CRIZOTINIB (XALCORI®, PFIZER)

- **Indications**: treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.
- Kinase Inhibitor - specifically ALK receptor tyrosine kinase.

CRIZOTINIB

- Targets the EML4-ALK fusion gene
  - key oncogenic driver that contributes to cell proliferation and tumor survival. *1.7% of lung cancers; non smokers
- Crizotinib has been shown to block important growth and survival pathways in tumors, which may lead to regression or stabilization of tumors

CRIZOTINIB

- **Dose**: 250 mg taken orally twice daily with or without food.
- Dosing interruption and/or dose reduction
  - 200 mg taken orally twice daily based on individual safety and tolerability
  - Subsequent reduction to 250 mg orally once daily if necessary.
- The most common adverse reactions (=25%)
  - vision disorders, nausea, diarrhea, vomiting, edema, and constipation

PEGINTERFERON ALFA-2B (SYLATRON®, MERCK)

- **Indication**: Adjuvant treatment of melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy.
- **Contraindications**:
  - patients with hx of anaphylaxis to peginterferon alfa-2b or interferon alfa-2b
  - patients with autoimmune hepatitis
  - patients with hepatic decompensation (Childs class B & C).
- **Warning**: Permanently discontinue in patients with severe or worsening s/sx of depression, psychosis, or encephalopathy.
**PEGINTERFERON ALFA-2B**

- Once a week subq injection; self injectable
  - 6 mcg/kg/week x 8 doses, then followed by 3 mcg/kg/week for up to 5 years.
- Premed: acetaminophen 500 – 1000 mg orally 30 min. prior to first dose and then PRN.
- Dose Modifications:
  - Hold if ANC <0.5 X 10^9/L; PLT <50 X 10^9/L; ECOG PS>2; non-heme toxicity >3
  - And resume at reduced dose when toxicity recovered
- Permanently discontinue for:
  - Persistent or worsening severe neuropsychiatric disorders
  - Grade 4 non-heme toxicity
  - Inability to tolerate a dose of 1 mcg/kg/week
  - New or worsening retinopathy.

**IPILIMUMAB**

(YERVOY®, BRISTOL-MEYERS SQUIBB)

- Ipilimumab is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody indicated for the treatment of unresectable or metastatic melanoma.
- Dose: 3 mg/kg administered intravenously over 90 minutes every 3 weeks for a total of four doses.
- Most common adverse reactions (≥5%): fatigue, diarrhea, pruritus, rash, and colitis.

**IPILIMUMAB**

- Immune Mediated Adverse Events
  - * Boxed warning
  - Risk Evaluation & Mitigation Strategy (REMS)
  - Permanently discontinue for severe reactions.
  - Withhold dose for moderate immune-mediated adverse reactions until:
    - return to baseline
    - improvement to mild severity
    - or complete resolution
  - and patient is receiving less than 7.5 mg prednisone or equivalent per day.

**VEMURAFENIB**

(ZELBORAF®, GENENTECH)

- Indication:
  - A kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAFV600E mutation as detected by an FDA-approved test.
- Limitation of Use:
  - Not recommended for use in patients with wild-type BRAF melanoma.
**Vemurafenib**

- Available in a 240 mg tablet
- **Recommended dose:** 960 mg orally twice daily
  - 12 hours apart with or without a meal.
  - Should be swallowed whole with a glass of water.
  - Should not be chewed or crushed.
- Management of symptomatic adverse drug reactions may require dose reduction, treatment interruption, or treatment discontinuation of drug.
  - Dose reductions resulting in a dose below 480 mg twice daily are not recommended.

**Warnings & Precautions:**
- Liver abnormalities
- Photosensitivity
- Serious ophthalmologic reactions, including uveitis, iritis and retinal vein occlusion
- New primary malignant melanomas
- May cause fetal harm

**Dose Modifications:**
- Grade 1 or Grade 2 (tolerable) A.E.: Maintain dose 960 mg BID
- Grade 2 (intolerable) or Grade 3:
  - 1st: interrupt until grade 0-1 (resume at 720 mg BID)
  - 2nd: interrupt until grade 0-1 (resume at 480 mg BID)
  - 3rd: D/C
- Grade 4:
  - 1st: D/C OR interrupt until grade 0-1 and resume at 480 mg BID
  - 2nd: D/C

**Abiraterone Acetate (Zytiga, Centocor Ortho Biotech Inc)**

- **Indication:** Metastatic Prostate Ca; Castration resistant, prior tx with docetaxel
  - Targets protein cytochrome P450 17A1 (CYP17A1) which plays important role in production of testosterone.
- **Dose:** 1000 mg PO in combination with prednisone 5 mg bid
ABIRATERONE ACETATE

- Adverse Reactions:
  - Edema (27%)
  - Triglycerides increased (63%)
  - Hypokalemia (28%; grades 3/4: 5%)
  - Hypophosphatemia (24%; grades 3/4: 7%)
  - Hot flush (19%)
  - Cough (11%)

BRENTUXIMAB VEDOTIN (ADCETRIS®, SEATTLE GENETICS)

- A CD30-directed antibody-drug conjugate
- Indications:
  - Treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT)
  - or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates
- Contraindications: Concomitant use of brentuximab and bleomycin is contraindicated due to pulmonary toxicity

BRENTUXIMAB VEDOTIN

- Available: 50 mg single-use vial.
- Recommended dose: 1.8 mg/kg administered only as an intravenous infusion over 30 minutes every 3 weeks
- Continue treatment until a maximum of 16 cycles, disease progression or unacceptable toxicity.

