Objectives

- Identify new drugs that have been FDA approved for cancer treatment in 2013/2014.
- Recognize how new drugs are given generic names.
- Identify how to gain information about new drugs based on the generic naming system.

Progress in Cancer Therapies 2014

- 3 new cancer/hematology drugs have gained FDA approval to date
  - Ramucirumab (Cyramza™) Lilly as single agent for advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma after being treated with a fluoropyrimidine or platinum containing regimen
  - Ceritinib (Zykadia™) Novartis as single agent for pts with ALK positive metastatic non-small cell lung cancer who have progressed on or are intolerant to crizotinib
  - Siltuximab (SylvaT™) Janssen as single agent for patients with multicentric Castleman's disease who are HIV and HHV-8 negative

A Few Questions for You

- 3 new cancer/hematology drugs have gained FDA approval to date
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Unless otherwise noted, all graphic slides are courtesy of the National Cancer Institute Advances in Targeted Therapy Tutorial

http://www.cancer.gov/cancertopics/understandingcancer/targetedtherapies
Progress in Cancer Therapies 2014

- 2 molecularly targeted agents gained new approvals
  - Ibrutinib (Imbruvica™) for chronic lymphocytic leukemia after at least 1 previous therapy
  - Ofatumumab (Arzerra™) for previously untreated patients with chronic lymphocytic leukemia

- 2 molecularly targeted therapies gained FDA approval to be used in combination:
  - The FDA has granted an accelerated approval to the combination of the MEK inhibitor trametinib (Mekinist™) and the BRAF inhibitor dabrafenib (Tafinlar®) as a treatment for patients with unresectable or metastatic melanoma who harbor a BRAF V600E or V600K mutation.

- Mercaptopurine (Purixan): Oral suspension approved for ALL

http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm

Progress in Cancer Therapies 2013

- 7 new molecularly targeted agents FDA approved for cancer treatment:
  - pomalidomide (Pomalyst®)
  - ado-trastuzumab emtansine (Kadcyla™)
  - dabrafenib (Tafinlar™)
  - trametinib (Mekinist™)
  - afatinib (Gilotrif™)
  - obinutuzumab (Gazyva™)
  - ibrutinib (Imbruvica™)

- 1 radiotherapeutic agent FDA approved for cancer treatment:
  - radium 223 dichloride (Xofigo® Injection)

http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm

Seven New Molecularly Targeted Therapies
FDA approved in 2013

- pomalidomide (Pomalyst®) Celgene: Multiple myeloma after receiving at least 2 prior therapies that have included lenalidomide and bortezomib and after demonstrating disease progression on or within 60 days of completion of last therapy

- ado-trastuzumab emtansine (Kadcyla™) Genentech: Patients with HER2-positive (HER2+) metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination, for metastatic disease or developed disease recurrence during or within six months of completing adjuvant therapy

http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm

Seven New Molecularly Targeted Therapies
FDA approved in 2013

- dabrafenib (Tafinlar™) GlaxoSmithKline: Treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.

- trametinib (Mekinist™) GlaxoSmithKline: Treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutation as detected by an FDA-approved test.

http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm

Seven New Molecularly Targeted Therapies
FDA approved in 2013

- afatinib (Gilotrif™), Boehringer Ingelheim Pharmaceuticals: First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. The safety and efficacy of afatinib have not been established in patients whose tumors have other EGFR mutations. Concurrent with this action, FDA approved the therascreen EGFR RGQ PCR Kit (QIAGEN) for detection of EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm

Seven New Molecularly Targeted Therapies
FDA approved in 2013

- obinutuzumab (Gazyva™) Genentech, Inc.; previously known as GA101: for use in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL).

- ibrutinib (Imbruvica™) Pharmacycics, Inc.: treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm
Radium 223 dichloride (Xofigo® Injection) Bayer HealthCare Pharmaceuticals: Treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease. Radium 223 dichloride, also known as Radium Ra 223 dichloride, is an alpha-particle emitting radiotherapeutic drug that mimics calcium and forms complexes with hydroxyapatite at areas of increased bone turnover, such as bone metastases.

