Targeted Therapies: The Cancer Revolution

Implications in Hospice Patients

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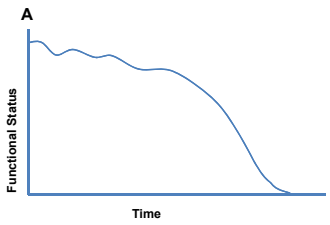
Cancer Trajectory



Cancer

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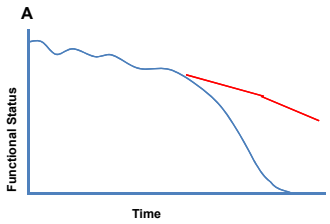
Cancer Trajectory



Cancer

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Objectives

- Review mechanism of action of targeted therapies- The Basics – Targeted therapies 101
- Discuss diseases with greatest impact on outcome with targeted therapies
- Discuss side effects of these agent, as it relates to Hospice physicians
- Discuss checkpoint inhibitors- Immunotherapy
- CART cell

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Drugs with Major Impact

- Imatinib for CML
- Transtuzumab for HER-2 positive breast cancer
- Rituximab for B-cell malignancies

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Diseases impacted by targeted therapies

- CML,
- Lymphomas/ CLL
- Breast cancer
- Colon cancer
- Kidney cancer
- Lung cancer

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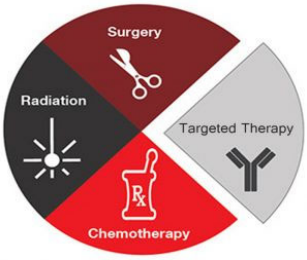
Cancer treatments



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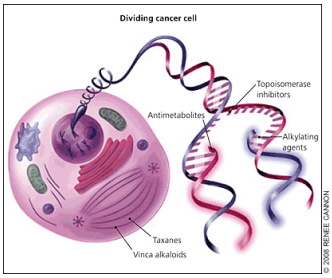
Chemotherapy



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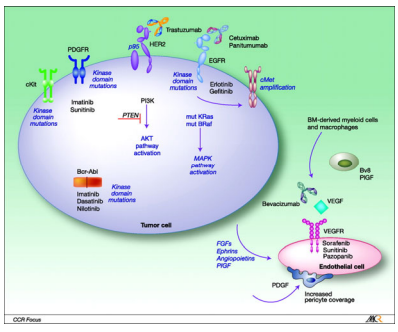

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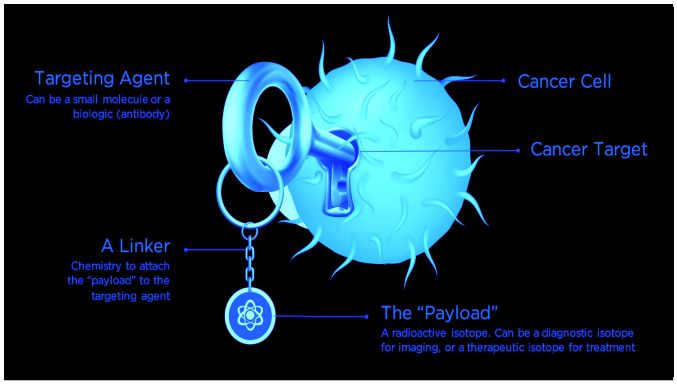
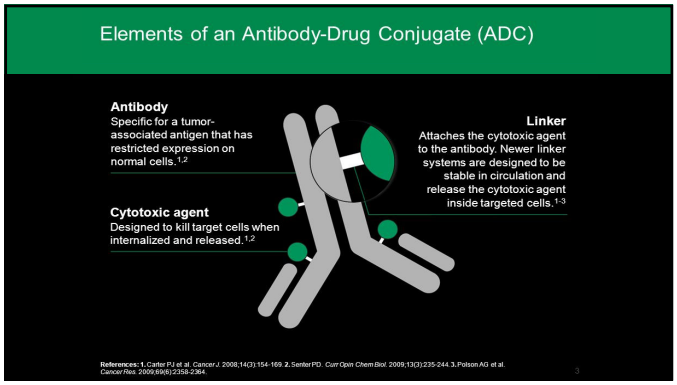
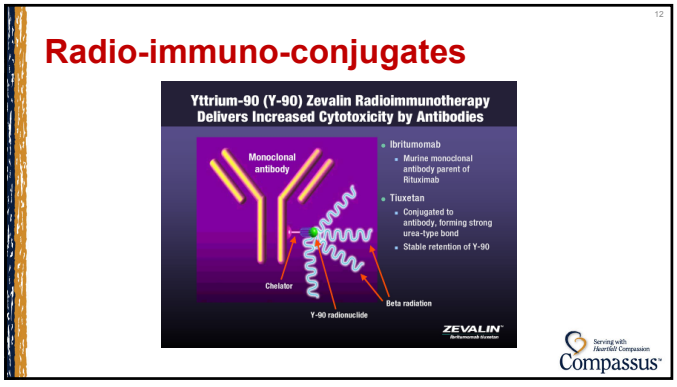