VANDETENIB (CAPRELSA®, ASTRA ZENECA)

- Kinase Inhibitor
- Indication: treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.
  - Use in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because of the treatment related risks.
**VANDETENIB**

- **Dose:** 300 mg once daily with or without food.
  - Available in 100 mg and 300 mg tablets
- **Exposure increased in patients with impaired renal function.**
  - The starting dose of Vandetiinib should be reduced to 200 mg in patients with moderate to severe renal impairment and the QT interval should be monitored closely.
- **BLACK BOX WARNING: QT PROLONGATION, TORSADES DE POINTES, AND SUDDEN DEATH**
  *Risk Evaluation & Mitigation Strategy (REMS) required*

**Most Common A.E (> 20%)**

- diarrhea (57%)
- rash (53%)
- acne (35%)
- nausea (33%)
- hypertension (33%)
- headache (26%)
- fatigue (24%),
- decreased appetite (21%)
- abdominal pain (21%)
- The most common laboratory abnormalities (>20%)
  - decreased calcium (57%)
  - increased ALT (51%)
  - decreased glucose (24%)

**Warnings & Precautions:**

- **Renal Impairment:** The starting dose should be reduced to 200 mg in patients with moderate to severe renal impairment and the QT interval should be monitored closely.
- There is no information available for patients with end-stage renal disease requiring dialysis.
- **Hepatic Impairment:** Not recommended for patients with moderate and severe hepatic impairment, since safety and efficacy have not been established.

**ASPARAGINASE ERWINIA CHRYSANTHemi (ERWINAZE®, EUSA PHARMA)**

- **Indication:**
  - ERWINAZE (asparaginase Erwinia chrysanthemi) is an asparagine-specific enzyme indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to E. coli derived asparaginase.
  - Available in 10,000 International Units lyophilized powder per vial
Asparaginase Erwina Chrysanthemi

To substitute for a dose of pegaspargase:
- Recommended dose is 25,000 International Units/m² administered intramuscularly three times a week (Monday/Wednesday/Friday) for six doses for each planned dose of pegaspargase.

To substitute for a dose of native *E. coli* asparaginase:
- Recommended dose is 25,000 International Units/m² administered intramuscularly for each scheduled dose of native *E. coli* asparaginase.
- Limit the volume of reconstituted ERWINAZE at a single injection site to 2 mL.

Contraindications:
- History of serious hypersensitivity reactions to ERWINAZE, including anaphylaxis
- History of serious pancreatitis with prior L-asparaginase therapy
- History of serious thrombosis with prior L-asparaginase therapy
- History of serious hemorrhagic events with prior L-asparaginase therapy

Warnings and Precautions:
- Discontinue ERWINAZE if serious hypersensitivity reactions, including anaphylaxis
- Severe or hemorrhagic pancreatitis can occur
- Glucose intolerance can occur and, in some cases, may be irreversible.
  - Perform appropriate monitoring and treat hyperglycemia with insulin, as necessary
- Thrombosis, hemorrhage:
  - Discontinue ERWINAZE until resolved

Axitinib

**Indications:** treatment of advanced renal cell carcinoma after failure of one prior systemic therapy.

**Starting dose:** 5 mg orally twice daily.
- Available in: 1 mg and 5 mg tablets
- Dose adjustments can be made based on individual safety and tolerability.
- Administer approximately 12 hours apart with or without food; to be swallowed whole with a glass of water.

Most Common A.E (> 20%):
- Diarrhea
- Hypertension
- Fatigue
- Decreased appetite
- Nausea
- Constipation
- Dysphonia
- Palmar-plantar erythrodysesthesia (hand-foot) syndrome
- Weight loss
- Vomiting
- Asthenia

If a strong CYP3A4/5 inhibitor is required, decrease the Axitinib dose by approximately half.
- For patients with moderate hepatic impairment, decrease the starting dose by approximately half.
- No Contraindications.
**AXITINIB**

**Warnings and Precautions**
- Hypertensive crisis
- Thrombotic events
- Hemorrhagic events
- GI perforation & fistula including death have occurred
- RPLS (Reversible Posterior Leukoencephalopathy Syndrome)
- Hypothyroidism
- Proteinuria
- Elevated LFT's
- Fetal harm in pregnant women
- Stop drug 24 prior to surgery

AXITINIB/Inlyta Prescribing Information; Pfizer
5/3/2012

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**VISMODEGIB**

**(ERIVEDGE®, GENENTECH)**

- **Indication:**
  - treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.
  - Inhibits abnormal signaling of Hedgehog pathway

Vismodegib Prescribing Information; Genentech
5/3/2012

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**VISMODEGIB**

- **Dose:** 150 mg taken orally once daily until disease progression or until unacceptable toxicity.
  - Available in 150 mg capsules.
  - May be taken with or without food
    - capsules should be swallowed whole (not open or crushed)
  - If a dose is missed – patients should not make up that dose but resume dosing with the next scheduled dose.

