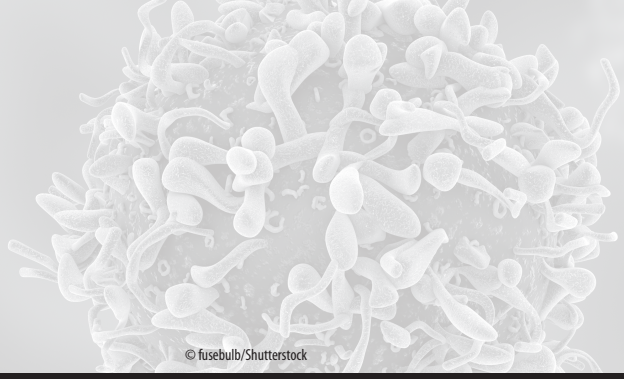
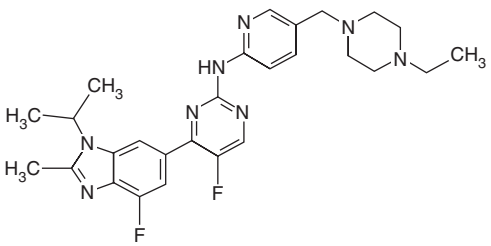


2

Chemotherapeutic and Biologic Drugs

Edward Chu, Laurie J. Harrold, and M. Sitki Copur

Abemaciclib



TRADE NAMES	Verzenio, PD 0332991	**CLASSIFICATION**	Signal transduction inhibitor, CDK inhibitor
CATEGORY	Targeted agent	**DRUG MANUFACTURER**	Eli Lilly

MECHANISM OF ACTION

- Inhibitor of cyclin-dependent kinase (CDK) 4 and 6.
- Inhibition of CDK4 and CDK6 leads to inhibition of cell proliferation and growth by blocking progression of cells from G1 to the S-phase of the cell cycle.

- Decreased expression of retinoblastoma protein phosphorylation (pRB) results in reduced E2F expression and signaling.
- Induces cell senescence.

MECHANISM OF RESISTANCE

- Acquired CDK6 amplification resulting in increased CDK6 expression.
- Increased expression of CDK2 and CDK4.
- Loss of pRb expression.
- Overexpression of cyclins A and E.
- Increased expression of 3-phosphoinositide-dependent protein kinase 1 (PDK1) with activation of AKT pathway and other AGC kinases.

ABSORPTION

Oral bioavailability is on the order of 46%. High-fat, high-calorie meal increases the AUC (area under the curve) of parent drug and its active metabolites by 9% and increases C_{max} (maximum concentration) by 26%.

DISTRIBUTION

Significant binding (96.3%) to plasma proteins, serum albumin, and α1-acid glycoprotein with extensive tissue distribution. Steady-state drug levels are achieved within 5 days following repeat daily dosing.

METABOLISM

Extensively metabolized in the liver primarily by CYP3A4 microsomal enzymes, with formation of the major metabolite N-desethylabemaciclib (M2) and other additional metabolites, including M20, M18, and an oxidative metabolite (M1). These metabolites have similar biologic activity as the parent drug. Acylation and glucuronidation play only minor roles in drug metabolism. Nearly 81% of drug is recovered in feces and only 3% in urine, with the majority of eliminated drug being in metabolite form. The elimination half-life of the drug is 18.3 hours.

INDICATIONS

1. Approved by the Food and Drug Administration (FDA) in combination with an aromatase inhibitor for patients with hormone receptor (HR)-positive, HER2-negative advanced or metastatic breast cancer as initial endocrine-based therapy in postmenopausal women.
2. FDA-approved in combination with fulvestrant for patients with HR-positive, HER2-negative advanced or metastatic breast cancer in women with disease progression following endocrine therapy.
3. FDA-approved as monotherapy for patients with HR-positive, HER2-negative advanced or metastatic breast cancer in women with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

DOSAGE RANGE

1. Combination therapy with fulvestrant or an aromatase inhibitor—150 mg PO bid.
2. Monotherapy—200 mg PO bid.

DRUG INTERACTION 1
Drugs that stimulate liver microsomal CYP3A4 enzymes, including phenytoin, carbamazepine, rifampin, phenobarbital, and St. John's Wort—These drugs may increase the metabolism of abemaciclib, resulting in lower drug levels and potentially reduced clinical activity.

DRUG INTERACTION 2
Drugs that inhibit liver microsomal CYP3A4 enzymes, including ketoconazole, itraconazole, erythromycin, and clarithromycin—These drugs may reduce the metabolism of abemaciclib, resulting in increased drug levels and potentially increased toxicity.

SPECIAL CONSIDERATIONS
1. Dose reduction is not required in the setting of mild or moderate hepatic impairment (Child-Pugh Class A or B). Use with caution in patients with severe hepatic impairment, and dose reduction is recommended.
2. Dose reduction is not required in the setting of mild or moderate renal impairment. Has not been studied in the setting of severe renal impairment, end-stage renal disease, or in patients on dialysis.
3. Closely monitor complete blood count (CBC) and platelet count every 2 weeks during the first 2 months of therapy and at monthly intervals thereafter.
4. Closely monitor liver function tests (LFTs) at baseline and periodically while on therapy. LFTs should be monitored every 2 weeks for the first 2 months, monthly for the next 2 months, and then as clinically indicated.
5. Monitor for signs and symptoms of infection.
6. Monitor for signs and symptoms of venous thromboembolism.
7. Pregnancy category D.

TOXICITY 1
Myelosuppression with neutropenia, anemia, and thrombocytopenia.

TOXICITY 2
Fatigue, asthenia, and anorexia.

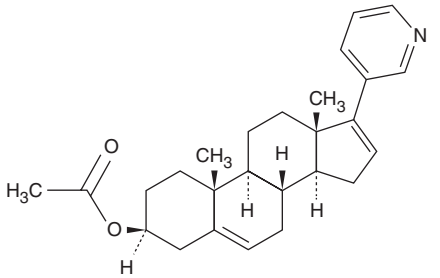
TOXICITY 3
Increased risk of infections, with upper respiratory infection being most common.

TOXICITY 4
Nausea/vomiting, abdominal pain, and diarrhea.

TOXICITY 5
Increased risk of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE).

TOXICITY 6
Hepatotoxicity with elevated SGOT and SGPT.

Abiraterone Acetate



TRADE NAME	Zytiga	**CLASSIFICATION**	Miscellaneous agent
CATEGORY	Hormonal agent	**DRUG MANUFACTURERS**	Janssen Biotech Johnson & Johnson

MECHANISM OF ACTION

- Prodrug of abiraterone.
- Selective inhibition of 17α-hydroxylase/C17, 20-lyase (CYP17). This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis.
- Inhibition of CYP17 leads to inhibition of the conversion of pregnenolone and progesterone to their 17α-hydroxy derivatives.
- Inhibition of CYP17 leads to inhibition of subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione.
- Associated with a rebound increase in mineralocorticoid production by the adrenals.

MECHANISM OF RESISTANCE

- Upregulation of CYP17.
- Induction of androgen receptor (AR) and AR splice variants that result in ligand-independent AR transactivation.
- Expression of truncated androgen receptors.

ABSORPTION

Following oral administration, maximum drug levels are reached within 1.5–4 hours. Oral absorption is increased with food, and in particular, food with high fat content.

DISTRIBUTION

Highly protein bound (> 99%) to albumin and α1-acid glycoprotein.

METABOLISM

Following oral administration, abiraterone acetate is rapidly hydrolyzed to abiraterone, the active metabolite. The two main circulating metabolites of

abiraterone are abiraterone sulphate and N-oxide abiraterone sulphate, both of which are inactive. Nearly 90% of an administered dose is recovered in feces, while only 5% is eliminated in urine. The terminal half-life of abiraterone ranges from 5 to 14 hours, with a median half-life of 12 hours.

INDICATIONS

1. FDA-approved in combination with prednisone for patients with metastatic, castration-resistant prostate cancer (CRPC) who have received prior chemotherapy containing docetaxel.
2. FDA-approved in combination with prednisone for patients with metastatic high-risk castration-sensitive prostate cancer (CSPC).

DOSAGE RANGE

Recommended dose is 1,000 mg PO once daily in combination with prednisone 5 mg PO bid.

DRUG INTERACTIONS

- Use with caution in the presence of CYP2D6 substrates.
- Use with caution in the presence of CYP3A4 inhibitors and inducers.

SPECIAL CONSIDERATIONS

1. No dosage adjustment is necessary for patients with baseline mild hepatic impairment. In patients with moderate hepatic impairment (Child-Pugh Class B), reduce dose to 250 mg once daily. If elevations in ALT or AST $> 5 \times$ upper limit of normal (ULN) or total bilirubin $> 3 \times$ ULN occur in patients, discontinue treatment. Avoid use in patients with severe hepatic impairment, as the drug has not been tested in this patient population.
2. No dosage adjustment is necessary for patients with renal impairment.
3. Abiraterone acetate should be taken on an empty stomach with no food being consumed for at least 2 hours before and for at least 1 hour after an oral dose. Tablets should be swallowed whole with water.
4. Closely monitor for adrenal insufficiency, especially if patients are withdrawn from prednisone, undergo a reduction in prednisone dose, or experience concurrent infection or stress.
5. Pregnancy category X. Breastfeeding should be avoided.

TOXICITY 1

Fatigue.

TOXICITY 2

Mild nausea and vomiting.

TOXICITY 3

Mild elevations in SGOT/SGPT.

TOXICITY 4

Hypertension.

TOXICITY 5

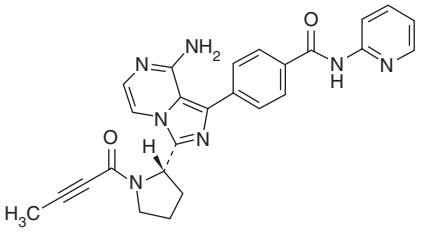
Peripheral edema.

TOXICITY 6
Hypokalemia.

TOXICITY 7
Arthralgias, myalgias, and muscle spasms.

TOXICITY 8
Hot flashes.

Acalabrutinib



TRADE NAME	Calquence, ACP-196	**CLASSIFICATION**	Signal transduction inhibitor, BTK inhibitor
CATEGORY	Targeted agent	**DRUG MANUFACTURER**	Acerta and AstraZeneca

MECHANISM OF ACTION

- Irreversible second-generation, small-molecule inhibitor of Bruton's tyrosine kinase (BTK).
- Parent drug and its active metabolite, ACP-5862, form a covalent bond with cysteine residue in the BTK active sites, leading to enzymatic inhibition.
- BTK is a key signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways.

MECHANISM OF RESISTANCE

- Mutations in the Cys481 residue in the BTK active site lead to reduced binding affinity to acalabrutinib.
- Mutations in the gene encoding phospholipase C-γ2 (PLCG2).
- Increased expression of kinases SYK and LYN, which are critical for activation of mutant PLCG2.

ABSORPTION
Absolute oral bioavailability is approximately 25%. Peak plasma drug levels are achieved in 0.75 hour after ingestion, and food does not appear to alter bioavailability.

DISTRIBUTION
Extensive binding (97.5%) to plasma proteins. Steady-state drug levels are reached in approximately 8 days.

METABOLISM
Metabolism in the liver primarily by CYP3A4 and to a minor extent by glutathione conjugation and amide hydrolysis. ACP-5862 is the major active metabolite, with 50% inhibitory activity against BTK when compared to parent drug. Elimination is mainly hepatic (84%), with excretion in the feces. Renal elimination accounts for only 12% of an administered dose. Most of the drug is eliminated in metabolite form, as only < 1% is excreted as unchanged drug. Short terminal half-life of the parent drug approaching 1 hour.

INDICATIONS
FDA-approved under accelerated approval based on overall response rate for patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

DOSAGE RANGE
Recommended dose is 100 mg PO bid. Should be swallowed whole with or without food.

DRUG INTERACTION 1
Phenytoin and other drugs that stimulate the liver microsomal CYP3A4 enzymes, including carbamazepine, rifampin, phenobarbital, and St. John's Wort—These drugs may increase the metabolism of acalabrutinib, resulting in its inactivation.

DRUG INTERACTION 2
Drugs that inhibit the liver microsomal CYP3A4 enzymes, including ketoconazole, itraconazole, erythromycin, and clarithromycin—These drugs may decrease the metabolism of acalabrutinib, resulting in increased drug levels and potentially increased toxicity.