Targeting Agent
Can be a small molecule or a biologic (antibody)
Cancer Cell
Cancer Target
A Linker
Chemistry to attach the "payload" to the targeting agent
The "Payload"
A radioactive isotope. Can be a diagnostic isotope for imaging, or a therapeutic isotope for treatment


Elements of an Antibody-Drug Conjugate (ADC)
Antibody
Specific for a tumor-associated antigen that has restricted expression on normal cells.[1,2]
Linker
Attaches the cytotoxic agent to the antibody. Newer linker systems are designed to be stable in circulation and release the cytotoxic agent inside targeted cells.[1-3]
Cytotoxic agent
Designed to kill target cells when internalized and released.[1,2]
References: 1. Carter PJ et al. Cancer J. 2008;14(3):154-169. 2. Senter PD. Curr Opin Chem Biol. 2009;13(3):235-244. 3. Polson AG et al. Cancer Res. 2009;69(6):2358-2364.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Radio-immuno-conjugates
Yttrium-90 (Y-90) Zevalin Radioimmunotherapy Delivers Increased Cytotoxicity by Antibodies
Monoclonal antibody
Chelator
Y-90 radionuclide
Beta radiation
ZEVALIN
ibritumomab
Murine monoclonal antibody parent of Rituximab
Tiuxetan
Conjugated to antibody, forming strong urea-type bond
Stable retention of Y-90
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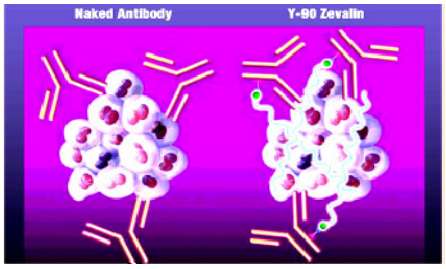
Ibritumomab Tiuxetin - Zevalin



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Targeted agents with a linker

- **Targeted agent conjugated with chemotherapeutic agent**
  - TDM-1 – Ado-Transtuzumab- HER-2 target linked to Mtansine
  - Brentuximab CD30 targeted agent linked to a microtubule.
    - **Hodgkin's lymphoma**
    - **Anaplastic large cell Lymphoma**
- **Targeted agent conjugated to a radioisotope**
  - Ibritumomab Tiuxetin (Zevalin) radio-isotope linked to Rituxan
    - **Low grade lymphomas**

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Targeted therapies

- **Small molecule**
  - Imatini**b** - Gleevec
  - Sunitinib - Sutent
  - Sorafenib - Nexavar
  - Pazopinib - Votrient
  - Ibrutinib – Imbruvica
- **Antibody therapy**
  - Rituxima**ab** - Rituxan
  - Transtuzumab - Herceptin
  - Bevacuzumab - Avastin

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Targeted therapies

- **Tyrosine Kinase inhibitors**
  - Imat**inib** - Gleevec
  - Sunit**inib** - Sutent
  - Sorafe**nib** - Nexavar
  - Pazopi**nib** - Votrient
  - Ibruti**nib** – Imbruvica
- **Pi-3 Kinase inhibitors**
  - Idealali**sib**
  - Copanli**sib**

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Targeted therapies

- **Hedgehog inhibitors**
  - **Vismode**gib
  - **Sonide**gib
- **MToR inhibitors**
  - **Everoli**mus
  - **Temsiroli**mus
- **Antibody therapy**
  - **Rituxi**mab - **Rituxan**
  - **Transtuzu**mab - **Herceptin**
  - **Bevacuzu**mab - **Avastin**

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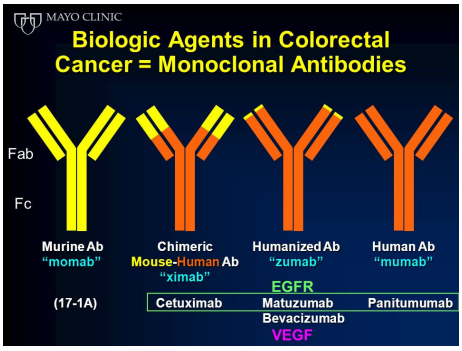

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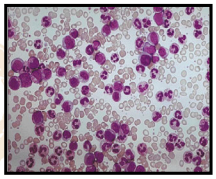
Targeted Therapies

Chronic Myeloid Leukemia



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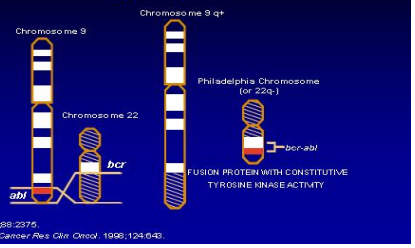
The Ph Chromosome and the *bcr-abl* Gene: The t(9;22) Translocation



Melo. *Blood*. 1996;88:2375.
Pasternak et al. *J Cancer Res Clin Oncol*. 1998;124:643.

