopenia
- lymphopenia
- infusion reactions
- hypotension
- hyponatremia
- increased alanine aminotransferase
- anemia
- vomiting
- diarrhea
- hypokalemia
- capillary leak syndrome
- neutropenia

- urticaria
- hypoalbuminemia
- increased aspartate aminotransferase
- 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.

#### 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).

#### Additional Information

For additional information regarding Unituxin or neuroblastoma, please visit <http://www.unither.com/>, Center Watch.com.

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