DRUG INTERACTION 3
Warfarin—Patients receiving warfarin should be closely monitored for alterations in their clotting parameters, prothrombin time (PT) and international normalized ratio (INR) and/or bleeding, as acalabrutinib may inhibit the metabolism of warfarin by the liver P450 system. Dose of warfarin may require careful adjustment in the presence of acalabrutinib therapy.

DRUG INTERACTION 4
Proton pump inhibitors—Patients should avoid the use of proton pump inhibitors, as they may reduce oral bioavailability and lead to reduced drug plasma concentrations. If treatment with a gastric acid–reducing agent is required, an antacid or an H2-antagonist should be considered.

SPECIAL CONSIDERATIONS
1. Dose reduction is not required in the setting of mild or moderate hepatic impairment (Child-Pugh Class A or B). Use with caution in patients with severe hepatic impairment, as the drug has not been studied in this setting.
2. Dose reduction is not required in the setting of mild or moderate renal impairment. Has not been studied in the setting of severe renal impairment, end-stage renal disease, or in patients on dialysis.
3. Acalabrutinib capsules should be swallowed whole with water.
4. Closely monitor CBCs on a monthly basis.
5. Acalabrutinib may increase the risk of bleeding in patients on antiplatelet or anticoagulant therapies.
6. Consider holding acalabrutinib for 3–7 days pre- and post-surgery to reduce the potential risk for bleeding.
7. Closely monitor patients for fever and signs of infection.
8. Patients should be advised to protect against sun exposure.
9. Pregnancy category D. Breastfeeding should be avoided.

TOXICITY 1
Bleeding in the form of ecchymoses, gastrointestinal (GI) bleeding, and hematuria.

TOXICITY 2
Infections with pneumonia being most common. Hepatitis B virus reactivation and progressive multifocal leukoencephalopathy (PML) have been reported.

TOXICITY 3
Myelosuppression with neutropenia, thrombocytopenia, and anemia.

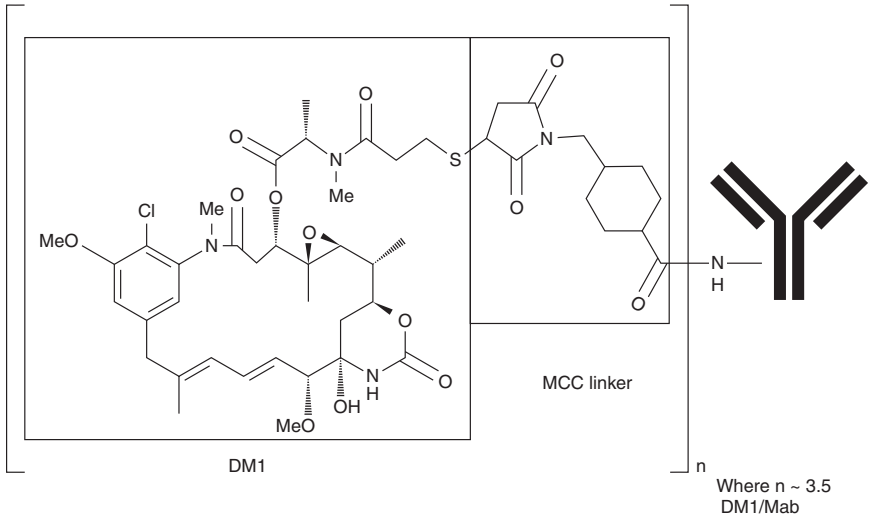
TOXICITY 4
Abdominal pain, diarrhea, and nausea/vomiting are the most common GI side effects.

TOXICITY 5
Second primary cancers with skin cancer and other solid tumors.

TOXICITY 6
Fatigue, headache, and myalgias.

TOXICITY 7
Rare instances of atrial fibrillation/atrial flutter.

Ado-trastuzumab emtansine



TRADE NAME	Kadcyla	**CLASSIFICATION**	Antibody-drug conjugate
CATEGORY	Biologic response modifier agent/ chemotherapy drug	**DRUG MANUFACTURER**	Genentech/ Roche

MECHANISM OF ACTION

- HER2-targeted antibody-drug conjugate that is made up of trastuzumab and the small-molecule microtubule inhibitor DM1.
- Upon binding to the HER2 receptor, ado-trastuzumab emtansine undergoes receptor-mediated internalization and lysosomal degradation, leading to intracellular release of the DM1 molecule.
- Binding of DM1 to tubulin leads to disruption of the microtubule network, resulting in cell-cycle arrest and apoptosis.
- Inhibits HER2 downstream signaling pathways.
- Immunologic-mediated mechanisms, such as antibody-dependent cell-mediated cytotoxicity (ADCC), may also be involved in antitumor activity.

MECHANISM OF RESISTANCE

- Reduced expression of HER2 receptor.
- Poor internalization of the HER2-T-DM1 complexes.
- Impaired lysosomal proteolytic, activity leading to reduced intracellular levels of the DM1 molecule.
- Defective intracellular and endosomal trafficking of the HER2-T-DM1 complex.
- Increased expression of p95HER2.

- Activation of the neuregulin-HER3 signaling pathway.
- Alterations in tubulins resulting in reduced affinity to DM1.
- Multidrug-resistant phenotype with increased expression of the P170 glycoprotein, leading to enhanced DM1 efflux.

ABSORPTION
Administered only via the intravenous (IV) route.

DISTRIBUTION
Extensive binding (93%) of ado-trastuzumab emtansine to plasma proteins.

METABOLISM
DM1 is metabolized by the liver microsomal enzymes CYP3A4/5. The median terminal half-life of ado-trastuzumab emtansine is on the order of 4 days.

INDICATIONS
1. FDA-approved for patients with HER2-positive metastatic breast cancer who have received prior treatment with trastuzumab and a taxane chemotherapy.
2. Patients should already have been treated for their metastatic breast cancer or have had their early-stage disease recur during or within 6 months after completion of adjuvant therapy.

DOSAGE RANGE
Recommended dose is 3.6 mg/kg IV every 3 weeks.

DRUG INTERACTIONS
None well characterized to date.

SPECIAL CONSIDERATIONS
1. Ado-trastuzumab emtansine can **NOT** be substituted for or with trastuzumab.
2. Baseline and periodic evaluations of left ventricular ejection fraction (LVEF) should be performed while on therapy. Treatment should be held if the LVEF drops < 40% or is between 40% and 45% with a 10% or greater absolute reduction from pretreatment baseline. Therapy should be permanently stopped if the LVEF function has not improved or has declined further. This is a black-box warning.
3. Monitor LFTs and serum bilirubin levels closely, as serious hepatotoxicity has been observed. This is a black-box warning.
4. Carefully monitor for infusion-related reactions, especially during the first infusion.
5. Monitor patients for pulmonary symptoms. Therapy should be held in patients presenting with new or progressive pulmonary symptoms and should be terminated in patients diagnosed with treatment-related pneumonitis or interstitial lung disease (ILD).
6. Closely monitor CBC and specifically platelet counts.
7. HER2 testing using an FDA-approved diagnostic test to confirm the presence of HER2 protein overexpression or gene amplification is

required for determining which patients should receive ado-trastuzumab emtansine therapy.

8. No dose adjustment is recommended for patients with mild or moderate hepatic dysfunction. Use with caution in patients with severe hepatic dysfunction as the drug has not been studied in this setting.
9. No dose adjustment is recommended for patients with mild or moderate renal dysfunction. Use with caution in patients with severe renal dysfunction, as there is only very limited information about the drug in this setting.
10. Pregnancy category D. Breastfeeding should be avoided.

TOXICITY 1
Cardiac toxicity with cardiomyopathy.

TOXICITY 2
Infusion-related reactions.

TOXICITY 3
Hepatotoxicity with transient elevations in LFTs. Severe drug-induced liver injury and hepatic encephalopathy have been reported rarely. Rare cases of nodular regenerative hyperplasia of the liver have also been reported.

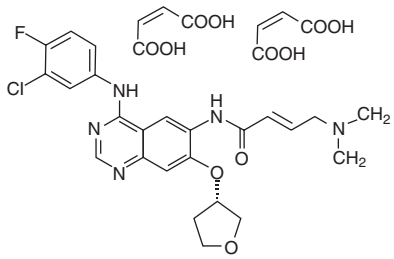
TOXICITY 4
Myelosuppression with thrombocytopenia.

TOXICITY 5
Pulmonary toxicity presenting as cough, dyspnea, and infiltrates. Observed rarely in about 1% of patients.

TOXICITY 6
Neurotoxicity with peripheral sensory neuropathy.

TOXICITY 7
Asthenia, fatigue, and pyrexia.

Afatinib



TRADE NAME	Gilotrif	**CLASSIFICATION**	Signal transduction inhibitor
CATEGORY	Chemotherapy drug	**DRUG MANUFACTURER**	Boehringer Ingelheim

MECHANISM OF ACTION

- Potent and selective small-molecule inhibitor of the kinase domains of EGFR, HER2, and HER4, resulting in inhibition of autophosphorylation and inhibition of downstream ErbB signaling.
- Inhibition of the ErbB tyrosine kinases results in inhibition of critical mitogenic and antiapoptotic signals involved in proliferation, growth, invasion/metastasis, angiogenesis, and response to chemotherapy and/or radiation therapy.

MECHANISM OF RESISTANCE

- Mutations in ErbB tyrosine kinases leading to decreased binding affinity to afatinib.
- Presence of KRAS mutations.
- Presence of BRAF mutations.
- Activation/induction of alternative cellular signaling pathways such as PI3K/Akt, IGF-1R, and c-Met.
- Increased expression/activation of mTORC1 signaling pathway.

ABSORPTION

Oral bioavailability is on the order of 92%. Peak plasma drug levels are achieved in 2–5 hours after ingestion.

DISTRIBUTION

Extensive binding (95%) to plasma proteins. Steady-state drug levels are reached in approximately 8 days.

METABOLISM

Metabolism in the liver primarily by CYP3A4 microsomal enzymes. Elimination is mainly hepatic (85%), with excretion in the feces. Renal elimination of parent drug and its metabolites accounts for only about 4% of an administered dose. The terminal half-life of the parent drug is 37 hours.

INDICATIONS

1. FDA-approved as first-line treatment of metastatic non–small cell lung cancer (NSCLC) with EGFR exon 19 deletion or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.
2. FDA-approved for metastatic, squamous NSCLC progressing after platinum-based chemotherapy.

DOSAGE RANGE

Recommended dose is 40 mg/day PO.

DRUG INTERACTION 1

Phenytoin and other drugs that stimulate the liver microsomal CYP3A4 enzymes, including carbamazepine, rifampin, phenobarbital, and St. John's Wort—These drugs may increase the metabolism of afatinib, resulting in its inactivation and lower effective drug levels.

DRUG INTERACTION 2

Drugs that inhibit the liver microsomal CYP3A4 enzymes, including ketoconazole, itraconazole, erythromycin, and clarithromycin—These drugs may decrease the metabolism of afatinib, resulting in increased drug levels and potentially increased toxicity.

DRUG INTERACTION 3

Warfarin—Patients receiving warfarin should be closely monitored for alterations in their clotting parameters (PT and INR) and/or bleeding, as afatinib may inhibit the metabolism of warfarin by the liver P450 system. Dose of warfarin may require careful adjustment in the presence of afatinib therapy.

SPECIAL CONSIDERATIONS

1. Dose reduction is not recommended in patients with mild or moderate hepatic impairment. However, afatinib has not been studied in patients with severe hepatic dysfunction and should be used with caution in this setting.
2. Closely monitor patients for new or progressive pulmonary symptoms, including cough, dyspnea, and fever. Afatinib therapy should be interrupted pending further diagnostic evaluation.
3. In patients who develop a skin rash, topical antibiotics such as Cleocin (clindamycin) gel or erythromycin cream/gel or oral clindamycin, oral doxycycline, or oral minocycline may help.
4. Patients should be warned to avoid sunlight exposure.
5. Closely monitor in patients with a history of keratitis, ulcerative keratitis, or severe dry eye and in those who wear contact lenses.
6. Avoid Seville oranges, starfruit, pomelos, grapefruit, and grapefruit juice while on afatinib therapy.
7. Pregnancy category D. Breastfeeding should be avoided.

TOXICITY 1

Skin toxicity in the form of rash, erythema, and acneiform skin rash occurs in 90% of patients. Pruritus, dry skin, and nail bed changes are also observed. Grade 3 skin toxicity occurs in nearly 20% of patients, with bullous, blistering, and exfoliating lesions occurring rarely.