Vismodegib Prescribing Information; Genentech
5/3/2012

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**VISMODEGIB**

- **Most common adverse reactions (≥10%)**
  - Muscle spasms
  - Alopecia
  - Dysgeusia & Ageusia
  - Decreased appetite & Weight loss
  - Fatigue
  - Nausea +/-Vomiting
  - Constipation or Diarrhea
  - Arthralgias

*Other Adverse Reactions:
- Amenorrhea
  - In clinical trials, a total of 3 of 10 pre-menopausal women developed amenorrhea.
- Laboratory Abnormalities
  - Treatment-emergent Grade 3 laboratory abnormalities observed in clinical trials were:
    - hyponatremia in 6 patients (4%)
    - hypokalemia in 2 patients (1%)
    - azotemia in 3 patients (2%)

Vismodegib Prescribing Information; Genentech
5/3/2012

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**RUXOLITINIB**

**(JAKAFI®, INCYTE CORP.)**

- kinase inhibitor
- **Indications:** treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.
- JAK 1 and 2 inhibitor
- Available in 5 mg, 10 mg, 15 mg, 20 mg and 25 mg tabs.

Ruxolitinib Prescribing Information; Incyte Corp
5/3/2012
**RUXOLITINIB**

**Starting Dose:**
- 20 mg BID for patients with a platelet count greater than 200 X 10^9/L
- 15 mg twice daily for patients with a platelet count between 100 X 10^9/L and 200 X 10^9/L
- Increase dose based on response to max of 25 mg BID
  - CBC before and every 2-4 weeks until dose is stabilized; modify dose for thrombocytopenia
  - DC after 6 months if no spleen reduction or sx improvement.

**Warnings & Precautions:**
- **Renal Impairment:**
  - Reduce starting dose to 10 mg BID with moderate (CrCl 30-59 mL/min) or severe renal impairment (CrCl 15-29 mL/min) and a platelet count between 100 X 10^9/L and 150 X 10^9/L.
  - Avoid in end stage renal disease (CrCl less than 15 mL/min) not requiring dialysis and in patients with moderate or severe renal impairment and a platelet count less than 100 X 10^9/L.

**Drug Interactions:**
- Strong CYP3A4 Inhibitors
  - Reduce Ruxolitinib starting dose to 10 mg twice daily for patients with a platelet count greater than or equal to 100 X 10^9/L and concurrent use of strong CYP3A4 inhibitors.
  - Avoid in patients with platelet counts less than 100 X 10^9/L.

**FDA UPDATES: BEVACIZUMAB**

**BEVACIZUMAB (AVASTIN)**

**FDA UPDATE**
- **12/2011 Indications and Usage, Metastatic Breast Cancer – Removed**
- **09/2011 Warnings and Precautions:**
  - Ovarian Failure
  - Osteonecrosis of the jaw
  - Risk of venous thromboembolic events & bleeding in patients on anti-coagulation after 1st VTE while on bevacinumab.
BEVACIZUMAB (AVASTIN) – FDA SAFETY UPDATE

Ovarian Failure
- The incidence of ovarian failure was higher (34% vs. 2%) in premenopausal women receiving Avastin in combination with mFOLFOX chemotherapy as compared to those receiving mFOLFOX chemotherapy alone for adjuvant treatment for colorectal cancer, a use for which Avastin is not approved.
- Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin.

Venous Thromboembolic Events (VTE)
- A randomized, 4-arm study in 1401 patients with mCRC, prospectively evaluating the incidence of VTE (all grades), the overall incidence of first VTE was higher in the Avastin containing arms (13.5%) than the chemotherapy alone arms (9.6%).
- Among the 116 patients treated with anticoagulants following an initial VTE event (73 in the Avastin plus chemotherapy arms and 43 in the chemotherapy alone arms), the overall incidence of subsequent VTEs was also higher among the Avastin treated patients (31.5% vs. 25.6%).
- In this subgroup of patients treated with anticoagulants, the overall incidence of bleeding, the majority of which were grade 1, was higher in the Avastin treated arms than the chemotherapy arms (27.4% vs. 20.9%).

Osteonecrosis of the jaw (ONJ)
- Reported in patients receiving bevacizumab but not bisphosphonates in the postmarketing setting.
- The pathogenesis of the osteonecrosis is unclear.
- Possible that antiangiogenic properties of bevacizumab may result in bone tissue avascularization leading to ischemic changes in the microvasculature of the jaw, resulting in osteonecrosis.

REFERENCES
- Prescribing Information/Package Inserts
  - http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm274394.htm accessed 5/2/2012

FDA-APPROVED EXPANDED INDICATIONS
- Colorectal cancer
  - Levoleucovorin
- Pancreatic neuroendocrine tumors
  - Everolimus
  - Sunitinib
- Squamous cell carcinoma of the head and neck
  - Cetuximab
**COLORECTAL CANCER (CRC)**
- Levoleucovorin (Fusilev®, Spectrum Pharmaceuticals)
  - Indication - For use in combination chemotherapy with 5-FU in the palliative treatment of patients with advanced metastatic colorectal cancer

(Spectrum Pharmaceuticals Inc. 2011. Fusilev® Package Insert.)