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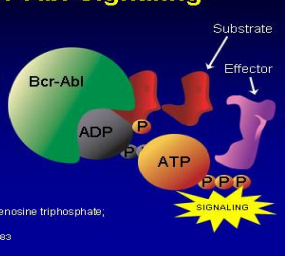
Normal Bcr-Abl Signaling

The kinase domain activates a substrate protein, eg, PI3 kinase, by phosphorylation

This activated substrate initiates a signaling cascade culminating in cell proliferation and survival



ADP = adenosine diphosphate; ATP = adenosine triphosphate; P = phosphate.

Savage and Antman. *N Engl J Med*. 2002;346:683
Scheijen and Griffin. *Oncogene*. 2002;21:3314.

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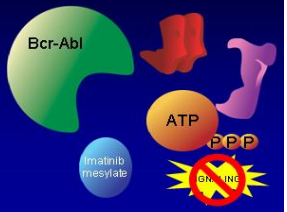
Imatinib Mesylate: Mechanism of Action

Imatinib mesylate occupies the ATP binding pocket of the Abl kinase domain

This prevents substrate phosphorylation and signaling

A lack of signaling inhibits proliferation and survival



Savage and Antman. *N Engl J Med*. 2002;346:683.

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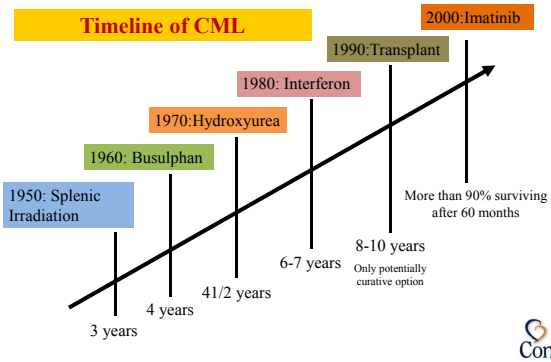
Timeline of CML



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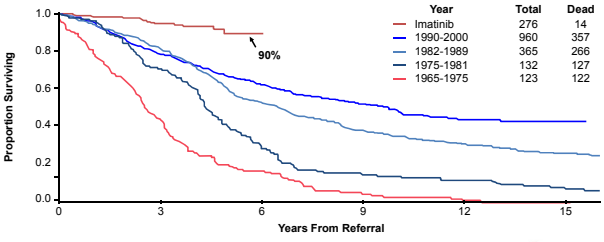
Survival in Early Chronic-Phase CML



The University of Texas M. D. Anderson Cancer Center database.

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CML targeted therapies

- Imatinib – Gleevec
- Dasatinib (Sprycel)
- Nilotinib (Tasigna)
- Ponatinib (Iclusig)
- Bosutinib (Bosulif)

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Side Effects of *selective* TKIs

- Imatinib-
  - Nausea, abdominal pain, Diarrhea, peripheral edema, anemia
- Dasatinib-
  - Pleural effusion, CHF, pericardial effusion,
- Nilotinib –
  - IHD, edema, PAD, pericardial effusion QT prolonged, death 0.4%
- Ponatinib-
  - IHD, Arrythmias, PAD, edema, rash, intestinal perforation
- Bosutinib-
  - Rash, diarrhea, vomiting abdominal pain

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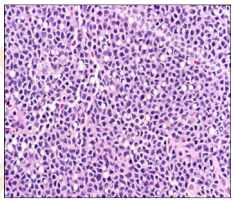
Targeted Therapies

B-cell Malignancies
Lymphomas CLL



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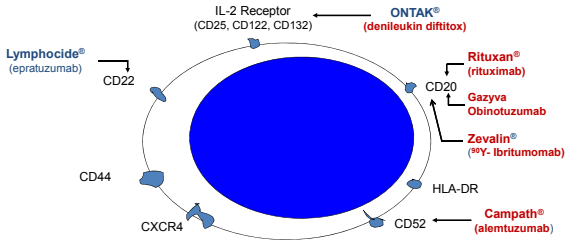
Targeted Therapies In Lymphomas and CLL



Hulkkonen. *Leukemia.* 2002;16:178; Tsilivakos. *Leukemia.* 1994;8:1571; Rosolen. *Blood.* 1989;73:1968; Nakase. *Leukemia Res.* 1994;18:855.