TOXICITY 2

Diarrhea is the most common GI toxicity. Mild nausea/vomiting and mucositis.

TOXICITY 3

Pulmonary toxicity in the form of ILD manifested by increased cough, dyspnea, fever, and pulmonary infiltrates. Observed in 1.5% of patients, and incidence appears to be higher in Asian patients.

TOXICITY 4
Hepatic toxicity with mild to moderate elevations in serum transaminases. Usually transient and clinically asymptomatic.

TOXICITY 5
Fatigue and anorexia.

TOXICITY 6
Keratitis presenting as acute eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain, and/or red eye.

Albumin-Bound Paclitaxel (Nab-paclitaxel)

TRADE NAME	Abraxane	**CLASSIFICATION**	Taxane, antimicrotubule agent
CATEGORY	Chemotherapy drug	**DRUG MANUFACTURER**	Celgene

MECHANISM OF ACTION
- Albumin-bound form of paclitaxel with a mean particle size of about 130 nm. Selective binding of albumin-bound paclitaxel to specific albumin receptors present on tumor cells versus normal cells.
- Active moiety is paclitaxel, which is isolated from the bark of the Pacific yew tree, *Taxus brevifolia*.
- Cell cycle–specific, active in the mitosis (M) phase of the cell cycle.
- High-affinity binding to microtubules enhances tubulin polymerization. Normal dynamic process of microtubule network is inhibited, leading to inhibition of mitosis and cell division.

MECHANISM OF RESISTANCE
- Alterations in tubulin with decreased binding affinity for drug.
- Multidrug-resistant phenotype with increased expression of P170 glycoprotein. Results in enhanced drug efflux with decreased intracellular accumulation of drug. Cross-resistant to other natural products, including vinca alkaloids, anthracyclines, taxanes, and etoposide.

ABSORPTION
Administered only via the IV route.

DISTRIBUTION
Distributes widely to all body tissues. Extensive binding (< 90%) to plasma and cellular proteins.

METABOLISM

Metabolized extensively by the hepatic P450 microsomal system. About 20% of the drug is excreted via fecal elimination. Less than 10% is eliminated as the parent form, with the majority being eliminated as metabolites. Renal clearance is relatively minor, with less than 1% of the drug cleared via the kidneys. The clearance of nab-paclitaxel is 43% greater than paclitaxel, and the volume of distribution is about 50% higher than paclitaxel. Terminal elimination half-life is on the order of 27 hours.

INDICATIONS

1. FDA-approved for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy.
2. FDA-approved for the treatment of locally advanced or metastatic NSCLC, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.
3. FDA-approved for the treatment of locally advanced or metastatic pancreatic cancer in combination with gemcitabine.

DOSAGE RANGE

1. Recommended dose for metastatic breast cancer is 260 mg/m^2 IV on day 1 every 21 days.
2. An alternative regimen is a weekly schedule of 125 mg/m^2 IV on days 1, 8, and 15 every 28 days.
3. Recommended dose for NSCLC is 100 mg/m^2 IV on days 1, 8, and 15 every 21 days.
4. Recommended dose for pancreatic cancer is 125 mg/m^2 IV on days 1, 8, and 15 every 28 days.

DRUG INTERACTIONS

None well characterized to date.

SPECIAL CONSIDERATIONS

1. Contraindicated in patients with baseline neutrophil counts < 1500 cells/mm^3.
2. Closely monitor CBC with differential on a periodic basis.
3. Has not been studied in patients with renal dysfunction.
4. Use with caution in patients with abnormal liver function, as patients with abnormal liver function may be at higher risk for toxicity. The drug should **NOT** be given to patients with metastatic pancreatic cancer who have moderate to severe liver dysfunction. For diseases other than metastatic pancreatic cancer, dose reduction is recommended in patients with moderate or severe hepatic dysfunction.
5. In contrast to paclitaxel, no premedication is required to prevent hypersensitivity reactions prior to administration of the drug.
6. Abraxane can **NOT** be substituted for or with other paclitaxel formulations, as the albumin form of paclitaxel may significantly alter the drug's clinical activity.

7. Closely monitor infusion site for infiltration during drug administration, as injection site reactions have been observed.
8. Use with caution when administering with known substrates or inhibitors of CYP2C8 and CYP3A4.
9. Pregnancy category D. Breastfeeding should be avoided.

TOXICITY 1
Myelosuppression with dose-limiting neutropenia and anemia. Thrombocytopenia relatively uncommon.

TOXICITY 2
Neurotoxicity mainly in the form of sensory neuropathy with numbness and paresthesias. Dose-dependent effect. In contrast to paclitaxel, Abraxane-mediated neuropathy appears to be more readily reversible.

TOXICITY 3
Ocular and visual disturbances seen in 13% of patients, with severe cases seen in 1%.

TOXICITY 4
Asthenia, fatigue, and weakness.

TOXICITY 5
Alopecia with loss of total body hair.

TOXICITY 6
Nausea/vomiting, diarrhea, and mucositis are the main GI toxicities. Mucositis is generally mild (seen in less than 10%). Mild-to-moderate nausea and vomiting, usually of brief duration.

TOXICITY 7
Transient elevations in serum transaminases, bilirubin, and alkaline phosphatase.

TOXICITY 8
Injection site reactions.

TOXICITY 9
Cardiac toxicity with chest pain, supraventricular tachycardia, hypertension, pulmonary embolus, peripheral edema, and rare cases of cardiac arrest.

Aldesleukin

TRADE NAMES	Interleukin-2, IL-2, Proleukin	**CLASSIFICATION**	Immunotherapy, cytokine
CATEGORY	Biologic response modifier agent	**DRUG MANUFACTURER**	Prometheus

MECHANISM OF ACTION

- Glycoprotein cytokine that functions as a T-cell growth factor.
- Biologic effect of interleukin-2 (IL-2) is mediated by specific binding to the interleukin-2 receptor (IL-2R).
- Precise mechanism by which IL-2 mediates its anticancer activity remains unknown but appears to require an intact immune system.
- Enhances lymphocyte mitogenesis and lymphocyte cytotoxicity.
- Induces lymphokine-activated (LAK) and natural killer (NK) cell activity.
- Induces interferon-γ production.

MECHANISM OF RESISTANCE

- Up to 75% of patients may develop anti–IL-2 antibodies.
- Increased expression of counter-regulatory factors, such as glucocorticoids, which act to reduce the efficacy of interleukin-2.

ABSORPTION

Administered only via the parenteral route. Peak plasma levels are achieved in 5 hours after subcutaneous (SC) administration.

DISTRIBUTION

After short IV infusion, high plasma concentrations of IL-2 are achieved followed by rapid distribution into the extravascular space.

METABOLISM

IL-2 is catabolized by renal tubular cells to amino acids. The major route of elimination is through the kidneys by both glomerular filtration and tubular secretion. The elimination half-life is 85 minutes.

INDICATIONS

1. Metastatic renal cell cancer.
2. Metastatic malignant melanoma.

DOSAGE RANGE

Renal cell cancer—600,000 IU/kg IV every 8 hours for a maximum of 14 doses. Following 9 days of rest, the schedule is repeated for another 14 doses, for a maximum of 28 doses per course.

DRUG INTERACTION 1
Corticosteroids—May decrease the antitumor efficacy of IL-2 due to its inhibitory effect on the immune system.

DRUG INTERACTION 2
Nonsteroidal anti-inflammatory drugs (NSAIDs)—May enhance the capillary leak syndrome observed with IL-2.

DRUG INTERACTION 3
Antihypertensives—IL-2 potentiates the effect of antihypertensive medications. For this reason, all antihypertensives should be stopped at least 24 hours before IL-2 treatment.

SPECIAL CONSIDERATIONS
1. Use with caution in patients with pre-existing cardiac, pulmonary, central nervous system (CNS), hepatic, and/or renal impairment, as there is an increased risk for developing serious and sometimes fatal reactions.
2. Pretreatment evaluation should include CBC; serum chemistries, including LFTs, renal function, and electrolytes; pulmonary function tests (PFTs); and stress thallium.
3. Patients should be monitored closely throughout the entire treatment, including vital signs every 2–4 hours, strict input and output, and daily weights. Continuous cardiopulmonary monitoring is important during therapy.
4. Monitor for capillary leak syndrome (CLS), which begins almost immediately after initiation of therapy. Manifested by hypotension, peripheral edema, ascites, pleural and/or pericardial effusions, weight gain, and altered mental status.
5. Early administration of dopamine (1–5 mg/kg/min) in the setting of CLS may maintain perfusion to the kidneys and preserve renal function.
6. Use with caution in the presence of concurrent medications known to be nephrotoxic and hepatotoxic, as IL-2 therapy is associated with both nephrotoxicity and hepatotoxicity.
7. Use with caution in patients with known autoimmune disease, as treatment with IL-2 is associated with autoimmune thyroiditis, leading to thyroid function impairment.
8. Allergic reactions have been reported in patients receiving iodine contrast media up to 4 months following IL-2 therapy.
9. Pregnancy category C. Breastfeeding should be avoided.

TOXICITY 1
Flu-like symptoms, including fever, chills, malaise, myalgias, and arthralgias. Observed in all patients.

TOXICITY 2
Vascular leak syndrome. Usual dose-limiting toxicity, characterized by weight gain, arrhythmias, tachycardia, hypotension, edema, oliguria and renal insufficiency, pleural effusion, and pulmonary congestion.

TOXICITY 3
Myelosuppression with anemia, thrombocytopenia, and neutropenia.

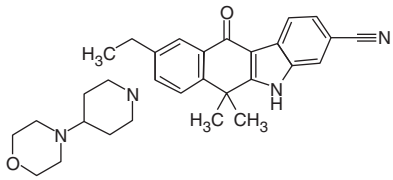
TOXICITY 4
Hepatotoxicity presenting as increases in serum bilirubin levels along with changes in serum transaminases. Usually reversible within 4–6 days after discontinuation of IL-2 therapy.

TOXICITY 5
Neurologic and neuropsychiatric findings can develop both acutely and chronically during treatment. Somnolence, delirium, and confusion are common but generally resolve after drug termination. Alterations in cognitive function and impaired memory more common with continuous-infusion IL-2.

TOXICITY 6
Erythema, skin rash, urticaria, and generalized erythroderma may occur within a few days of starting therapy.

TOXICITY 7
Alterations in thyroid function, including hyperthyroidism and hypothyroidism.

Alectinib



TRADE NAME	Alecensa	**CLASSIFICATION**	Signal transduction inhibitor
CATEGORY	Chemotherapy drug	**DRUG MANUFACTURER**	Genentech/Roche

MECHANISM OF ACTION

- Inhibits multiple receptor tyrosine kinases (RTKs), including anaplastic lymphoma kinase (ALK) and RET, which leads to inhibition of downstream signaling proteins, such as STAT3 and Akt.
- Pre-clinical studies show that it inhibits tumor cell lines that have ALK fusions, amplifications, or activating mutations. Major active metabolite of alectinib is M4, which displays similar in vitro potency and activity as the parent drug.
- Retains activity in NSCLC tumors resistant to crizotinib.

MECHANISM OF RESISTANCE

- Development of ALK mutations, including V1180L gatekeeper mutation, and I1171T and I1171N mutations. These mutations result in reduced binding of alectinib to the ALK fusion protein.
- Amplification of the MET gene, resulting in activation of the hepatocyte growth factor (HGF)-MET signaling pathway.
- Increased activation of the neuregulin 1 (NRG1)-HER3-EGFR signaling axis.

ABSORPTION

Rapidly absorbed after an oral dose, with peak plasma levels achieved within 4 hours. Absolute oral bioavailability is approximately 37%. Food with a high fat content can significantly increase drug concentrations by up to 3-fold.

DISTRIBUTION

Extensive binding of alectinib and M4 metabolite (> 99%) to plasma proteins.

METABOLISM

Metabolized in the liver primarily by CYP3A4 microsomal enzymes, with formation of the major active metabolite M4. Elimination is mainly hepatic, with excretion in feces (98%), with 84% as unchanged parent drug and 6% as M4 metabolite. Renal elimination is relatively minor, with < 0.5% of an administered dose being recovered in the urine. Steady-state drug levels of parent alectinib and the M4 metabolite are achieved in approximately 7 days. The terminal half-life of alectinib is approximately 33 hours and 31 hours for the M4 metabolite.

INDICATIONS

FDA-approved for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib as detected by an FDA-approved test.