**LEVOLEUCOVORIN WITH 5-FLUOROURACIL DOSAGE AND ADMINISTRATION**
- Levoleucovorin 100mg/m² by slow IV injection over a minimum of 3 minutes, followed by 5-fluorouracil at 370mg/m² by IV injection
- Levoleucovorin 10mg/m² by IV injection followed by 5-fluorouracil at 425 mg/m² by IV injection
- Levoleucovorin is dosed at half the usual leucovorin dose

(Spectrum Pharmaceuticals Inc. 2011. Fusilev® Package Insert.)

**LEUCOVORIN TRIALS IN CRC**
- Expanded approval based on
  1. 2 historical trials demonstrated safety and efficacy of two different 5-fluorouracil/leucovorin combinations
  2. A third trial demonstrated no difference in response, survival or toxicity between IV leucovorin and IV l-leucovorin

(Spectrum Pharmaceuticals Inc. 2011. Fusilev® Package Insert.) (Goldberg et al., 1997)

**LEVOLEUCOVORIN TRIALS IN CRC SAFETY PROFILE**
- Side effects were similar in frequency and severity for patients who received either leucovorin or levoleucovorin
- Toxicities occurring in ≥10% of patients
  - Any grade – stomatitis, diarrhea, nausea, vomiting, asthenia, dermatitis, alopecia, anorexia, abdominal pain
  - Grade 3-4 – diarrhea, stomatitis, asthenia

(Spectrum Pharmaceuticals Inc. 2011. Fusilev® Package Insert.)

**LEVOLEUCOVORIN WARNINGS AND PRECAUTIONS**
- Rate of administration
- Potential for enhanced toxicity with 5-fluorouracil
- Potential for interaction with trimethoprim-sulfamethoxazole

(Spectrum Pharmaceuticals Inc. 2011. Fusilev® Package Insert.)

**PANCREATIC NEUROENDOCRINE TUMORS (pNET)**
- Everolimus (Afinitor®, Novartis Pharmaceuticals Corporation)
  - Approved 05/05/2011
- Sunitinib (Sutent®, Pfizer, Inc.)
  - Approved 05/20/2011

(Novartis Pharmaceuticals Corporation. 2011. Afinitor® Package Insert.)
(Pfizer, Inc. 2011. Sutent® Package Insert.)
EVEROLIMUS FOR PANCREATIC NEUROENDOCRINE TUMORS

- Everolimus (Afinitor®, Novartis Pharmaceuticals Corporation)
  - Approved 05/05/2011
  - Indicated for the treatment of patients with progressive neuroendocrine tumors of pancreatic origin (PNET) that are unresectable, locally advanced or metastatic.

(Everolimus for PNET)

EVEROLIMUS FOR PNET DOSAGE AND ADMINISTRATION

- 10mg orally once daily, at the same time
- Consistently take either with or without food
- Swallow tablet whole with a glass of water

(Clinical Trial of Everolimus)

EVEROLIMUS FOR PNET DOSE ADJUSTMENTS

- Reduce to 5mg daily with moderate hepatic impairment (Child-Pugh B)
- Reduce to 5mg daily or temporarily interrupt treatment for severe or intolerable toxicities
- Avoid concomitant use of strong Cytochrome P450 3A4 inhibitors
- Dose adjust with moderate 3A4 inhibitors (2.5mg) or inducers (10-20mg)

(Radiant-3: Non-Laboratory Safety Findings for Everolimus)

RADIANT-3: NON-LABORATORY SAFETY FINDINGS FOR EVEROLIMUS

- Adverse Reactions, Any Grade, Incidence ≥30%
  - Stomatitis (70%), rash (59%), diarrhea (50%), fatigue (45%), edema (39%), abdominal pain (36%)*, nausea (32%)*, fever (31%), headache (30%), decreased appetite (30%)
- Adverse Reactions, Grade 3/4, Incidence ≥5%
  - Stomatitis (7%) and diarrhea (5.9%)*
  - ≤5% greater frequency than placebo findings

CLINICAL TRIAL OF EVEROLIMUS IN PNET

- RAD001 in Advanced Neuroendocrine Tumors, third trial (RADIANT-3) (N=410)
  - Everolimus 10mg po daily + best supportive care vs. placebo + best supportive care (crossover to everolimus was allowed for patients who progressed on placebo)
  - Improved progression-free survival, response, and duration of response favoring everolimus (overall survival data not yet mature)

(Yao et al., 2011)

RADIANT-3: LABORATORY SAFETY FINDINGS FOR EVEROLIMUS

- Lab Abnormalities, Any Grade, Incidence ≥50%
  - ↓ Hemoglobin (86%), hyperglycemia (75%), ↑ alkaline phosphatase (74%), hypercholesterolemia (66%), ↑ bicarbonate (56%), ↑ aspartate transaminase (AST) (56%)
- Lab Abnormalities, Grade 3/4, Incidence ≥5%
  - Hyperglycemia (17%), lymphopenia (16%), ↓ hemoglobin (15%), hypophosphatemia (10%), ↑ alkaline phosphatase (8%)*
  - ≤5% greater frequency than placebo findings