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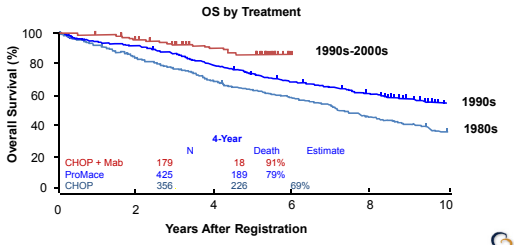
Improving Survival of *Follicular* NHL: Impact of Antibody-Based Therapy



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Treatment of *aggressive* NHL

CHOP

- CYTOXAN 750 mg/m2 DAY 1
- DOXORUBICIN 50mg/m2 DAY 1
- VINCRISTINE 1.4mg/m2 mg DAY 1
- PREDNISONE 100mg /day 1- 5

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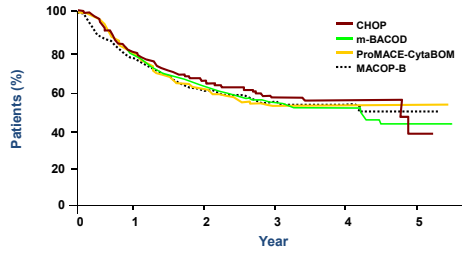
National High Priority Lymphoma Study- S8516



Adapted from Fisher. *N Engl J Med.* 1993;328:1002.

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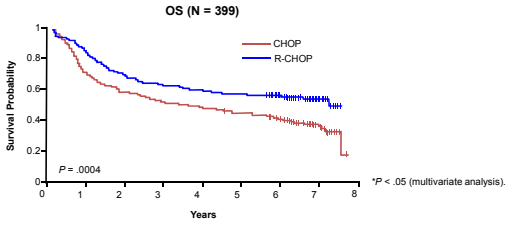
CHOP ± Rituximab in DLBCL: 7-Yr Survival Results



*P < .05 (multivariate analysis).

Coiffier B, et al. ASCO 2007. Abstract 8009.

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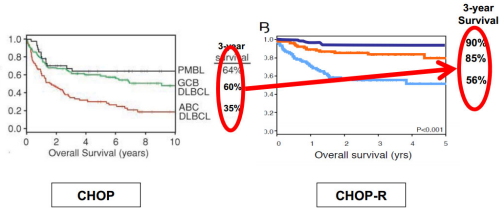
Cell-of-origin-related survival characteristics in diffuse large B cell lymphoma treated with CHOP VS R-CHOP



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Side effects of Rituximab

- Need to check for Hep-B as it can reactivate hepatitis
- Serious allergic reactions
- Rash, skin peeling, mouth ulcer
- Low wbc counts- increased risk of infections
- Tumor Lysis syndrome
- Nausea, vomiting fatigue
- Cardiac, kidney, stomach issues
- Progressive multifocal leukoencephalopathy

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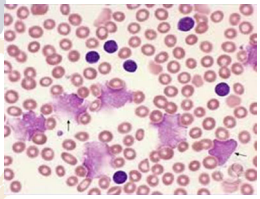
Targeted Therapies

CLL



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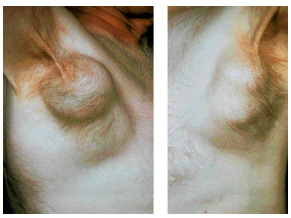
CLL- Diagnosis

- **Massive lymphadenopathy**
- **Axillary lymphadenopathy**



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Famine to Feast...

Cytotoxic Chemotherapy	Monoclonal Antibodies	Kinase Inhibitors and Others
• Fludarabine	• Rituximab	• Ibrutinib
• Cyclophosphamide	• Ofatumumab	• Idelalisib
• Bendamustine	• Obinutuzumab	• Venetoclax
• Chlorambucil		• Acalibrutinib
		• Lenalidomide

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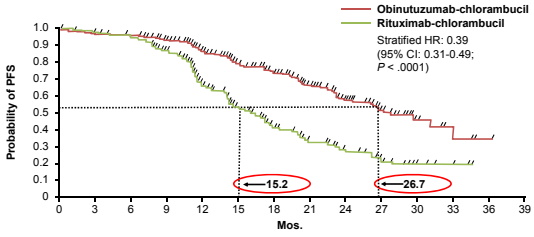
CLL11 Trial: Obinotuzumab PFS Head-to-Head Comparison



Goede V, et al. N Engl J Med. 2014;[Epub ahead of print].