DOSAGE RANGE

Recommended dose is 600 mg PO daily with food.

DRUG INTERACTION 1

Drugs such as ketoconazole, itraconazole, erythromycin, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole may decrease the rate of metabolism of alectinib, resulting in increased drug levels and potentially increased toxicity.

DRUG INTERACTION 2

Drugs such as rifampin, phenytoin, phenobarbital, carbamazepine, and St. John's Wort may increase the rate of metabolism of alectinib, resulting in its inactivation and lower effective drug levels.

SPECIAL CONSIDERATIONS

1. No dose adjustment is needed for patients with mild hepatic dysfunction. The drug has not been evaluated in patients with moderate or severe hepatic dysfunction.
2. No dose reduction is needed for patients with mild or moderate renal dysfunction. The drug has not been evaluated in patients with severe renal dysfunction or end-stage renal disease.
3. Patients receiving alectinib along with oral warfarin anticoagulant therapy should have their coagulation parameters (PT and INR) monitored frequently.
4. Monitor LFTs and serum bilirubin every 2 weeks for the first 2 months of treatment and then periodically, as alectinib may cause hepatotoxicity. More frequent testing is required in patients who develop LFT elevations. May need to suspend, dose-reduce, or permanently stop alectinib with the development of drug-induced hepatotoxicity.
5. Closely monitor patients for new or progressive pulmonary symptoms, including cough, dyspnea, and fever.
6. Closely monitor heart rate and blood pressure for evidence of bradycardia.
7. Monitor creatine phosphokinase (CPK) levels every 2 weeks during the first month of treatment and in patients with unexplained muscle pain, tenderness, or weakness.
8. ALK testing using an FDA-approved test is required to confirm the presence of ALK-positive NSCLC for determining which patients should receive alectinib therapy.
9. Pregnancy category D. Breastfeeding should be avoided.

TOXICITY 1

Hepatotoxicity with elevations in serum transaminases (SGOT, SGPT).

TOXICITY 2

Nausea/vomiting, constipation, diarrhea, and abdominal pain are the most common GI side effects.

TOXICITY 3

Pulmonary toxicity with increased cough, dyspnea, fever, and pulmonary infiltrates.

TOXICITY 4

Constitutional side effects with fatigue, asthenia, and anorexia.

TOXICITY 5

Bradycardia.

TOXICITY 6

Myalgia or musculoskeletal pain with CPK elevation.

TOXICITY 7

Skin rash.

A

Alemtuzumab

TRADE NAME	Campath	**CLASSIFICATION**	Monoclonal antibody
CATEGORY	Biologic response modifier agent	**DRUG MANUFACTURER**	Genzyme

MECHANISM OF ACTION

- Recombinant humanized monoclonal antibody (Campath-1H) directed against the 21- to 28-kDa cell-surface glycoprotein CD52 that is expressed on most normal and malignant B and T lymphocytes, NK cells, monocytes, and macrophages.
- CD52 antigen is not expressed on the surface of hematopoietic stem cells and mature plasma cells.
- Immunologic mechanisms involved in antitumor activity, including ADCC and/or complement-mediated cell lysis.

MECHANISM OF RESISTANCE

None well characterized to date.

ABSORPTION

Administered only via the IV route.

DISTRIBUTION

Peak and trough levels rise during the first few weeks of therapy and approach steady-state levels by week 6. However, there is marked variability, and drug levels correlate roughly with the number of circulating CD52+ B cells.

METABOLISM

Metabolism has not been extensively characterized. Half-life is on the order of 12 days, with minimal clearance by the liver and kidneys.

INDICATIONS

1. Relapsed and/or refractory B-cell chronic lymphocytic leukemia (B-CLL)—Indicated in patients who have been treated with alkylating agents and who have failed fludarabine therapy.
2. T-cell prolymphocytic leukemia—Clinical activity in patients who failed first-line therapy.

DOSAGE RANGE

Recommended dose is 30 mg/day IV three times per week for a maximum of 12 weeks.

DRUG INTERACTIONS

None known.

SPECIAL CONSIDERATIONS

1. Contraindicated in patients with active systemic infections, underlying immunodeficiency (HIV-positive, AIDS, etc.), or known type I hypersensitivity or anaphylactic reactions to alemtuzumab or any of its components.
2. Patients should be premedicated with acetaminophen, 650 mg PO, and diphenhydramine, 50 mg PO, 30 minutes before drug infusion to reduce the incidence of infusion-related reactions.
3. Alemtuzumab should be initiated at a dose of 3 mg, administered daily as a 2-hour IV infusion. When this daily dose of 3 mg is tolerated, the daily dose can then be increased to 10 mg. Once the 10-mg daily dose is tolerated, a maintenance dose of 30 mg daily can then be initiated. This maintenance dose of 30 mg/day is administered three times each week on alternate days (Monday, Wednesday, and Friday) for a maximum of 12 weeks. Dose escalation to the 30-mg daily dose usually can be accomplished within 7 days. Alemtuzumab should **NOT** be given by IV push or bolus.
4. Monitor closely for infusion-related events, which usually occur within the first 30–60 minutes after the start of the infusion and most commonly during the first week of therapy. Pulse, blood pressure, and oral temperature should be measured every 15–30 minutes. Immediate institution of diphenhydramine (50 mg IV), acetaminophen (625 mg PO), hydrocortisone (200 mg IV), and/or vasopressors may be required. Resuscitation equipment should be readily available at bedside.
5. Patients should be placed on anti-infective prophylaxis upon initiation of therapy to reduce the risk of serious opportunistic infections. This should include Bactrim DS, 1 tablet PO bid three times per week, and famciclovir or equivalent, 250 mg PO bid. Fluconazole may also be included in the regimen to reduce the incidence of fungal infections. If a serious infection occurs while on therapy, alemtuzumab should be stopped immediately and only reinitiated following the complete resolution of the underlying infection.
6. Monitor CBC and platelet counts on a weekly basis during alemtuzumab therapy. Treatment should be stopped for severe hematologic toxicity or in any patient with evidence of autoimmune anemia and/ or thrombocytopenia.
7. Most significant antitumor effects of alemtuzumab are observed in peripheral blood, bone marrow, and spleen. Tumor cells usually cleared from blood within 1–2 weeks of initiation of therapy, while normalization in bone marrow may take up to 6–12 weeks. Lymph nodes, especially those that are large and bulky, seem to be less responsive to therapy.
8. Pregnancy category C. Should be given to a pregnant woman only if clearly indicated. Breastfeeding should be avoided during treatment and for at least 3 months following the last dose of drug.

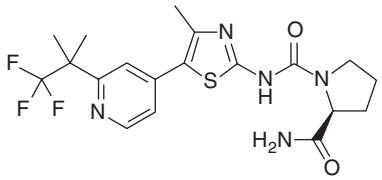
TOXICITY 1

Infusion-related symptoms, including fever, chills, nausea and vomiting, urticaria, skin rash, fatigue, headache, diarrhea, dyspnea, and/or hypotension. Usually occur within the first week of initiation of therapy.

TOXICITY 2
Significant immunosuppression with an increased incidence of opportunistic infections, including *Pneumocystis jiroveci* (formerly *carinii*), cytomegalovirus (CMV), herpes zoster, *Candida, Cryptococcus*, and *Listeria* meningitis. Prophylaxis with anti-infective agents is indicated as outlined previously. Recovery of CD4 and CD8 counts is slow and may take over 1 year to return to normal.

TOXICITY 3
Myelosuppression with neutropenia most common, but anemia and thrombocytopenia also observed. In rare instances, pancytopenia with marrow hypoplasia occurs, which can be fatal.

Alpelisib



TRADE NAME	Piqray	**CLASSIFICATION**	Signal transduction inhibitor, PI3K inhibitor
CATEGORY	Targeted agent	**DRUG MANUFACTURER**	Novartis

MECHANISM OF ACTION
- Phosphatidylinositol-3-kinase (PI3K) inhibitor with specific activity against the p110α isoform.
- Inhibits several key signaling pathways, including Akt.
- The combination of alpelisib and fulvstrant has enhanced antitumor activity compared to either treatment alone in *in vivo* models of ER+, PIK3CA mutated breast cancer.

MECHANISM OF RESISTANCE
None well characterized to date.

ABSORPTION
Oral bioavailability is approximately 25%. Peak plasma drug levels are achieved in 2–4 hours after ingestion, and there is no food effect on bioavailability.

DISTRIBUTION
Extensive binding (89%) to plasma proteins. Steady-state drug levels are reached in approximately 3 days.

METABOLISM
Metabolism primarily by chemical and enzymatic hydrolysis to form the BZG791 metabolite. Also metabolized by CYP3A4 but to a lesser extent. Elimination is mainly hepatic (81%), with excretion in the feces. Renal elimination accounts for 14% of an administered dose. Approximately 36% of an administered dose is eliminated in feces as unchanged parent form, and 32% is eliminated as the BZG791 metabolite. The terminal half-life of the parent drug is 8–9 hours.

INDICATIONS
FDA-approved in combination with fulvestrant for post-menopausal women and men with HR-positive, HER2-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

DOSAGE RANGE
Recommended dose is 300 mg PO once daily.

DRUG INTERACTION 1
Phenytoin and other drugs that stimulate the liver microsomal CYP3A4 enzymes, including carbamazepine, rifampin, phenobarbital, and St. John's Wort—These drugs may increase the metabolism of alpelisib, resulting in lower effective drug levels.

DRUG INTERACTION 2
Drugs that inhibit the liver microsomal CYP3A4 enzymes, including ketoconazole, itraconazole, erythromycin, and clarithromycin—These drugs may decrease the metabolism of alpelisib, resulting in increased drug levels and potentially increased toxicity.

DRUG INTERACTION 3
Warfarin—Patients receiving warfarin should be closely monitored for alterations in their clotting parameters (PT and INR) and/or bleeding, as alpelisib may inhibit warfarin metabolism by the liver P450 system. Dose of warfarin may require careful adjustment in the presence of alpelisib therapy.

SPECIAL CONSIDERATIONS
1. Dose reduction is not required in the setting of mild to severe hepatic impairment (Child-Pugh Class A, B, and C).
2. Dose reduction is not required in the setting of mild or moderate renal impairment. Has not been studied in the setting of severe renal impairment, in end-stage renal disease, or in patients on dialysis.
3. Monitor for signs and symptoms of severe hypersensitivity reactions.
4. Monitor blood glucose levels at least once per week for the first 8 weeks of treatment, followed by once every 2 weeks, and then as clinically indicated. Patients with diabetes mellitus should have their blood glucose levels under control before starting therapy.
5. Patients should be educated on the signs and symptoms of severe skin reactions. Patients with a prior history of Stevens-Johnson syndrome,

erythema multiforme, or toxic epidermal necrolysis should not be treated with alpelisib.
6. Patients should start on anti-diarrheal medication, increase oral fluid intake, and notify their physician if diarrhea should occur while on therapy.
7. May cause fetal harm when administered to a pregnant woman. Breastfeeding should be avoided.

TOXICITY 1
Hyperglycemia.

TOXICITY 2
Severe hypersensitivity reactions with dyspnea, flushing, rash, fever, or tachycardia. Anaphylaxis and anaphylactic shock have been observed.

TOXICITY 3
Maculopapular skin rash and more serious reactions, including Stevens-Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis.

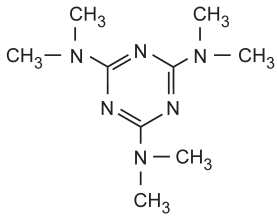
TOXICITY 4
Non-infectious pneumonitis with cough, dyspnea, pulmonary infiltrates, and hypoxia.

TOXICITY 5
Diarrhea, nausea/vomiting, and mucositis.

TOXICITY 6
Fatigue, asthenia, and anorexia.

TOXICITY 7
Skin reactions, including maculopapular rash, pruritus, and exfoliative rash.

Altretamine



TRADE NAMES	Hexalen, Hexamethylmelamine, HMM	**CLASSIFICATION**	Nonclassic alkylating agent
CATEGORY	Chemotherapy drug	**DRUG MANUFACTURER**	MGI Pharma

MECHANISM OF ACTION

- Triazine derivative that requires biochemical activation in the liver for its antitumor activity.
- Exact mechanism(s) of action unclear but appears to act like an alkylating agent. Forms cross-links with DNA, resulting in inhibition of DNA synthesis and function.
- May also inhibit RNA synthesis.