(Yao et al., 2011)
**EVEROLIMUS WARNINGS AND PRECAUTIONS**
- Non-infectious pneumonitis (11%-14%)
- Infections
- Oral ulcerations (44%-64%)
- Renal failure events
- Monitor renal function, glucose, lipids and hematologic parameters prior to initiating therapy and periodically thereafter
- Avoid exposure to live vaccines

**SUNITINIB FOR PANCREATIC NEUROENDOCRINE TUMORS**
- Sunitinib (Sutent®, Pfizer, Inc.)
  - Approved 05/20/2011
  - Indicated for the treatment of progressive, well-differentiated pancreatic neuroendocrine tumors in patients with unresectable locally advanced or metastatic disease

**SUNITINIB FOR P NET DOSAGE AND ADMINISTRATION**
- 37.5mg orally, daily, with or without food, continuously without scheduled off-treatment time
- Dose interruptions and/or adjustments in decrements of 12.5mg based on safety and tolerability.
- Avoid concomitant use of strong Cytochrome P450 3A4 inhibitors
- Dose adjust with strong 3A4 inhibitors (25mg minimum) or inducers (62.5 maximum)

**CLINICAL TRIAL OF SUNITINIB IN P NET**
- Sunitinib 37.5mg orally, daily or placebo (an open-label sunitinib extension protocol was available to those who progressed on placebo) (N=171)
- Improved progression-free survival, objective response rates, and overall survival (hazard ratio for death – 0.41)

**SUNITINIB IN P NET NON-LABORATORY SAFETY FINDINGS**
- Adverse Events, Any Grade, Occurring in ≥30%
  - Diarrhea (59%), nausea (45%), asthenia (34%), vomiting (34%)*, and fatigue (32%)*
- Adverse Events, Grade 3/4, Occurring ≥5%
  - Hypertension (10%), palmar-plantar erythrodysesthesia (6%), diarrhea (5%)*, asthenia (5%)*, fatigue (5%)*, abdominal pain (5%)*

**SUNITINIB IN P NET LABORATORY SAFETY FINDINGS**
- Lab Abnormalities, Any Grade, Incidence ≥50%
  - ↑ Aspartate transaminase (AST) (72%)*, ↑ alanine aminotransferase (ALT) (61%), ↑ alkaline phosphatase (63%)*, hyperglycemia (71%)*, neutropenia (71%), ↓ hemoglobin (65%), thrombocytopenia (60%), lymphopenia (56%)

*≤5% greater frequency than placebo findings
SUNITINIB IN pNET
LABORATORY SAFETY FINDINGS
- Lab Abnormalities, Grade 3/4, Incidence ≥5%
  - Neutropenia (16%), hyperglycemia (12%), ↑ alkaline phosphatase (10%)*, lymphopenia (7%)*, ↓ phosphorus (7%)*, ↑ lipase (5%)*, ↑ aspartate transaminase (AST) (5%)*, ↑ creatinine (5%)*, thrombocytopenia (5%)*

*≥5% greater frequency than placebo findings

Pfizer, Inc. 2011. Sutent® Package Insert.)

SUNITINIB
WARNINGS AND PRECAUTIONS
- Hepatotoxicity (0.3%)
- Left ventricular dysfunction (1%-27%)
- QT interval prolongation and Torsade de Pointes (<0.1%)
- Hypertension (4%-34%)
- Hemorrhagic Events (18%-37%)
- Thyroid dysfunction (4%-16%)
- Wound healing
- Adrenal function

Pfizer, Inc. 2011. Sutent® Package Insert.)

SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (SCCHN)
- Cetuximab (Erbitux®, Eli Lilly and Company)
  - Approved 11/07/2011
  - Indicated in combination with platinum-based therapy with 5-FU for the first-line treatment of patients with recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck.

Eli Lily and Company. 2011. Erbitux® Package Insert.)

CETUXIMAB IN SCCHN
DOSAGE AND ADMINISTRATION
- Erbitux in combination with platinum-based therapy with 5-FU
  - The recommended initial dose is 400 mg/m2 administered on the day of initiation of platinum-based therapy with 5-FU as a 120-minute intravenous infusion (maximum infusion rate 10 mg/min). Complete Erbitux administration 1 hour prior to platinum-based therapy with 5-FU.

Eli Lilly and Company. 2011. Erbitux® Package Insert.)

CETUXIMAB IN SCCHN
DOSAGE AND ADMINISTRATION
- Erbitux in combination with platinum-based therapy with 5-FU
  - The recommended subsequent weekly dose (all other infusions) is 250 mg/m2 infused over 60 minutes (maximum infusion rate 10 mg/min) until disease progression or unacceptable toxicity when administered in combination with platinum-based therapy with 5-FU. Complete Erbitux administration 1 hour prior platinum-based therapy with 5-FU.

Eli Lilly and Company. 2011. Erbitux® Package Insert.)
**CETUXIMAB DOSAGE AND ADMINISTRATION**

- Premedication Recommended
  - H1 antagonist (e.g., 50 mg of diphenhydramine) intravenously 30–60 minutes prior to the first dose
  - Premedication for subsequent doses based upon clinical judgment and presence/severity of prior infusion reactions.
- Do not infuse at rate > 10mg/min (600mg/hr)
- Infuse through a 0.22 micrometer in-line filter

(Eli Lilly and Company. 2011. Erbitux® Package Insert.)