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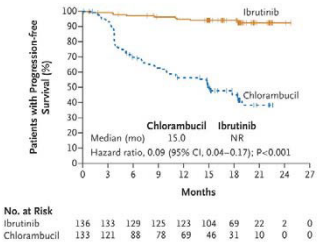
BTK Inhibitor



Burger JA et al N Engl J Med 2015; 373: 2425-2437

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Side effects of BTK Inhibitors- Ibrutinib

- Bleeding- Gi bleeding, Hematuria, post procedural hemorrhage
- Cardiac arrythmias- Atrial fibrillation
- Infections, PML, PJP have occurred
- Rebound elevation of WBC count
- HTN, tumor lysis, embryo-fetal toxicity
- Cytopenias, nausea, fatigue, musculoskeletal pain

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Targeted Therapies

Breast Cancer

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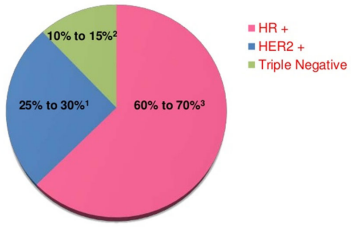
Current Clinical Subtypes in Breast Cancer



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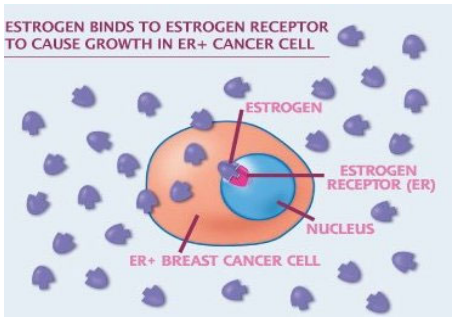

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Targeted therapy

- **Selective estrogen receptor modulators – SERM's**
  - **Tamoxifen** (Nolvadex)
  - Raloxifene (Avista)
  - Fulvestrant (Faslodex) **SERD**
- **Aromatase inhibitors**
  - Anastrozole (Arimidex)
  - Letrozole (femara)
  - Exemestane (Aromasin)

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Side effects of SERM's and AI's

- **SERM's**
  - Hot flashes
  - Vaginal dryness
  - Thromboembolism
  - Uterine cancer
  - Mood swings
- **AI's**
  - Osteopenia/osteoporosis
  - Arthralgias
  - hyperlidemia

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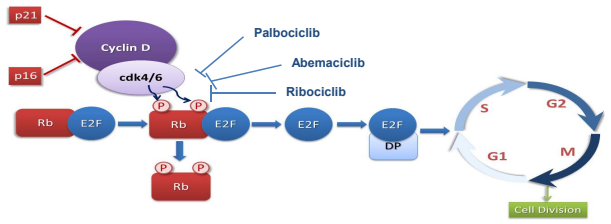
CDK 4/6 Regulates G1➔S Cell Cycle Progression



CDK 4/6, cyclin-dependent kinase 4/6; M, mitosis; Rb, retinoblastoma.
Adapted from Finn et al, *Breast Cancer Res.* 2016; DOI: 10.1186/s13058-0

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CDK 4/6 inhibitors

- **Palbociclib – Ibrance**
  - Neutropenia, fatigue, nausea
- **Ribociclib**
  - Neutropenia, **QT prolongation**
- **Abemaciclib**
  - CNS penetration, less neutropenia, **diarrhea**
- **M-ToR Inhibitor**
  - Everolimus- Mucositis, Pneumonitis

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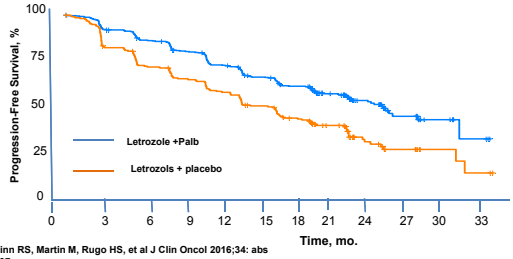
PFS: Investigator-Assessed (ITT Population)

March 2017: Palbociclib received regular FDA approval for HR+/HER2- advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine based therapy in postmenopausal



Finn RS, Martin M, Rugo HS, et al J Clin Oncol 2016;34: abs 507

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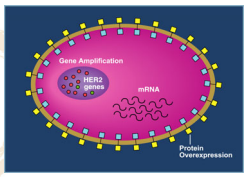
Targeted Therapies