MECHANISM OF RESISTANCE

- Mechanisms of resistance have not been well characterized.
- Does not exhibit cross-resistance to other classic alkylating agents and does not exhibit multidrug-resistant phenotype.

ABSORPTION

Oral absorption is extremely variable secondary to extensive first-pass metabolism in the liver. Peak plasma levels are achieved 0.5–3 hours after an oral dose.

DISTRIBUTION

Widely distributed throughout the body, with highest concentrations found in tissues with high fat content. About 90% of drug is bound to plasma proteins.

METABOLISM

Extensively metabolized in the liver by the microsomal P450 system. Less than 1% of parent compound is excreted in urine. About 60% of drug is eliminated in urine as demethylated metabolites (pentamethylmelamine and tetramethylmelamine) within the first 24 hours. The terminal elimination half-life is on the order of 4–10 hours.

INDICATIONS

Ovarian cancer—Active in advanced disease and in persistent and/or recurrent tumors following first-line therapy with a cisplatin- and/or alkylating agent–based regimen.

DOSAGE RANGE

Usual dose is 260 mg/m^2/day PO for either 14 or 21 days on a 28-day schedule. Total daily dose is given in four divided doses after meals and at bedtime.

DRUG INTERACTION 1

Cimetidine—Cimetidine increases the half-life and subsequent toxicity of altretamine. In contrast, ranitidine does not affect drug metabolism.

DRUG INTERACTION 2

Phenobarbital—Phenobarbital may decrease the half-life and toxicity of altretamine.

DRUG INTERACTION 3
Monoamine oxidase (MAO) inhibitors—Concurrent use of MAO inhibitors with altretamine may result in significant orthostatic hypotension.

SPECIAL CONSIDERATIONS
1. Closely monitor patient for signs of neurologic toxicity.
2. Vitamin B6 (pyridoxine) may be used to decrease the incidence and severity of neurologic toxicity. However, antitumor activity may be compromised with vitamin B6 treatment.
3. Pregnancy category D. Breastfeeding should be avoided.

TOXICITY 1
Nausea and vomiting. Usually mild to moderate, observed in 30% of patients, and worsens with increasing cumulative doses of drug.

TOXICITY 2
Myelosuppression. Dose-limiting toxicity. Leukocyte and platelet nadirs occur at 3–4 weeks, with recovery by day 28. Anemia occurs in 20% of patients.

TOXICITY 3
Neurotoxicity in the form of somnolence, mood changes, lethargy, depression, agitation, hallucinations, and peripheral neuropathy. Observed in about 25% of patients.

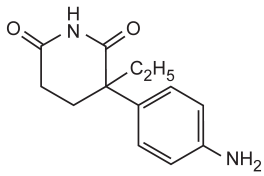
TOXICITY 4
Hypersensitivity skin rash.

TOXICITY 5
Elevations in LFTs, mainly alkaline phosphatase.

TOXICITY 6
Flu-like syndrome in the form of fever, malaise, arthralgias, and myalgias.

TOXICITY 7
Abdominal cramps and diarrhea are occasionally observed.

Aminoglutethimide



TRADE NAME	Cytadren	CLASSIFICATION	Adrenal steroid inhibitor
CATEGORY	Hormonal agent	DRUG MANUFACTURER	Novartis

MECHANISM OF ACTION

- Nonsteroidal inhibitor of corticosteroid biosynthesis.
- Produces a chemical adrenalectomy with a decreased synthesis of estrogens, androgens, glucocorticoids, and mineralocorticoids.

ABSORPTION

Excellent bioavailability via the oral route. Peak plasma concentrations occur within 1–1.5 hours after ingestion.

DISTRIBUTION

Approximately 25% of the drug is bound to plasma proteins. Significant reduction in distribution with prolonged treatment.

METABOLISM

Metabolized in the liver by the cytochrome P450 system, with N-acetylaminoglutethimide being the major metabolite. Metabolism is under genetic control, and acetylator status of patients is important. About 40%–50% of the drug is excreted unchanged in the urine. Initial half-life of drug is about 13 hours but decreases to 7 hours with chronic treatment, suggesting that the drug may accelerate its own rate of degradation.

INDICATIONS

1. Breast cancer—Hormone-responsive, advanced disease.
2. Prostate cancer—Hormone-responsive, advanced disease.

DOSAGE RANGE

Usual dose is 250 mg PO qid (1,000 mg total).

DRUG INTERACTION 1

Warfarin, phenytoin, phenobarbital, theophylline, medroxyprogesterone, and digoxin—Aminoglutethimide enhances the metabolism of warfarin, phenytoin, phenobarbital, theophylline, medroxyprogesterone, and digoxin, thereby decreasing their clinical activity.

DRUG INTERACTION 2

Dexamethasone—Aminoglutethimide enhances the metabolism of dexamethasone but not hydrocortisone.

SPECIAL CONSIDERATIONS

1. Administer hydrocortisone along with aminoglutethimide to prevent adrenal insufficiency. The use of higher doses during the initial 2 weeks of therapy reduces the frequency of adverse events. For example, start

at 100 mg PO daily for the first 2 weeks, then 40 mg PO daily in divided doses. Higher doses of steroid replacement may be required under conditions of stress, such as surgery, trauma, or acute infection.
2. Closely monitor patient for signs and symptoms of hypothyroidism. Monitor thyroid function tests on a regular basis.
3. Monitor for signs and symptoms of orthostatic hypotension. May need to add fludrocortisone (Florinef) 0.1–0.2 mg PO qd.
4. Monitor patient for signs of somnolence and lethargy. Severe cases may warrant immediate discontinuation of drug.
5. Discontinue drug if skin rash persists for more than 1 week.
6. Pregnancy category D. Breastfeeding should be avoided.

TOXICITY 1
Maculopapular skin rash. Usually seen in the first week of therapy. Self-limited, with resolution in 5–7 days, and discontinuation of therapy not necessary.

TOXICITY 2
Fatigue, lethargy, and somnolence. Occur in 40% of patients, and onset is within the first week of therapy. Dizziness, nystagmus, and ataxia are less common (10% of patients).

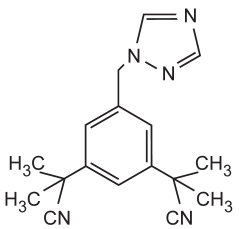
TOXICITY 3
Mild nausea and vomiting.

TOXICITY 4
Hypothyroidism.

TOXICITY 5
Adrenal insufficiency. Occurs in the absence of hydrocortisone replacement. Presents as postural hypotension, hyponatremia, and hyperkalemia.

TOXICITY 6
Myelosuppression. Leukopenia and thrombocytopenia rarely occur.

Anastrozole



TRADE NAME	Arimidex	**CLASSIFICATION**	Nonsteroidal aromatase inhibitor
CATEGORY	Hormonal agent	**DRUG MANUFACTURER**	AstraZeneca

MECHANISM OF ACTION

- Potent and selective nonsteroidal inhibitor of aromatase.
- Inhibits the synthesis of estrogens by inhibiting the conversion of adrenal androgens (androstenedione and testosterone) to estrogens (estrone, estrone sulfate, and estradiol). Serum estradiol levels are suppressed by 90% within 14 days and nearly completely suppressed after 6 weeks of therapy.
- No inhibitory effect on adrenal corticosteroid or aldosterone biosynthesis.

MECHANISM OF RESISTANCE

- Decreased expression of estrogen receptors (ER).
- Mutations in ER leading to decreased binding affinity to anastrozole.
- Overexpression of growth factor receptors, such as EGFR, HER2/neu, IGF-1R, or TGF-β, that counteract the inhibitory effects of anastrozole.
- Presence of ESR1 mutations.

ABSORPTION

Excellent bioavailability via the oral route, with 85% of a dose absorbed within 2 hours of ingestion. Absorption is not affected by food.

DISTRIBUTION

Widely distributed throughout the body. About 40% of drug is bound to plasma proteins.

METABOLISM

Extensively metabolized in the liver (up to 85%), by N-dealkylation, hydroxylation, and glucuronidation, to inactive forms. Half-life of drug is about 50 hours. Steady-state levels of drug are achieved after 7 days of a once-daily administration. The major route of elimination is fecal, with renal excretion accounting for only 10% of drug clearance.

INDICATIONS

1. Metastatic breast cancer—FDA-approved for the first-line treatment of postmenopausal women with hormone-receptor-positive or hormone-receptor-unknown disease.
2. Metastatic breast cancer—Postmenopausal women with hormone-receptor-positive, advanced disease, and progression while on tamoxifen therapy.
3. Adjuvant treatment of postmenopausal women with hormone-receptor-positive, early-stage breast cancer; FDA-approved.

DOSAGE RANGE

1. Metastatic breast cancer—Recommended dose is 1 mg PO qd for both first- and second-line therapy.
2. Early-stage breast cancer—Recommended dose is 1 mg PO qd for adjuvant therapy. The optimal duration of therapy is unknown. In the ATAC trial, anastrozole was given for 5 years.

DRUG INTERACTIONS

None have been well characterized.

SPECIAL CONSIDERATIONS

1. No dose adjustments are required for patients with either hepatic or renal dysfunction.
2. Caution patients about the risk of hot flashes.
3. No need for glucocorticoid and/or mineralocorticoid replacement.
4. Closely monitor women with osteoporosis or at risk of osteoporosis by performing bone densitometry at the start of therapy and at regular intervals. Treatment or prophylaxis for osteoporosis should be initiated when appropriate.
5. Pregnancy category D. Breastfeeding should be avoided.

TOXICITY 1

Asthenia is most common toxicity and occurs in up to 20% of patients.

TOXICITY 2

Mild nausea and vomiting. Constipation or diarrhea can also occur.

TOXICITY 3

Hot flashes. Occur in 10% of patients.

TOXICITY 4

Dry, scaling skin rash.

TOXICITY 5

Arthralgias occur in 10%–15% of patients, involving hands, knees, hips, lower back, and shoulders. Early morning stiffness is usual presentation.

TOXICITY 6

Headache.

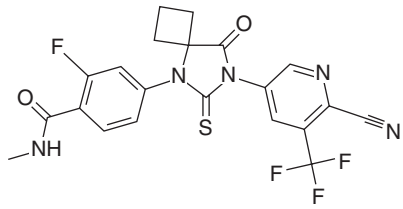
TOXICITY 7

Peripheral edema in 7% of patients.

TOXICITY 8

Flu-like syndrome in the form of fever, malaise, and myalgias.

Apalutamide



TRADE NAME	Erleada	**CLASSIFICATION**	Antiandrogen
CATEGORY	Hormonal drug	**DRUG MANUFACTURER**	Janssen

MECHANISM OF ACTION

- Nonsteroidal antiandrogen agent that binds to androgen receptor (AR) and inhibits AR translocation, inhibits DNA binding, and inhibits AR-mediated transcription.

MECHANISM OF RESISTANCE

- Decreased expression of AR.
- Mutation in AR leading to decreased binding affinity to drug.

ABSORPTION

Well absorbed by the GI tract with 100% bioavailability. Peak plasma levels observed 2 hours after oral administration. Food delays absorption by about 2 hours. Steady-state levels are achieved in 4 weeks.

DISTRIBUTION

Extensively bound to plasma proteins (96%).

METABOLISM

Extensive metabolism occurs in the liver by CYP3A4 and CYP2C8 to form the active metabolite N-desmethyl apalutamide as well as inactive metabolites. About 65% of an administered dose is eliminated in urine and 24% eliminated in feces. Only a small fraction (1.5–2%) of parent drug and its active metabolite, respectively, are cleared in urine and feces. The elimination half-life is on the order of 3 days.

INDICATIONS

FDA-approved for nonmetastatic castration-resistant prostate cancer.

DOSAGE RANGE

Recommended dose is 240 mg PO once daily, either alone or in combination with a luteinizing hormone–releasing hormone (LHRH) analog.

DRUG INTERACTION 1
Phenytoin and other drugs that stimulate the liver microsomal CYP3A4 enzymes, including carbamazepine, rifampin, phenobarbital, and St. John's Wort—These drugs may increase the metabolism of apalutamide, resulting in reduced drug levels.

DRUG INTERACTION 2
Drugs that inhibit the liver microsomal CYP3A4 enzymes, including ketoconazole, itraconazole, erythromycin, and clarithromycin—These drugs may decrease the metabolism of apalutamide, resulting in increased drug levels and potentially increased toxicity.