One New Radiotherapeutic Agent
FDA approved thus far in 2013

- radium 223 dichloride (Xofigo® Injection) Bayer HealthCare Pharmaceuticals: Treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease. Radium 223 dichloride, also known as Radium Ra 223 dichloride, is an alpha-particle emitting radiotherapeutic drug that mimics calcium and forms complexes with hydroxyapatite at areas of increased bone turnover, such as bone metastases.

http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm

Progress in Cancer Therapies 2013

- 7 molecularly targeted therapies gained new FDA approved indications
  - bevacizumab for use in metastatic colorectal cancer with a fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy after progression on a first-line bevacizumab-containing regimen
  - regorafenib for use in locally advanced, metastatic gastrointestinal stromal tumor (GIST) previously treated with imatinib, sunitinib and sunitinib malate.
  - erlotinib (Tarceva®, Astellas Pharma Inc.) for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations. This indication for erlotinib is being approved concurrently with the cobas® EGFR Mutation Test, a companion diagnostic test for patient selection.

http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm

Progress in Cancer Therapies 2013

- 7 molecularly targeted therapies gained new FDA approved indications
  - docetaxel (Taxotere® injection, Sanofi Inc.) for the treatment of adults and elderly patients with metastatic breast cancer who did not tolerate other treatment
  - idelalisib capsules (Zydelig®, Celgene Corporation) for the treatment of patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib
  - pertuzumab injection (Perjeta®, Genentech, Inc.) for use in combination with trastuzumab and docetaxel for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory or early-stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer. Pertuzumab was first approved in June 2013, for treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic breast cancer
  - naxitinib (Nexavar, Bayer HealthCare) to include the treatment of patients with radioative iodine (RAI)-resistant metastatic differentiated thyroid cancer (DTC)

http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm

Changes in Cancer Therapies 2013

- FDA in October 2013 asked the manufacturer of ponatinib (Iclusig®) to suspend marketing and sales because of the risk of life-threatening blood clots and severe narrowing of blood vessels.
- December 2013 the FDA allowed the drug to be marketed again with a black box warning about the potential for vascular occlusion, heart failure, and hepatotoxicity. A REMS program is also in place as well as revised indications for patient population and updated dosing considerations.
- Originally approved by FDA in December 2012 for use in chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL), who are no longer benefiting from previous treatment or who did not tolerate other treatment.

http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm

How are Targeted Therapies different than Cytotoxic Chemotherapy?

New therapies disrupt cancer processes with precision.

http://www.cancer.gov/cancertopics/understandingcancer/targetedtherapies
Tips for Learning about New Cancer Therapies

- Know the type of drug
  - Small molecule, monoclonal antibody
- Know the generic name
- Know the target and what it does normally in the body/what other FDA approved drugs are similar
- Know if the drug is “personalized” to tumor’s genetic profile

Types of Targeted Therapies

Small Molecules can cross cell membranes

Example of a small molecule: imatinib (Gleevec®)
Once potential targets are identified, then drugs are designed to best attack the target.

Monoclonal antibodies work outside the cell (can prevent signaling molecules/receptors from interacting).

Monoclonal antibodies work outside the cell (can deliver radioactive molecules or toxins to cancer cell).

Once inside the cell the cytotoxic is released and causes cell death.

Monoclonal antibodies work outside the cell (can trigger an immune response that destroys the cell).

Example of a monoclonal antibody: trastuzumab (Herceptin®).
Tips for Learning about New Cancer Therapies

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- Know the generic name

- Know the target and what is does normally in the body/what other FDA approved drugs are similar

- Know if the drug is “personalized” to tumor’s genetic profile

I know the generic name; but how do I pronounce it??


Nibs (tinibs, anibs, rafenibs)

- Small molecules

- Oral
  - Adherence
  - Possible drug/food, drug/drug interactions
  - Patient education

- Examples
  - Erlotinib, imatinib, pazopanib, sunitinib, sorafenib,

Mabs

- Monoclonal antibodies

- Intravenous/subcutaneous

- Potential for infusion reactions

- Examples: tositumomab, rituximab, trastuzumab, panitumumab, bevacizumab

What does the name mean?

Monoclonal antibody = mab

- tositumomab and iodine 131
  - mo = mouse

- rituximab
  - xi = chimeric or cross between mouse and human

- trastuzumab, bevacizumab
  - zu = humanized

- panitumumab
  - u = fully human

What does the name mean?