HER-2 Positive Disease



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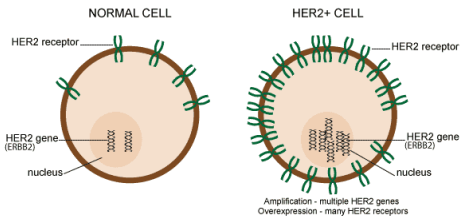
HER-2 positive breast cancer



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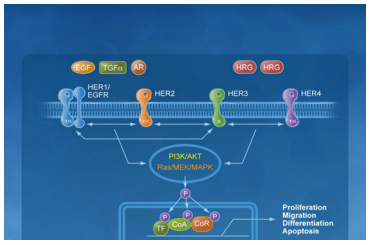
HER-2 signaling pathway



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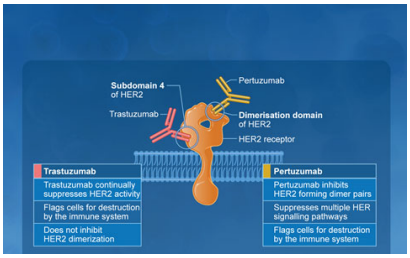
Transtuzumab, Pertuzumab



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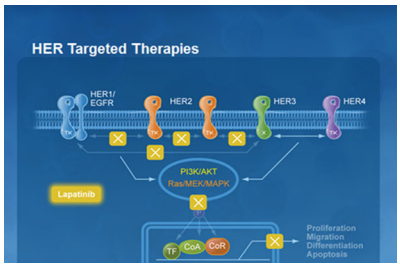
Small Molecules Lapatinib, Neratinib



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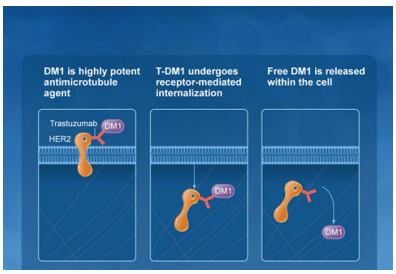
Ado-Transtuzumab- TDM-1



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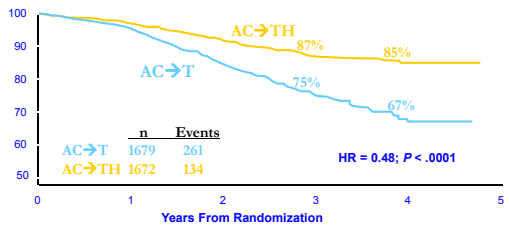
B31/N9831: Transtuzumab + Chemo (DFS)



Romond EH et al. ASCO 2005. Oral presentation;
Romond EH et al. *N Engl J Med*. 2005;353:1673-1684.

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HER-2 targeted therapies

- **Monoclonal antibodies**
  - Transtuzumab Herceptin
  - Pertuzumab Perjeta
- **Monoclonal antibodies linked to chemotherapy**
  - TDM-1 Ado-Transtuzumab
- **Small molecules**
  - Lapatinib
  - Neratinib

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HER-2 directed therapies

- **90% of patients with HER-2 positive disease died in the past**
- **Now 90% of patients are living or are cured**
- **HER-2 positivity has gone from worst to best**
- **New staging system downstaging HER-2 positive disease because of the good prognosis**

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Side effects of HER-2 directed therapies

- **Serious**
  - Cardiac toxicity
  - Respiratory toxicity
  - Infusion reactions
- **Common side effects**
  - Nausea, vomiting headache
  - Body pain, weakness, rash

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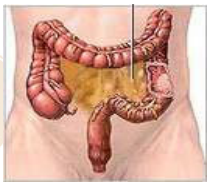
Targeted Therapies