**CLINICAL TRIAL OF CETUXIMAB WITH CHEMOTHERAPY IN SCCHN**

- ErbituX in First-Line Treatment of REcurrent or MEtastatic Head and Neck Cancer (EXTREME trial)
- Conducted in Europe using European cetuximab
- Cisplatin or carboplatin and 5-fluorouracil with or without cetuximab
- Cetuximab improved response rate, progression-free survival and overall survival

(Vermorken et al., 2008.)

**EUROPEAN-APPROVED CETUXIMAB VERSUS US-LICENSED ERBITUX®**

- Compared to the European-approved cetuximab, Erbitux® (US cetuximab) yields approximately 22% greater drug exposure
- Safety data may be underestimated in terms of incidence and severity
- Tolerability of the recommended dose is supported by data from additional Erbitux® studies
- FDA is requiring additional studies to confirm safety

(Eli Lilly and Company. 2011. Erbitux® Package Insert.)

**EXTREME: NON-LABORATORY SAFETY FINDINGS FOR CETUXIMAB**

- Adverse Events, Any Grade, Incidence ≥30%
  - Acneiform rash (70%), nausea (54%), infection (44%)
- Adverse Events, Grade 3/4, Incidence ≥5%
  - Infection (11%)*, skin reactions (9%), diarrhea (5%)*, anorexia (5%)*

*≤5% greater frequency than in chemo only

(Eli Lilly and Company. 2011. Erbitux® Package Insert.)

**EXTREME: LABORATORY SAFETY FINDINGS FOR CETUXIMAB**

- No lab abnormalities, any grade, occurred with ≥50% frequency
- Lab abnormalities, Grade 3/4, Incidence ≥5%
  - Hypokalemia (7%)*, hypomagnesemia (5%)*

*≤5% greater frequency than in chemo only

(Eli Lilly and Company. 2011. Erbitux® Package Insert.)
CETUXIMAB
WARNINGS AND PRECAUTIONS
- Infusion Reactions
- Cardiopulmonary Arrest
- Pulmonary Toxicity
- Dermatologic Toxicity
- Hypomagnesemia and Electrolyte Abnormalities

DENOSUMAB (PROLIA®, AMGEN)
- Approved September 16, 2011
- Indicated as a treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer and in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

DENOSUMAB (PROLIA®)
DOSAGE AND ADMINISTRATION
- The recommended dose of Prolia is 60 mg administered as a single subcutaneous injection once every 6 months.
- Administer Prolia via subcutaneous injection in the upper arm, the upper thigh, or the abdomen.
- All patients should receive calcium 1000 mg daily and at least 400 IU vitamin D daily

DENOSUMAB (PROLIA®)
CLINICAL TRIAL
- Efficacy evaluated in 1468 men with nonmetastatic prostate cancer receiving androgen deprivation therapy and at high risk for fracture - Either Prolia® 60 mg SQ or placebo every 6 months for 6 doses
- Efficacy evaluated in 252 women with breast cancer receiving adjuvant therapy with aromatase inhibitors and at high risk for fractures - Either Prolia® 60 mg SQ or placebo every 6 months for 4 doses

FDA-APPROVED NEW SUPPORTIVE CARE AGENTS
- Denosumab
- Fentanyl
- Glucarpidase
DENOSUMAB (PROLIA®)

CLINICAL TRIAL
- Supplemented with 1000 mg of calcium and 400 IU of vitamin D supplementation per day.

(Amgen, 2011, Prolia® Package Insert)

05/03/2012

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DENOSUMAB (PROLIA®)

CLINICAL TRIAL RESULTS
- Prostate Cancer
  - Compared to placebo, higher bone mineral density (BMD) at 2 years, consistent effect on BMD and reduced incidence of new vertebral fracture at 3 years
- Breast Cancer
  - Compared to placebo, BMD in lumbar spine higher at 12 months

(Amgen, 2011, Prolia® Package Insert)

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DENOSUMAB (PROLIA®)

CLINICAL TRIAL - SAFETY
- Most common adverse reactions in trial (>10%) were arthralgia (13.0% placebo vs. 14.3% Prolia®) and back pain (10.5% placebo vs. 11.5% Prolia®)

Amgen, 2011, Prolia® Package Insert

05/03/2012

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DENOSUMAB (PROLIA®)

CONTRAINDICATIONS
- Pre-existing hypocalcemia must be corrected prior to initiating therapy

Amgen, 2011, Prolia® Package Insert

05/03/2012

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FENTANYL

- Fentanyl Sublingual spray (Subsys®)
  - Approved 01/04/2012
- Fentanyl Citrate (Lazanda®)
  - Approved 06/30/2011
- Indicated for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain


05/03/2012

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**Fentanyl Sublingual Spray**

**Dosage and Administration**

- **5 strengths** – 100mcg (blue), 200mcg (green), 400mcg (magenta), 600mcg (purple), 800mcg (orange)
- **Starting dose is always 100mcg**
- Carefully spray dose under tongue
- A disposal bottle is provided with every carton

**Dose Adjustments**

- If no relief after 30 minutes, may repeat dose, at same strength, one time
- Wait ≥4 hrs before treating another pain episode.
- Increase dose when single dose of current strength fails to effectively treat BTP for several consecutive episodes
- If signs of excessive opioid effect following single dose, decrease subsequent doses
- If greater than 4 BTP episodes per day, re-evaluate the around-the-clock opioid.