- tositumomab and iodine 131
  - mo = mouse

What does the name mean? 
**Tu** = tumor

- tositumomab and iodine $\text{I}^{131}$
- rituximab
- trastuzumab
- panitumumab


What does the name mean? 
**ci** = circulatory
**li or l** = immunomodulator

- Bevacizumab
- Ipilimumab


Tips for Learning about New Cancer Therapies

- Know the generic name
- Know the type of drug
  - Small molecule, monoclonal antibody
- Know the target and what it does normally in the body/ know what other FDA approved drugs are similar
- Know if the drug is “personalized” to tumor’s genetic profile

Back to those new drugs......

**pomalidomide**

- **pomalidomide** (Pomalyst®) Celgene: Multiple myeloma after receiving at least 2 prior therapies that have included lenalidomide and bortezomib and after demonstrating disease progression on or within 60 days of completion of last therapy
  - Oral
  - Potential drug/drug and drug/food interactions with CYP3A, CYP3A4 or P-gp inducers/inhibitors
  - Potential that cigarette smoking may reduce the efficacy of pomalidomide
  - Thalidomide analogue. Pomalyst REMS program. Immunomodulatory with anti-neoplastic activity

[http://www.pomalyst.com](http://www.pomalyst.com)

**ado-trastuzumab emtansine**

- **ado-trastuzumab emtansine** (Kadcyla®) Genentech: Patients with HER2-positive (HER2+) metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination, for metastatic disease or developed disease recurrence during or within six months of completing adjuvant therapy
  - Monoclonal antibody, humanized; antibody-drug conjugate
  - IV infusion/potential for hypersensitivity rxns
  - Target is on the tumor; carries a microtubule cytotoxic drug
  - Cytotoxic side effects, plus anti-HER2 side effects
  - Targets: HER2/neu. Means HER2 testing must be done on the tumor to know if this drug is appropriate for patient (personalized). Similar drug: trastuzumab; however, this is the first antibody-drug conjugate for breast cancer

[http://www.kadcyla.com](http://www.kadcyla.com)
**dabrafenib**

- **dabrafenib (Tafinlar™)** GlaxoSmithKline: Treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test
  - Oral
  - Potential drug/drug and drug/food interactions: Consider co-administration with strong CYP3A4, CYP2C19, CYP2C9, CYP1A2 inhibitors or moderate CYP3A4 inhibitors. Drug interactions with CYP3A4 inhibitors may result in higher plasma levels of dabrafenib.
  - Targets: BRAF kinase. Tyrosine kinase inhibitor. BRAF testing must be done to determine if drug is appropriate treatment (personalized).
  - Side effects: Similar to vemurafenib. Hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, and palmar-plantar erythrodysesthesia syndrome, primary cutaneous malignancies, seborrheic dermatitis.

**http://www.tafinlar.com**

**afatinib**

- **afatinib (Gilotrif™)** Boehringer Ingelheim Pharmaceutical: First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. The safety and efficacy of afatinib have not been established in patients whose tumors have other EGFR mutations. Concurrent use with P-gp inhibitors may lead to increased plasma concentrations. Concomitant use with agents that are sensitive substrates of CYP3A4, CYP2C19, CYP2C9, CYP1A2, or CYP3A4 may result in loss of efficacy of these agents.
  - Oral
  - Potential drug/drug and drug/food interactions: Avoid coadministration with strong cytochrome P450 (CYP) inhibitors because of potential for drug interactions (such as with strong CYP3A4 inhibitors). Drugs that induce cytochrome P450 (CYP) enzymes can decrease afatinib exposure. Increase GILOTRIF by 10 mg per day as tolerated.
  - Targets: Kinase domains of EGFR (Erbb1), HER2 (Erbb2), and HER4 (Erbb4). EGFR testing is performed to determine if drug should be used (personalized).
  - Side effects: Similar to erlotinib. Diarrhea, dermatologic side effects such as rash, flushing, acneforms, and hand-foot syndrome, primary cutaneous malignancies, seborrheic dermatitis, decreased LVEF.