Colon Cancer



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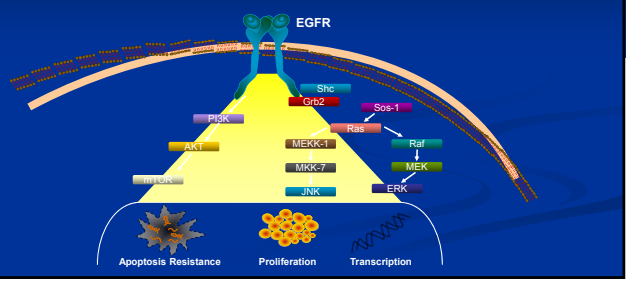
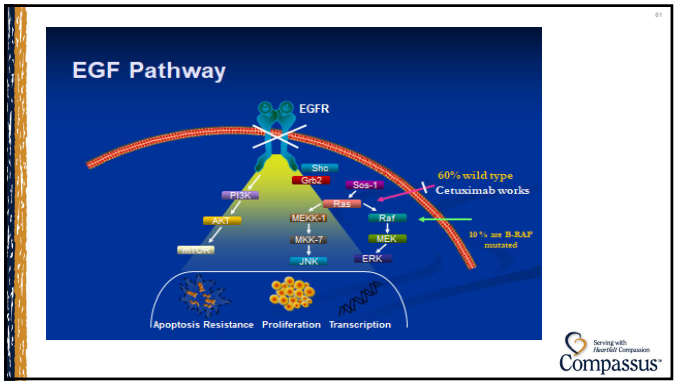
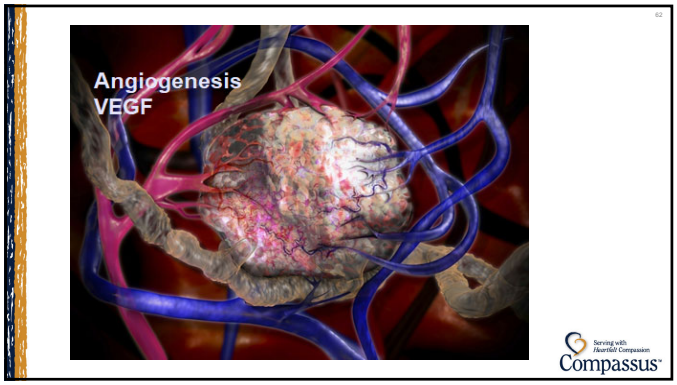
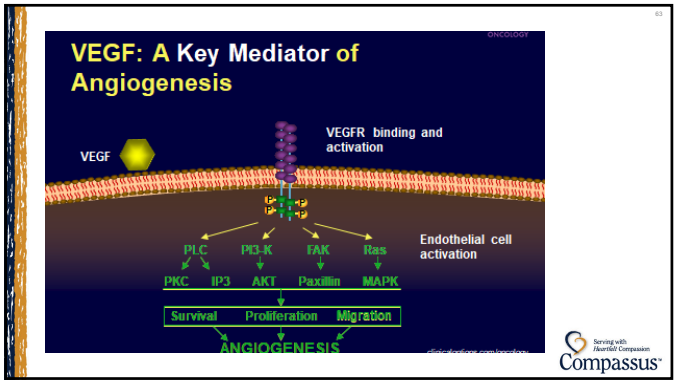
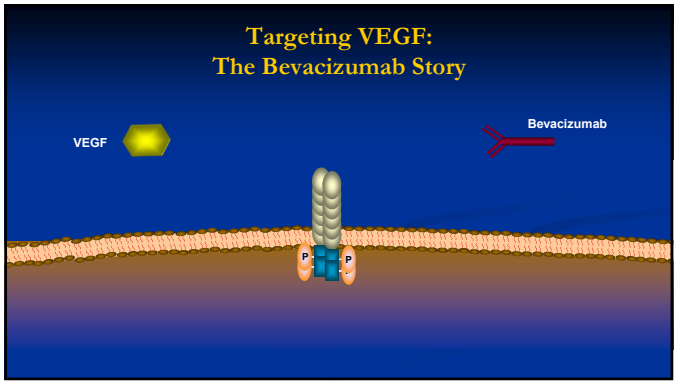
EGF Pathway

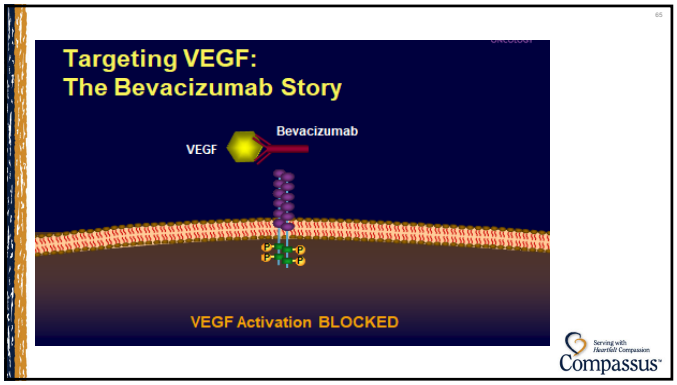



EGF Pathway
EGFR
Shc
Grb2
Sos-1
Ras
PI3K
AKT
mTOR
MEKK-1
MKK-7
JNK
Raf
MEK
ERK
60% wild type
Cetuximab works
10 % are B-RAF mutated
Apoptosis Resistance
Proliferation
Transcription
Compassus


Angiogenesis
VEGF
Compassus


VEGF: A Key Mediator of Angiogenesis
VEGF
VEGFR binding and activation
PLC
PI3-K
FAK
Ras
PKC
IP3
AKT
Paxillin
MAPK
Endothelial cell activation
Survival
Proliferation
Migration
ANGIOGENESIS
Compassus