**Clinical Trial of Fentanyl Sublingual Spray**

- 130 patients entered a titration phase to determine the effective dose of fentanyl sublingual spray
- Once the effective dose was determined for each patient, each patient was given 10 treatments, 7 with fentanyl sublingual spray and 3 with placebo

**Fentanyl Sublingual Spray**

**Dosage and Administration**

- Scheduled II controlled substance – monitor for abuse, addiction, physical dependence and tolerance
- Fentanyl plasma concentration may be affected by the concomitant administration of drugs that are inhibitors or inducers of the Cytochrome P450 3A4 pathway.
- Close monitoring is essential and dose adjustment may be necessary
  - Decreased doses with concomitant inhibitors
  - Increased doses with concomitant inducers

**Dose Adjustments**

- In patients with mucositis, exposure to fentanyl sublingual was greater than in patients without.
- For Grade 1 mucositis, monitor carefully
- For Grade 2 or higher, avoid use of fentanyl sublingual spray unless benefits outweigh potential risks

**Clinical Trial of Fentanyl Sublingual Spray - Results**

- Compared to placebo, fentanyl sublingual spray resulted in a greater reduction in pain intensity at 30 minutes
CLINICAL TRIAL OF FENTANYL SUBLINGUAL SPRAY – SAFETY

- Most common adverse events are those commonly seen with opioids – nausea (13.1%), vomiting (10.3%), somnolence (9.5%), constipation (5%), and dizziness (7.2%)
- Most serious adverse events included respiratory depression, circulatory depression, hypotension and shock.

FENTANYL SUBLINGUAL SPRAY CONTRAINDICATIONS

- In the management of pain in opioid non-tolerant patients
- In the management of acute or post-operative pain including headache, migraine headache, dental pain or in the emergency department.
- In patients with known hypersensitivity or intolerance to fentanyl or any of the components

FENTANYL SUBLINGUAL SPRAY WARNINGS AND PRECAUTIONS

- Respiratory depression
- Fentanyl sublingual spray and other fentanyl products
- Patient/caregiver instructions
- Additive CNS depressant effects
- Effects on ability to drive and use machines
- Chronic pulmonary disease
- Head injuries and increased intracranial pressure
- Cardiac disease
- MAO inhibitors

FENTANYL SUBLINGUAL SPRAY WARNINGS AND PRECAUTIONS

- Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) ACCESS Program
  - Healthcare prescribers, pharmacies and patients must enroll in the program
  - Outpatients must understand risks and benefits and sign a Patient-Prescriber agreement with their healthcare provider

FENTANYL PECTIN NASAL SPRAY (FPNS) DOSAGE AND ADMINISTRATION

- 2 strengths – 100mcg/ml and 400mcg/ml
- Dose is either 1 spray in one nostril or one spray in each nostril for a total dose of 100mcg, 200mcg, 400mcg or 800mcg
- Bottle dispensed in a child-proof container with a disposal pouch

FPNS DOSAGE AND ADMINISTRATION

- Scheduled II controlled substance – monitor for abuse, addiction, physical dependence and tolerance
- No clinically relevant differences in pharmacokinetic and safety profiles in patients with allergic/seasonal rhinitis
- Coadministration with oxymetazoline for treatment of rhinitis compromised FPNS absorption.
FPNS
DOSE ADJUSTMENTS
- Fentanyl plasma concentration may be affected by the concomitant administration of drugs that are inhibitors or inducers of the Cytochrome P450 3A4 pathway.
- Close monitoring is essential and dose adjustment may be necessary
  - Decreased doses with concomitant inhibitors
  - Increased doses with concomitant inducers

CLINICAL TRIAL OF FPNS FOR BREAKTHROUGH CANCER PAIN (BTCP)
- 114 patients entered a dose titration phase to determine each patient’s effective FPNS dose
- Once the effective dose for each patient was determined, each patient was provided 10 single dose vials randomly numbered 1-10, 7 of which contained FPNS at the predetermined effective dose and 3 of which contained placebo

CLINICAL TRIAL OF FPNS IN BTCP RESULTS
- Compared to placebo, FPNS more effectively relieved pain from 10 min-60 min, yielded a clinically meaningful pain reduction in more patients and reduced the need for additional doses of rescue medication
- The majority of patients (>68%) found it convenient and easy to use

CLINICAL TRIAL OF FPNS IN BTCP SAFETY
Adverse reactions occurring with ≥5% incidence (mild–moderate in severity)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Titration Phase</th>
<th>Maintenance Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6%</td>
<td>10%</td>
</tr>
<tr>
<td>Constipation</td>
<td>-</td>
<td>6%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6%</td>
<td>-</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>-</td>
<td>6%</td>
</tr>
</tbody>
</table>