**http://www.gilotrif.com**

**ibrutinib (Imbruvica™)**

- **ibrutinib (Imbruvica™)** Pharmacyclics, Inc.: Treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.
  - Oral
  - Potential drug/drug and drug/food interactions: Avoid co-administration with strong and moderate CYP3A4 inhibitors. If a moderate CYP3A4 inhibitor must be used, reduce IMBRUVICA dose (1.4-2.4). Avoid co-administration with strong P-gp inhibitors (e.g., atazanavir, ritonavir).
  - Targets: Bruton’s tyrosine kinase. Small molecule.
  - Side effects: Infections, myelosuppression, hemorrhage, renal toxicity, N/V, peripheral edema, fatigue, musculoskeletal pain, diarrhea, second primary cancers.

**http://www.imbruvica.com**

**trame tinib**

- **trametinib (Mekinist™)** GlaxoSmithKline: Treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutation as detected by an FDA-approved test.
  - Oral
  - No formal clinical studies have been conducted to evaluate human cytochrome P450 (CYP) enzyme-mediated drug interactions with trametinib. Based on in vitro studies, trametinib is not an inhibitor of CYP3A.
  - Targets: Mitogen-activated extracellular signal regulated kinase (MEK) and MEK5 activation of MEK1 and MEK2. MEK proteins are upstream regulators of the extracellular signal-regulated kinase (ERK) pathway, which promotes cellular proliferation. BRAF V600 mutations result in constitutive activation of the BRAF pathway, which includes MEK1 and MEK2. BRAF testing must be done to determine if drug is appropriate treatment (personalized).
  - MIK inhibitor side effects: Cardiomyopathy/decreased EFV, retinal vein occlusion, retinal pigment epithelial detachment, skin toxicity, interstitial lung disease.

**http://www.mekinist.com**

**obinutuzumab (Gazyva™)**

- **obinutuzumab (Gazyva™)** injection, for intravenous use, made by Genentech, Inc.; previously known as GA101) for use in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL).
  - Monoclonal antibody, humanized.
  - IV infusion/potential for hypersensitivity reactions. Must premedicate!
  - Target is on the tumor; CD20 antigen on the surface of pre B and mature B lymphocytes.
  - Side effects include infusion reactions (60%), neutropenia, thrombocytopenia, anemia, tumor lysis syndrome. Boxed warnings for Hepatitis B virus reactivation and progressive multifocal leukoencephalopathy.

**http://www.gazyva.com**

**radium 223 dichloride**

- **radium 223 dichloride (Xofigo™) Injection, for intravenous use, made by Genentech, Inc.; previously known as GA101) injection, for intravenous use, made by Genentech, Inc.; previously known as GA101). Radium 223 dichloride, also known as Radium Ra 223 dichloride, is an alpha particle emitting radiotherapeutic drug that targets calcium and forms complexes with hydroxyapatite at areas of increased bone turnover, such as in bone metastases.
  - Intravenous injection over one minute every 4 weeks X 6
  - Mechanism: Alpha particle-emitting radionuclide (ra dium-223 dichloride), which mimics calcium and forms complexes with hydroxyapatite at areas of increased bone turnover, such as bone metastases.
  - Side effects: Bone marrow suppression x, nausea, diarrhea, vomiting, and peripheral edema.

Patient education: Follow good hygiene practices while receiving radium-223 and for at least 1 week after the last injection, in order to minimize radiation exposure. Patients with impaired hearing who are administered radium-223 should wear hearing protection for 48 hours after each use. Clothing worn with patient local must be washed promptly and separately from other clothing. Clothing should be kept separate from other clothing. Clothing should be washed separately. Patients should have their hands and fingernails cleaned regularly. Hands, wearing gloves and hand washing will protect caregivers.

**http://www.xofigo.com**
The New Kids on the Block

Let’s Build the Slides

ramucirumab (Cyramza™)

- ramucirumab (Cyramza™) Genentech, Inc: as a single agent for unresectable or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma after being treated with a fluoropyrimidine or platinum containing regimen
  - Monoclonal antibody
  - What type of monoclonal??

www.cyramza.com

ramucirumab (Cyramza™)

- ramucirumab (Cyramza™) Genentech, Inc: as a single agent for unresectable or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma after being treated with a fluoropyrimidine or platinum containing regimen
  - Monoclonal antibody, fully human
  - Possibility of hypersensitivity reactions??

www.cyramza.com

ramucirumab (Cyramza™)