SPECIAL CONSIDERATIONS
1. Dose reduction is not required in the setting of mild or moderate hepatic impairment (Child-Pugh Class A or B). Has not been studied in the setting of severe hepatic impairment.
2. Dose reduction is not required in the setting of mild or moderate renal impairment. Has not been studied in the setting of severe renal impairment, in end-stage renal disease, or in patients on dialysis.
3. Monitor patients for fracture and fall risk.
4. Caution patients about the risk for seizures. Apalutamide treatment should be permanently discontinued in patients who develop a seizure while on therapy.
5. Caution patients about the potential for hot flashes. Consider the use of clonidine 0.1–0.2 mg PO daily, megestrol acetate 20 mg PO bid, or soy tablets 1 tablet PO tid for prevention and/or treatment.
6. Instruct patients on the potential risk of altered sexual function and impotence.
7. Pregnancy category D.

TOXICITY 1
Hot flashes, decreased libido, impotence, gynecomastia, nipple pain, and galactorrhea.

TOXICITY 2
Fall and fracture.

TOXICITY 3
Skin rash.

TOXICITY 4
Fatigue and anorexia.

TOXICITY 5
Arthralgias.

Arsenic trioxide (As_2O_3)

TRADE NAME	Trisenox	**CLASSIFICATION**	Natural product
CATEGORY	Chemotherapy and differentiating agent	**DRUG MANUFACTURER**	Cephalon, Teva

MECHANISM OF ACTION

- Precise mechanism of action has not been fully elucidated.
- Induces differentiation of acute promyelocytic leukemic cells by degrading the chimeric PML/RAR-α protein, resulting in release of the maturation block at the promyelocyte stage of myelocyte differentiation.
- Induces apoptosis through a mitochondrial-dependent pathway, resulting in release of cytochrome C and subsequent caspase activation.
- Direct antiproliferative activity by arresting cells at either the G1-S or G2-M checkpoints.
- Inhibits the process of angiogenesis through apoptosis of endothelial cells and/or inhibition of production of critical angiogenic factors, including vascular endothelial growth factor.

MECHANISM OF RESISTANCE

None well characterized to date.

ABSORPTION

Administered only via the IV route.

DISTRIBUTION

Widely distributes in liver, kidneys, heart, lung, hair, nails, and skin.

METABOLISM

The clinical pharmacology of arsenic trioxide has not been well characterized. Metabolism occurs via reduction of pentavalent arsenic to trivalent arsenic and methylation reactions mediated by methyltransferase enzymes that occur primarily in the liver. However, the methyltransferases appear to be distinct from the liver microsomal P450 system. The methylated trivalent arsenic metabolite is excreted mainly in the urine.

INDICATIONS

1. Acute promyelocytic leukemia (APL)—FDA-approved in combination with tretinoin for adults with newly diagnosed low-risk APL whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-α gene expression.
2. Acute promyelocytic leukemia (APL)—FDA-approved for induction of remission and consolidation in patients with APL who are refractory to or have relapsed following first-line therapy with all-trans retinoic acid (ATRA) and anthracycline-based chemotherapy and whose APL is

characterized by the presence of the t(15;17) translocation or PML/RAR-α gene expression.

DOSAGE RANGE

1. Newly diagnosed low-risk APL: treatment course consists of 1 induction cycle and 4 consolidation cycles
   - Induction therapy—0.15 mg/kg/day IV for a maximum of 60 days in combination with tretinoin.
   - Consolidation therapy—0.15 mg/kg/day IV for 5 days/week on weeks 1–4 of an 8-week cycle for a total of 4 cycles in combination with tretinoin.
2. Relapsed or refractory APL: treatment course consists of 1 induction cycle and 1 consolidation cycle
   - Induction therapy—0.15 mg/kg/day IV for a maximum of 60 days.
   - Consolidation therapy—Should be initiated 3–6 weeks after completion of induction treatment and only in those patients who achieve a complete bone marrow remission. The recommended dosage is 0.15 mg/kg/day IV for 5 days/week for a total of 5 weeks

DRUG INTERACTION 1

Medications that can prolong the QT interval, such as antiarrhythmics—Increased risk of prolongation of the QT interval and subsequent arrhythmias when arsenic trioxide is administered concomitantly.

DRUG INTERACTION 2

Amphotericin B—Increased risk of prolonged QT interval and Torsades de Pointes ventricular arrhythmia in patients receiving amphotericin and induction therapy with arsenic trioxide.

SPECIAL CONSIDERATIONS

1. Contraindicated in patients who are hypersensitive to arsenic.
2. Use with caution in patients who are on agents that prolong the QT interval, in those who have a history of Torsades de Pointes, pre-existing QT interval prolongation, untreated sinus node dysfunction, high-degree atrioventricular block, or in those who may be severely dehydrated or malnourished at baseline.
3. Use with caution in patients with renal impairment, as renal excretion is the main route of elimination of arsenic.
4. Use with caution in patients with severe hepatic impairment, as the drug has not been studied in this setting.
5. Before initiation of therapy, all patients should have a baseline electrocardiogram (ECG) performed, and serum electrolytes, calcium, magnesium, blood urea nitrogen (BUN), and creatinine should be evaluated. Any pre-existing electrolyte abnormalities should be corrected before starting therapy.
6. Serum electrolytes and magnesium should be closely monitored during therapy. Serum potassium concentrations should be maintained above 4 mEq/L and magnesium concentrations above 1.8 mg/dL.

7. Therapy should be stopped when the QT interval > 500 milliseconds (msec) and only resumed when the QT interval drops to below 460 msec, all electrolyte abnormalities are corrected, and cardiac monitoring shows no evidence of arrhythmias. This is a black-box warning.
8. Monitor closely for new-onset fever, dyspnea, weight gain, abnormal respiratory symptoms and/or physical findings, or chest x-ray abnormalities because 30% of patients will develop the APL differentiation syndrome. This syndrome can be fatal, and high-dose steroids with dexamethasone 10 mg IV bid should be started immediately and continued for 3–5 days. While this syndrome more commonly occurs with median baseline white blood cell counts of 5,000/mm^3, it can occur in the absence of leukocytosis. In most cases, therapy can be resumed once the syndrome has completely resolved. This is a black-box warning.
9. Prophylaxis with prednisone 0.5 mg/kg daily from day 1 until the end of induction therapy is recommended to prevent the APL differentiation syndrome.
10. Monitor patients for neurologic symptoms while on therapy. Patients are at risk for developing Wernicke's encephalopathy, which is a neurologic emergency that can be prevented and treated with parenteral thiamine. This is a black-box warning.
11. Monitor CBC every other day and bone marrow cytology every 10 days during induction therapy.
12. Pregnancy category D. Breastfeeding should be avoided, as arsenic is excreted in breast milk.

TOXICITY 1
Fatigue.

TOXICITY 2
Prolonged QT interval (> 500 msec) on ECG seen in 40%–50% of patients. Does not usually increase upon repeat exposure to arsenic trioxide, and QT interval returns to baseline following termination of therapy. Torsades de Pointes ventricular arrhythmia and/or complete AV block can be observed.

TOXICITY 3
APL differentiation syndrome. Occurs in about 30% of patients and is characterized by fever, dyspnea, skin rash, fluid retention and weight gain, and pleural and/or pericardial effusions. This syndrome is identical to the retinoic acid syndrome observed with retinoid therapy.

TOXICITY 4
Leukocytosis is observed in 50%–60% of patients with a gradual increase in white blood cells (WBCs) that peaks between 2 and 3 weeks after starting therapy. Usually resolves spontaneously without treatment and/or complications.

TOXICITY 5
Light-headedness most commonly observed during drug infusion.

TOXICITY 6
Mild nausea and vomiting, abdominal pain, and diarrhea.

TOXICITY 7
Musculoskeletal pain.

TOXICITY 8
Mild hyperglycemia.

TOXICITY 9
Neurologic symptoms with confusion, decreased level of consciousness, cognitive changes, ataxia, visual symptoms, seizures, and ocular motor dysfunction. Wernicke's encephalopathy is a neurologic emergency.

TOXICITY 10
Carcinogen and teratogen.

Asparaginase

TRADE NAMES	Elspar, L-Asparaginase	**CLASSIFICATION**	Enzyme
CATEGORY	Chemotherapy drug	**DRUG MANUFACTURER**	Merck

MECHANISM OF ACTION
- Purified from *Escherichia coli* and/or *Erwinia chrysanthemi*.
- Tumor cells lack asparagine synthetase and thus require exogenous sources of L-asparagine.
- L-Asparaginase hydrolyzes circulating L-asparagine to aspartic acid and ammonia.
- Depletion of the essential amino acid L-asparagine results in rapid inhibition of protein synthesis. Cytotoxicity of drug correlates well with inhibition of protein synthesis.

MECHANISM OF RESISTANCE
- Increased expression of the L-asparagine synthetase gene, which facilitates the cellular production of L-asparagine from endogenous sources.
- Formation of antibodies against L-asparaginase, resulting in inhibition of function.

ABSORPTION
L-Asparaginase is not orally bioavailable.

DISTRIBUTION
Remains in the vascular compartment after IV administration. After intramuscular (IM) injection, peak plasma levels are reached within 14–24 hours. Peak plasma levels after IM injection are 50% lower than those achieved with IV injection. Plasma protein binding is on the order of 30%. The apparent volume of distribution is about 70%–80% of the plasma volume. Cerebrospinal fluid (CSF) penetration is negligible (< 1% of plasma level).

METABOLISM
Metabolism is not well characterized. Minimal urinary and/or biliary excretion occurs. Plasma half-life depends on drug formulation: 40–50 hours for *E. coli*–derived L-asparaginase and 3–5 days for polyethylene glycol (PEG)–asparaginase.

INDICATIONS
Acute lymphocytic leukemia.

DOSAGE RANGE
1. Dose varies depending on specific regimens. L-Asparaginase is given at a dose of 6,000–10,000 IU/m^2 IM every 3 days for a total of nine doses. Treatment with L-asparaginase is started after completion of other chemotherapy drugs used in the induction therapy of acute lymphoblastic leukemia (vincristine, prednisone, and doxorubicin).
2. L-Asparaginase is given less commonly as a single agent at a dose of 200 IU/kg IV for 28 consecutive days.

DRUG INTERACTION 1
Methotrexate—L-Asparaginase can inhibit the cytotoxic effects of methotrexate and thus rescue from methotrexate antitumor activity and toxicity. It is recommended that these drugs be administered 24 hours apart.

DRUG INTERACTION 2
Vincristine—L-Asparaginase inhibits the clearance of vincristine, resulting in increased host toxicity, especially neurotoxicity. Vincristine should be administered 12–24 hours before L-asparaginase.

SPECIAL CONSIDERATIONS
1. An intradermal skin test dose of 2 IU should be performed before the initial administration of L-asparaginase or whenever the dose is being repeated more than 1 week from the immediately previous one. The patient should be observed for at least 1 hour before the full dose is given. A negative dermal test does not completely rule out the possibility of an allergic reaction.
2. Monitor patient for allergic reactions and/or anaphylaxis. Contraindicated in patients with a prior history of anaphylactic reaction. L-Asparaginase isolated from the *Erwinia* species may be tried in patients previously treated with *E. coli* asparaginase, but allergic reactions may still occur.

3. L-Asparaginase is a contact irritant in both powder and solution forms. The drug must be handled and administered with caution.
4. Induction treatment of acute lymphoblastic leukemia with L-asparaginase may induce rapid lysis of blast cells. Prophylaxis against tumor lysis syndrome with vigorous IV hydration, urinary alkalinization, and allopurinol is recommended for all patients.
5. Contraindicated in patients with either active pancreatitis or a history of pancreatitis. If pancreatitis develops while on therapy, L-asparaginase should be stopped immediately.
6. Close monitoring of LFTs, amylase, coagulation tests, and fibrinogen levels.
7. L-Asparaginase can interfere with thyroid function tests. This effect is probably due to a marked reduction in serum concentration of thyroxine-binding globulin, which is observed within 2 days after the first dose. Levels of thyroxine-binding globulin return to normal within 4 weeks of the last dose.
8. Pregnancy category C. Breastfeeding should be avoided.

TOXICITY 1
Hypersensitivity reaction. Occurs in up to 25% of patients. Mild form manifested by skin rash and urticaria. Anaphylactic reaction may be life-threatening and presents as bronchospasm, respiratory distress, and hypotension. Resuscitation drugs and equipment should be readily available at bedside before drug treatment.

TOXICITY 2
Fever, chills, nausea, and vomiting. Acute reaction observed in about two-thirds of patients.