FPNS OPEN-LABEL SAFETY STUDY
- 16 week study to evaluate long-term tolerability, acceptability and consistency of effect (N=403)
- 94% of episodes required no additional rescue medications
- >90% of patients remained on initial dose for the duration of the study
- 24.6% reported AEs – mild-moderate, consistent with opioid therapy
- >95% satisfied with convenience and ease of use

FPNS CONTRAINDICATIONS
- In the management of pain in opioid non-tolerant patients
- In the management of acute or post-operative pain including headache, migraine headache, dental pain or in the emergency department.
- In patients with known hypersensitivity or intolerance to fentanyl or any of the components
FPNS 
WARNINGS AND PRECAUTIONS
- FPNS and other fentanyl products
- Respiratory depression
- Information for patients and their caregivers
- Additive CNS depressant effects
- Effects on ability to drive and use machines
- Chronic pulmonary disease
- Head injuries and increased intracranial pressure
- Cardiac disease
- MAO inhibitors

(Archimedes Pharma US, Inc. 2011. Lazanda®, Package Insert.)
05/03/2012

GLUCARPIDASE (VORAXAZE®, BTG INTERNATIONAL)
- Approved January 17, 2012
- Indicated for the treatment of patients with toxic plasma methotrexate (MTX) concentrations (>1 micromole per liter) in patients with delayed methotrexate clearance due to impaired renal function

(BTG Pharmaceuticals. 2012. Voraxaze® Package Insert)
05/03/2012

GLUCARPIDASE CLINICAL TRIAL
- Efficacy evaluated in 22 patients from a single-arm, open-label study in patient with markedly delayed MTX clearance due to renal dysfunction
- All patient received glucarpidase 50 units/kg IVP over 5 minutes
  - Patients with a pretreatment MTX level >100 micromoles/L, were to receive a 2nd dose of glucarpidase 48 hrs after the 1st dose.

(BTG Pharmaceuticals. 2012. Voraxaze® Package Insert)
05/03/2012

GLUCARPIDASE DOSAGE AND ADMINISTRATION
- Dosed at 50 units/kg as a single IV injection over 5 minutes
- Leucovorin is a substrate for glucarpidase. Do not administer leucovorin within 2 hours of glucarpidase dose.
- Other exogenous substrates may be reduced folates and folate antimetabolites.

(BTG Pharmaceuticals. 2012. Voraxaze® Package Insert)
05/03/2012

GLUCARPIDASE CLINICAL TRIAL Efficacy Results
- 10 patients (45%) achieved a Rapid and Sustained Clinically Important Reduction (RSCIR)
- Of 9 patients with a pre-treatment MTX plasma concentration >50 micromoles/L, none achieved a RSCIR but all had a >95% rapid reduction in MTX concentration.

(BTG Pharmaceuticals. 2012. Voraxaze® Package Insert)
05/03/2012
GLUCARPIDASE CLINICAL TRIAL
SAFETY FINDINGS

- 290 patients in safety evaluation
- 8 deaths within 30 days of glucarpidase exposure not related to progressive disease
- 21 patients (7%) experienced treatment-related adverse events, most were Grade 1/2 but there was a Grade 3 flushing
- Most common non-hematologic, non-hepatic, non-renal toxicities were paresthesia (2%), flushing (2%), nausea and/or vomiting (2%), headache (1%) and hypotension (1%)

(GLT Pharmaceuticals. 2012. Voraxaze® Package Insert)

GLUCARPIDASE
WARNINGS AND PRECAUTIONS

- Serious allergic reactions - <1%
- Monitoring methotrexate concentration/Interference with assay
- Continuation and timing of leucovorin rescue

(GLT Pharmaceuticals. 2012. Voraxaze® Package Insert)

FDA NOTICES

RESPONSE TO CRITICAL SHORTAGE OF DOXIL® (CENTOCOR ORTHO BIOTECH PRODUCTS, LP)

- In response to critical shortage of Doxil®, (doxorubicin HCL liposome injection) the FDA is allowing the immediate temporary importation and distribution of Sun Pharma Global’s Lipodox

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm292658.htm

RESPONSE TO CRITICAL SHORTAGE OF METHOTREXATE

- Supplies of preservative-free methotrexate have been rapidly declining due to manufacturing issues at an Ohio manufacturing facility which ultimately closed voluntarily on 11/19/2011.
- In response, the FDA has completed a prioritized review of, and approved a preservative-free generic methotrexate manufactured by APP Pharmaceuticals.

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm292658.htm

REGULAR APPROVAL FOR IMATINIB MESYLATE (GLEEVEC®, NOVARTIS)

- Full approval granted for imatinib mesylate for the adjuvant treatment of adult patients following complete gross resection of Kit (CD117) positive gastrointestinal stromal tumors (GIST).
- Initially granted accelerated approval for this indication in December 2008.

http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/021588s035ltr_cor.pdf
IN THE PAST YEAR....

- New therapeutic and supportive care agents & expanded indications for existing agents, and FDA alerts and notifications provide increased pharmacologic options for the care of patients with cancer.
- The number of changes and the speed at which they occur highlight the need for every clinician to stay current with the ever-evolving landscape of cancer care.

REFERENCES

- http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm292658.htm accessed 4-02-2012
REFERENCES CONT’D