- ramucirumab (Cyramza™) Genentech, Inc: as a single agent for unresectable or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma after being treated with a fluoropyrimidine or platinum containing regimen
  - Monoclonal antibody, fully human
  - IV infusion/potential for hypersensitivity rxns
  - Target on tumor or elsewhere and where?? Personalized?

www.cyramza.com

ramucirumab (Cyramza™)

- ramucirumab (Cyramza™) Genentech, Inc: as a single agent for unresectable or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma after being treated with a fluoropyrimidine or platinum containing regimen
  - Monoclonal antibody, fully human
  - IV infusion/potential for hypersensitivity rxns
  - Target is not on the tumor; it is in the circulatory system. Targets vascular endothelial growth factor (VEGF). Antiangiogenic. Not personalized.
  - Side effects??!

www.cyramza.com
ramucirumab (Cyramza™)
- ramucirumab (Cyramza™) Genentech, Inc: as a single agent for unresectable or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma after being treated with a fluoropyrimidine or platinum containing regimen
  - Monoclonal antibody, fully human
  - IV infusion/potential for hypersensitivity reactions
  - Target is not on the tumor; it is in the circulatory system. Targets vascular endothelial growth factor (VEGF). Antiangiogenic. Not personalized.
  - Side Effects: Hypertension, hemorrhage, diarrhea, headache, intestinal obstruction

www.cyramza.com

Ceritinib (Zykadia™)
- Ceritinib (Zykadia™) as single agent for pts with ALK positive metastatic non-small cell lung cancer who have progressed on or are intolerant to crizotinib
  - Small molecule: oral
  - Potential for drug/drug or drug/food interactions?

www.zykadia.com

Ceritinib (Zykadia™)
- Ceritinib (Zykadia™) as single agent for pts with ALK positive metastatic non-small cell lung cancer who have progressed on or are intolerant to crizotinib
  - Small molecule: oral
  - Drug/food interactions with CYP3A inhibitors, inducers, and substrates
  - Target? Is it personalized?

www.zykadia.com

Ceritinib (Zykadia™)
- Ceritinib (Zykadia™) as single agent for pts with ALK positive metastatic non-small cell lung cancer who have progressed on or are intolerant to crizotinib
  - Small molecule: oral
  - Drug/food interactions with CYP3A inhibitors, inducers, and substrates
  - Targets ALK (most active) and also IGF-1R, InsR, and ROS1. Personalized to ALK positive tumors
  - Side effects: GI toxicity, hepatotoxicity, interstitial lung disease, QT prolongation, bradycardia, hyperglycemia, fatigue

www.zykadia.com
Siltuximab (Sylvant™)

- Siltuximab (Sylvant™) as single agent for patients with multicentric Castleman’s disease who are HIV and HHV-8 negative
  - Monoclonal or small molecule?
  - IV or oral?
  - Target? Personalized?
  - Side effects?

www.zydakia.com

Siltuximab (Sylvant™)

- Siltuximab (Sylvant™) as single agent for patients with multicentric Castleman’s disease who are HIV and HHV-8 negative
  - Monoclonal antibody; chimeric
  - IV infusion/potential for hypersensitivity rxs
  - Target: interleukin 6; IL6 antagonist. IL6 overproduction linked to systemic manifestations of MCD.
  - Side effects: hypersensitivity rxs, infections, GI perforation, no live vaccines allowed during tx, pruritis, increased weight, rash, hyperuricemia

www.zydakia.com

Trend with New Agents is Multidisciplinary Approach

- Dermatology: Rash, other dermatologic conditions, skin cancers
- Ophthalmology: Vision issues
- Cardiology: Prolonged QTC intervals, lowering of LVEF, hypertension
- Gastroenterology: Development of polyps, colitis
- Endocrinology: hypophysitis, diabetes, thyroid issues

Future Directions

Targeting Cancer Cell Processes

- Increased signaling for cell growth
- Cancer cell death
- Increased blood vessel formation

http://www.cancer.gov/cancertopics/understandingcancer/targetedtherapies

Enhancing immune system response

http://www.cancer.gov/cancertopics/understandingcancer/targetedtherapies
Targeting genetic alterations in the tumor

Drug resistance

Drug resistance

You can try this at home!

References

- http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/noc21579.htm

References

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- http://www.pomalyst.com
- http://www.sylvant.com
- http://www.tafinlar.com
- http://www.xofigo.com
- http://www.zykadia.com