TOXICITY 3
Mild elevation in LFTs, including serum bilirubin, alkaline phosphatase, and SGOT. Common and usually transient. Liver biopsy reveals fatty changes.

TOXICITY 4
Increased risk of both bleeding and clotting. Alterations in clotting with decreased levels of clotting factors, including fibrinogen, factors IX and XI, antithrombin III, proteins C and S, plasminogen, and α-2-antiplasmin. Observed in over 50% of patients.

TOXICITY 5
Pancreatitis develops in up to 10% of patients. Usually manifested as transient increase in serum amylase levels with quick resolution upon cessation of therapy.

TOXICITY 6
Neurologic toxicity, including lethargy, confusion, agitation, hallucinations, and/or coma. These side effects may require treatment discontinuation. Severe neurotoxicity resembles ammonia toxicity.

TOXICITY 7
Myelosuppression is mild and rarely observed.

TOXICITY 8
Decreased serum levels of insulin, lipoproteins, and albumin.

TOXICITY 9
Renal toxicity. Usually mild and manifested by mild elevations in BUN and creatinine, proteinuria, and elevated serum acid levels.

Atezolizumab

TRADE NAME	Tecentriq	**CLASSIFICATION**	Monoclonal antibody, PD-L1 inhibitor
CATEGORY	Immune checkpoint inhibitor, immunotherapy	**DRUG MANUFACTURER**	Genentech/ Roche

MECHANISM OF ACTION

- Humanized IgG4 antibody that binds to the programmed death-ligand 1 (PD-L1) ligand expressed on tumor cells and/or tumor infiltrating cells, which then blocks the interaction between the PD-L1 ligand and the programmed cell death 1 (PD-1) and B7.1 receptors found on T cells and antigen-presenting cells.
- Blockade of the PD-1 pathway-mediated immune checkpoint overcomes immune escape mechanisms and enhances T-cell immune response, leading to T-cell activation and proliferation.

MECHANISM OF RESISTANCE

- Increased expression and/or activity of other immune checkpoint pathways (e.g., TIGIT, TIM3, and LAG3).
- Increased expression of other immune escape mechanisms.
- Increased infiltration of immune suppressive populations within the tumor microenvironment, which include Tregs, myeloid-derived suppressor cells (MDSCs), and M2 macrophages.
- Release of various cytokines, chemokines, and metabolites within the tumor microenvironment, including CSF-1, tryptophan metabolites, TGF-β, and adenosine.

DISTRIBUTION
Distribution in body is not well characterized. Steady-state levels are achieved by 6–9 weeks.

METABOLISM

Metabolism of atezolizumab has not been extensively characterized. The terminal half-life is on the order of 27 days.

INDICATIONS

1. FDA-approved for locally advanced or metastatic urothelial cancer with disease progression during or following platinum-based chemotherapy or with disease progression within 12 months of neoadjuvant or adjuvant therapy with platinum-based chemotherapy.
2. FDA-approved for metastatic non–small cell lung cancer (NSCLC) with disease progression during or following platinum-based chemotherapy. Patients with EGFR or ALK genetic alterations should have disease progression on FDA-approved targeted therapy for these genetic alterations prior to treatment with atezolizumab.
3. FDA-approved for unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) in combination with nab-paclitaxel whose tumors express PD-L1 stained tumor-infiltrating immune cells of any intensity covering > 1% of the tumor area, as determined by an FDA approved test.
4. FDA-approved for first-line treatment of extensive-stage small cell lung cancer (SCLC) in combination with carboplatin and etoposide.

DOSAGE RANGE

1. Recommended dose as monotherapy for urothelial cancer and NSCLC is 840 mg IV every 2 weeks, 1,200 mg IV every 3 weeks, or 1,680 mg IV every 4 weeks.
2. NSCLC: 1,200 mg IV every 3 weeks when used in combination with paclitaxel, carboplatin, and bevacizumab.
3. SCLC: 840 mg IV followed by 100 mg/m^2 of nab-paclitaxel IV. For each 28-day cycle, atezolizumab is administered on days 1 and 15, and nab-paclitaxel is administered on days 1, 8, and 15.
4. TNBC: 1,200 mg IV every 3 weeks with carboplatin and etoposide. Following the completion of 4 cycles of chemotherapy, atezolizumab is administered 840 mg IV every 2 weeks, 1,200 mg IV every 3 weeks, or 1,680 mg IV every 4 weeks.

DRUG INTERACTIONS

None have been well characterized to date.

SPECIAL CONSIDERATIONS

1. Atezolizumab can result in significant immune-mediated adverse reactions due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system, with the most common reactions being pneumonitis, hepatitis, colitis, hypophysitis, pancreatitis, neurological disorders, and adrenal and thyroid dysfunction.
2. Atezolizumab should be withheld for any of the following:
   - Grade 2 pneumonitis
   - Grade 2 or 3 colitis

- SGOT/SGPT > 3× ULN and up to 5 × ULN or total bilirubin > 1.5 × ULN and up to 3 × ULN
- Symptomatic hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, or grade 3 or 4 hyperglycemia
- Grade 2 ocular inflammatory toxicity
- Grade 2 or 3 pancreatitis or grade 3 or 4 increases in serum amylase or lipase levels
- Grade 3 or 4 infection
- Grade 2 infusion-related reactions
- Grade 3 skin rash

3. Atezolizumab should be permanently discontinued for any of the following:
   - Grade 3 or 4 pneumonitis
   - SGOT/SGPT > 5 × ULN or total bilirubin > 3 × ULN
   - Grade 4 diarrhea or colitis
   - Grade 4 hypophysitis
   - Myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, or meningoencephalitis (all grades)
   - Grade 3 or 4 ocular inflammatory toxicity
   - Grade 4 or any grade of recurrent pancreatitis
   - Grade 3 or 4 infusion-related reactions
   - Grade 4 skin rash
4. The first infusion should be administered over 60 minutes. If the first infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.
5. Monitor for symptoms and signs of infection.
6. Monitor thyroid and adrenal function prior to and during therapy.
7. Dose modification is not needed for patients with renal dysfunction.
8. Dose modification is not needed for patients with mild hepatic dysfunction. Atezolizumab has not been studied in patients with moderate or severe hepatic dysfunction.
9. Pregnancy category D.

TOXICITY 1
Colitis with diarrhea and abdominal pain.

TOXICITY 2
Pneumonitis with dyspnea and cough.

TOXICITY 3
GI side effects with nausea/vomiting; dry mouth; hepatitis with elevations in SGOT/SGPT, alkaline phosphatase, and serum bilirubin.

TOXICITY 4
Endocrinopathies, including hypophysitis, thyroid disorders, adrenal insufficiency, and diabetes.

TOXICITY 5
Pancreatitis.

TOXICITY 6
Neurologic toxicity with neuropathy, myositis, and myasthenia gravis, Guillain-Barré syndrome, or meningoencephalitis.

TOXICITY 7
Musculoskeletal symptoms, which may present with arthralgias, oligoarthritis, polyarthritis, tenosynovitis, polymyalgia rheumatica, and myalgias.

TOXICITY 8
Infections with sepsis, herpes encephalitis, and mycobacterial infections. All-grade infections observed in up to 38% of patients and > grade 3 infections in 11% of patients, with urinary tract infections being the most common cause of > grade 3 infections.

TOXICITY 9
Infusion-related reactions.

TOXICITY 10
Ocular toxicity.

TOXICITY 11
Maculopapular skin rash, erythema, dermatitis, and pruritus.

TOXICITY 12
Fatigue, anorexia, and asthenia.

Avelumab

TRADE NAME	Bavencio	**CLASSIFICATION**	Monoclonal antibody, PD-L1 inhibitor
CATEGORY	Immune checkpoint inhibitor, immunotherapy	**DRUG MANUFACTURER**	EMD Serono/ Pfizer

MECHANISM OF ACTION

- Human IgG1 antibody that binds to the PD-L1 ligand expressed on tumor cells and/or tumor infiltrating cells, which then blocks the interaction between the PD-L1 ligand and the PD-1 and B7.1 receptors found on T cells and antigen-presenting cells.

- Blockade of the PD-1 pathway-mediated immune checkpoint overcomes immune escape mechanisms and enhances T-cell immune response, leading to T-cell activation and proliferation.
- Differs from other PD-L1/PD-1 immune checkpoint-blocking antibodies in that it may also induce ADCC.

MECHANISM OF RESISTANCE

- Increased expression and/or activity of other immune checkpoint pathways (e.g., TIGIT, TIM3, and LAG3).
- Increased expression of other immune escape mechanisms.
- Increased infiltration of immune suppressive populations within the tumor microenvironment, which include Tregs, myeloid-derived suppressor cells (MDSCs), and M2 macrophages.
- Release of various cytokines, chemokines, and metabolites within the tumor microenvironment, including CSF-1, tryptophan metabolites, TGF-β, and adenosine.

DISTRIBUTION

Mean volume of distribution in the body is 4.72 L. Steady-state levels are achieved by 4–6 weeks.

METABOLISM

Main mechanism of elimination of avelumab is proteolytic degradation. The terminal half-life is on the order of 6 days.

INDICATIONS

1. FDA-approved for adult and pediatric patients 12 years and older with metastatic Merkel cell cancer (MCC).
2. FDA-approved for locally advanced or metastatic bladder cancer with disease progression during or following platinum-based chemotherapy or with disease progression within 12 months of neoadjuvant or adjuvant therapy with platinum-based chemotherapy.
3. FDA-approved in combination with axitinib for the first-line treatment of advanced renal cell carcinoma (RCC).

DOSAGE RANGE

Recommended dose for bladder cancer, Merkel cell cancer, and RCC is 10 mg/kg IV every 2 weeks.

DRUG INTERACTIONS

None have been well characterized to date.

SPECIAL CONSIDERATIONS

1. Avelumab can result in significant immune-mediated adverse reactions due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system, with the most common reactions being pneumonitis, hepatitis, colitis, hypophysitis, pancreatitis, neurological disorders, and adrenal and thyroid dysfunction.

2. Closely monitor for infusion-related reactions. Patients should be pre-medicated with an antihistamine and with acetaminophen prior to the first 4 infusions. For mild or moderate infusion reactions, need to interrupt or slow the rate of infusion. For severe or life-threatening infusion reactions, the infusion should be stopped and permanently discontinued.
3. Monitor thyroid and adrenal function prior to and during therapy.
4. Monitor patients for hyperglycemia and/or other signs and symptoms of diabetes.
5. Dose modification is not needed for patients with renal dysfunction.
6. Dose modification is not needed for patients with mild or moderate hepatic dysfunction. Avelumab has not been studied in patients with severe hepatic dysfunction.
7. Pregnancy category D.

TOXICITY 1
Fatigue and asthenia.

TOXICITY 2
Infusion-related reactions.

TOXICITY 3
Nausea, vomiting, decreased appetite.

TOXICITY 4
Musculoskeletal symptoms, which may present with arthralgias, oligoarthritis, polyarthritis, tenosynovitis, polymyalgia rheumatica, and myalgias.

TOXICITY 5
Colitis with diarrhea and abdominal pain.

TOXICITY 6
Endocrinopathies, including hypophysitis, thyroid disorders, adrenal insufficiency, and diabetes.

TOXICITY 7
Neurologic toxicity with neuropathy, myositis, and myasthenia gravis, Guillain-Barré syndrome, or meningoencephalitis.

TOXICITY 8
Skin rash and pruritus.

TOXICITY 9
Dyspnea and cough.

TOXICITY 10
Hepatotoxicity with elevations in liver function tests (SGOT, SGPT) and serum bilirubin.

TOXICITY 11
Anemia, thrombocytopenia, lymphopenia, and neutropenia.

TOXICITY 12
Pancreatitis with elevations in serum lipase and serum amylase.

Axicabtagene ciloleucel

TRADE NAMES	Yescarta	**CLASSIFICATION**	CAR T-cell therapy
CATEGORY	Cellular therapy, immunotherapy	**DRUG MANUFACTURER**	Kite, Gilead

MECHANISM OF ACTION

- Axicabtagene ciloleucel is a CD19-directed genetically modified autologous T-cell immunotherapy that binds to CD19-expressing target cells and normal B cells.
- Axicabtagene ciloleucel is prepared from the patient's own peripheral blood mononuclear cells, which are enriched for T cells, and then genetically modified ex vivo by retroviral transduction to express a chimeric antigen receptor (CAR) made up of a murine anti-CD19 single-chain variable fragment linked to CD28 and CD3-zeta co-stimulatory domains. The anti-CD19 CAR T cells are expanded ex vivo and infused back to the patient, where they target CR19-expressing cells.
- Lymphocyte depletion conditioning regimen with cyclophosphamide and fludarabine leads to increased systemic levels of IL-15 and other pro-inflammatory cytokines and chemokines that enhance CAR T-cell activity.
- The conditioning regimen may also decrease immunosuppressive regulatory T cells, activate antigen-presenting cells, and induce pro-inflammatory tumor cell damage.
- Clinical studies have shown an association between higher CAR T-cell levels in peripheral blood and clinical response.

MECHANISM OF RESISTANCE
Selection of alternatively spliced CD19 isoforms that lack the CD19 epitope recognized by the CAR T cells.

ABSORPTION
Administered only via the IV route.

DISTRIBUTION

Peak levels of anti-CD19 CAR T cells are observed within the first 1–2 weeks after infusion.

METABOLISM

Metabolism of axicabtagene ciloleucel has not been well characterized.

INDICATIONS

FDA-approved for the treatment of relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

DOSAGE RANGE

A lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m^2 IV and fludarabine 30 mg/m^2 IV on the fifth, fourth, and third day should be administered before infusion of axicabtagene ciloleucel.

Patients should be premedicated with acetaminophen 650 mg PO and diphenhydramine 12.5 mg IV 1 hour before infusion of axicabtagene ciloleucel.

Dosing of axicabtagene ciloleucel is based on a target dose of 2×10^6 CAR-positive viable T cells per kilogram of body weight, with a maximum of 2×10^8 CAR-positive viable T cells.

DRUG INTERACTIONS

None have been well characterized to date.

SPECIAL CONSIDERATIONS

1. Axicabtagene ciloleucel is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).
2. Monitor for hypersensitivity infusion reactions. Patients should be premedicated with acetaminophen 650 mg PO and diphenhydramine 12.5 mg IV at 1 hour prior to CAR T-cell infusion. Prophylactic use of systemic corticosteroids should be avoided, as they may interfere with the clinical activity of axicabtagene ciloleucel.
3. Monitor patients at least daily for 7 days following infusion for signs and symptoms of cytokine release syndrome (CRS), which may be fatal or life-threatening in some cases. Patient need to be monitored for up to 4 weeks after infusion. Please see package insert for complete guidelines regarding the appropriate management for CRS. This is a black-box warning.
4. Monitor for signs and symptoms of neurologic toxicities, which may be fatal or life-threatening in some cases. This is a black-box warning.
5. Monitor for signs and symptoms of infection.
6. Monitor CBCs periodically after infusion.
7. Immunoglobulin levels should be monitored after treatment with axicabtagene ciloleucel. Infection precautions, antibiotic prophylaxis, and immunoglobulin replacement may need to be instituted.

8. Patients should be advised not to drive and not to engage in operating heavy or potentially dangerous machinery for at least 8 weeks after receiving axicabtagene ciloleucel.
9. Patients will require lifelong monitoring for secondary malignancies.
10. Pregnancy category D. Breastfeeding should be avoided.

TOXICITY 1
Hypersensitivity infusion reactions.

TOXICITY 2
CRS with fever, hypotension, tachycardia, chills, and hypoxia. More serious events include cardiac arrhythmias (both atrial and ventricular), decreased cardiac ejection fraction, cardiac arrest, capillary leak syndrome, hepatotoxicity, renal failure, and prolongation of coagulation parameters PT and partial thromboplastin time (PTT).

TOXICITY 3
Neurologic toxicity, which includes headache, delirium, encephalopathy, tremors, dizziness, aphasia, imbalance and gait instability, and seizures.

TOXICITY 4
Myelosuppression with thrombocytopenia and neutropenia, which in some cases can be prolonged for several weeks after infusion.

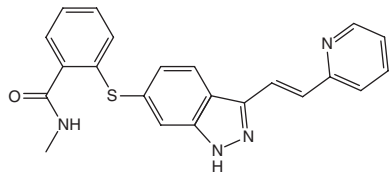
TOXICITY 5
Infections with non-specific pathogen, bacterial, and viral infections most common.

TOXICITY 6
Hypogammaglobulinemia.

TOXICITY 7
Hepatitis B reactivation.

TOXICITY 7
Secondary malignancies.

Axitinib



TRADE NAMES	Inlyta, AG-13736	**CLASSIFICATION**	Signal transduction inhibitor, antiangiogenesis agent
CATEGORY	Targeted agent	**DRUG MANUFACTURER**	Pfizer

MECHANISM OF ACTION

- Small-molecule inhibitor of the ATP-binding domains of VEGFR-1, VEGFR-2, and VEGFR-3 tyrosine kinases.
- Shows limited effects on platelet-derived growth factor (PDGFR) and c-Kit (CD117).
- Interferes with processes involved in tumor growth and proliferation, metastasis, and angiogenesis.

MECHANISM OF RESISTANCE

- Increased expression of VEGFR-1, VEGFR-2, and VEGFR-3.
- Activation of angiogenic switch with increased expression of alternative pro-angiogenic pathways.
- Increased pericyte coverage to tumor vessels with increased expression of VEGF and other pro-angiogenic factors.
- Recruitment of pro-angiogenic inflammatory cells from bone marrow, such as tumor-associated macrophages, monocytes, and myeloid-derived suppressor cells (MDSCs).

ABSORPTION

Rapid oral absorption when given with food, with a mean absolute bioavailability of approximately 60%. Peak plasma concentrations are reached 2–6 hours after oral ingestion, and steady state is achieved within 2–3 days of dosing.

DISTRIBUTION

Volume of distribution is 160 L. Extensively bound (> 99%) to albumin and to α1-acid glycoprotein.

METABOLISM

Metabolism is primarily in the liver by CYP3A4 and CYP3A5 enzymes and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1. Sulfoxide and N-glucuronide metabolites are significantly less potent against VEGFR-2 compared to parent drug. Hepatobiliary excretion is the main route of drug elimination. Approximately 40% is eliminated in feces, of which 12% as unchanged drug, and 23% in the urine as metabolites. The terminal half-life is 2–5 hours.

INDICATIONS

1. FDA-approved for the treatment of advanced renal cell carcinoma after failure of one prior systemic therapy.
2. FDA-approved in combination with avelumab for the first-line treatment of renal cell carcinoma (RCC).

DOSAGE RANGE

Recommended starting dose for RCC is 5 mg PO bid. Dose can be increased or decreased based on tolerability or safety. Dose increase—If dose is tolerated for at least 2 consecutive weeks, dose can be increased to 7 mg PO bid, then up to 10 mg PO bid. Dose reduction—To minimize the risk of adverse events, the dose can be decreased to 3 mg PO bid, then to 2 mg PO bid.

DRUG INTERACTION 1

Drugs such as ketoconazole, itraconazole, erythromycin, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole may decrease the rate of metabolism of axitinib, resulting in increased drug levels and potentially increased toxicity.

DRUG INTERACTION 2

Drugs such as rifampin, phenytoin, phenobarbital, carbamazepine, and St. John's Wort may increase the rate of metabolism of axitinib, resulting in its inactivation and lower effective drug levels.

DRUG INTERACTION 3

Proton pump inhibitors, H2-receptor inhibitors, and antacids—Drugs that alter the pH of the upper GI tract may alter axitinib solubility, thereby reducing drug bioavailability and decreasing systemic drug exposure.

SPECIAL CONSIDERATIONS

1. No dose adjustment is needed for patients with creatinine clearance (CrCl) > 15 mL/min. However, caution should be used in patients with end-stage renal disease.
2. Dose adjustment is not required in patients with mild hepatic impairment. The dose of axitinib should be reduced by 50% in patients with moderate impairment (Child-Pugh Class B). Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).
3. Axitinib should be taken approximately 12 hours apart with or without food and should be taken with water.
4. Patients should be warned of the increased risk of arterial thromboembolic events, including myocardial ischemia and stroke.
5. Patients should be warned of the increased risk of venous thromboembolic events, including DVT and PE.
6. Blood pressure should be well controlled prior to starting axitinib therapy. Closely monitor blood pressure while on therapy and treat as needed with standard oral antihypertensive medication.
7. Axitinib therapy should be stopped at least 24 hours prior to scheduled surgery.
8. Closely monitor thyroid function tests and thyroid-stimulating hormone (TSH), as axitinib therapy results in hypothyroidism.
9. Closely monitor LFTs and serum bilirubin while on therapy.
10. Avoid Seville oranges, starfruit, pomelos, grapefruit, and grapefruit products while on therapy.
11. Pregnancy category D. Breastfeeding should be avoided.

TOXICITY 1
Hypertension occurs in 40% of patients and usually within the first month of treatment.

TOXICITY 2
Increased risk of arterial and venous thromboembolic events.

TOXICITY 3
Bleeding complications.

TOXICITY 4
GI perforations and wound-healing complications.

TOXICITY 5
Diarrhea, nausea/vomiting, and constipation.

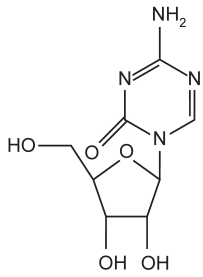
TOXICITY 6
Proteinuria develops in up to 10% of patients.

TOXICITY 7
Hypothyroidism.

TOXICITY 8
Elevations in SGOT/SGPT and serum bilirubin.

TOXICITY 9
Reversible posterior leukoencephalopathy syndrome (RPLS) occurs rarely (< 1%) and presents with headache, seizure, lethargy, confusion, blindness, and other visual disturbances.

Azacitidine



TRADE NAME	Vidaza	**CLASSIFICATION**	Antimetabolite, hypomethylating agent
CATEGORY	Chemotherapy drug	**DRUG MANUFACTURER**	Celgene

MECHANISM OF ACTION

- Cytidine analog.
- Cell cycle–specific with activity in the S-phase.
- Requires activation to the nucleotide metabolite azacitidine triphosphate.
- Incorporation of azacitidine triphosphate into RNA, resulting in inhibition of RNA processing and function.
- Incorporation of azacitidine triphosphate into DNA, resulting in inhibition of DNA methyltransferases, which then leads to loss of DNA methylation and gene reactivation. Aberrantly silenced genes, such as tumor suppressor genes, are reactivated and expressed.

MECHANISM OF RESISTANCE

None well characterized to date.

ABSORPTION

Not available for oral use and is administered via the SC and IV route. The bioavailability of SC azacitidine is 89% relative to IV azacitidine.

DISTRIBUTION

Distribution in humans has not been fully characterized. The drug is able to cross the blood-brain barrier.

METABOLISM

Precise route of elimination and metabolic fate of azacitidine are not well characterized in humans. In vitro studies suggest that azacitidine may be metabolized by the liver. One of the main elimination pathways is via deamination by cytidine deaminase, found principally in the liver but also in plasma, granulocytes, intestinal epithelium, and peripheral tissues. Urinary excretion is the main route of elimination of the parent drug and its metabolites. The half-lives of azacitidine and its metabolites are approximately 4 hours.

INDICATIONS

FDA-approved for treatment of patients with myelodysplastic syndromes (MDS), including refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia.

DOSAGE RANGE

Recommended dose is 75 mg/m^2 SC or IV daily for 7 days. Cycles should be repeated every 4 weeks.

DRUG INTERACTIONS
None characterized to date.

SPECIAL CONSIDERATIONS
1. Patients should be treated for a minimum of 4 cycles, as it may take longer than 4 cycles for clinical benefit.
2. Patients should be pretreated with effective antiemetics to prevent nausea/vomiting.
3. Monitor complete blood counts on a regular basis during therapy.
4. Use with caution in patients with underlying kidney dysfunction. If unexplained elevations in BUN or serum creatinine occur, the next cycle should be delayed, and the subsequent dose should be reduced by 50%. If unexplained reductions in serum bicarbonate levels to < 20 mEq/L occur, the subsequent dose should be reduced by 50%.
5. Pregnancy category D. Breastfeeding should be avoided.

TOXICITY 1
Myelosuppression with neutropenia and thrombocytopenia.

TOXICITY 2
Fatigue and anorexia.

TOXICITY 3
GI toxicity in the form of nausea/vomiting, constipation, and abdominal pain.

TOXICITY 4
Renal toxicity with elevations in serum creatinine, renal tubular acidosis, and hypokalemia.

TOXICITY 5
Peripheral edema.