Targeted therapies for colon cancer

- **KRAS wildtype**
  - Cetuximab
  - Panitumumab
- **BRAF mutation**
  - Vemurefenib
- **VEGF inhibitor**
  - Bevacuzumab (Avastin)
- **Multitargeted inhibitor**
  - regorefenib

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Side effects of EGFR directed therapies

- Cetuximab
  - Anaphylactic reaction
  - Rash- acneform eruption
  - Chest pain, wheezing , shortness of breath
  - Redness or crusting around hair follicles
- Panitumumab
  - Less anaphylaxis

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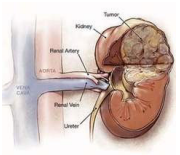
Targeted therapies

Kidney Cancer



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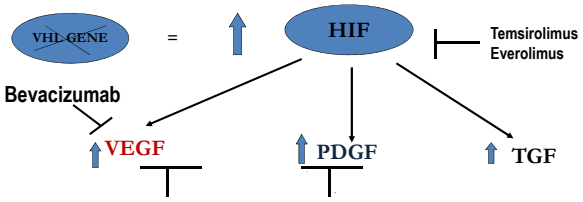
Renal Cell Carcinoma



Sunitinib & Sorafenib, Pazopanib, Axitinib
Cabozentanib, Lenvatinib,

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Therapeutic Inhibition of VEGF in RCC

- **Binding antibodies to the VEGF protein**
  - Bevacizumab
- **VEGFR inhibitors**
  - Sunitinib, Sorafenib, Pazopinib, Axitinib
  - Cabozentenib, Lenvatinib
- **MTOR Inhibitors**
  - Temsirolimus Inhibits HIF directly
  - Everolimus

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Side effects of *non-selective* TKI's

- Hypertension
- Fatigue, asthenia
- Hand/foot syndrome/ Rash
- Diarrhea
- Nausea vomiting
- Taste changes
- Bowel perforation
- Thrombo-embolic phenomenon

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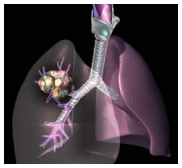
Targeted Therapies

Non-Small Cell Lung Cancer



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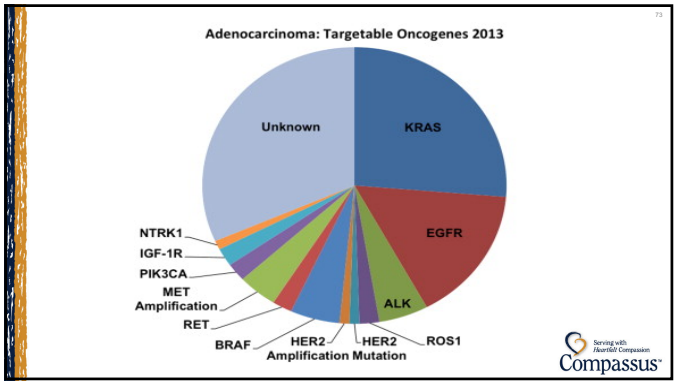

Targets for NSCLC

- **EGFR -10-15% -** Erlotinib, Gefitinib, Afatinib, Osimertanib
- **EML/ALK 2-3 % -** Crizotinib, Ceritinib, Alectinib, Brigatinib
- **ROS-1 -1-2% -** Crizotinib
- **Splicing 14 mutation (1-2%) –** Crizotinib
- **BRAF – (1-2%)** Trametenib + Dabrefinib, Vemurafenib
- **HER-2 – (1-2%)** Lapatinib (HER-2 insertion 19 del, not HER-2 amplified)
- **RET – (2-3%)-** MEK inhibitors- Cabozentenib, Vandetenib
- **NTRK 1- (1-2%)** Larotrectinib
- **PDL-1 –** Immunotherapy-

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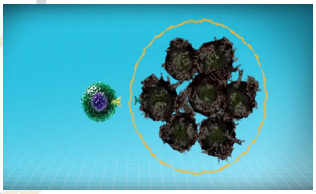
Immunotherapy

Checkpoint Inhibitors



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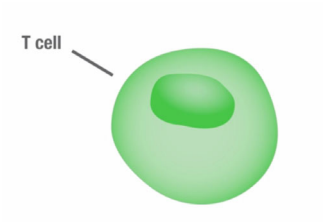
Immunotherapy



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Immunotherapy

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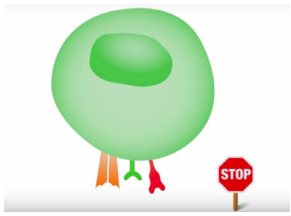
Immunotherapy



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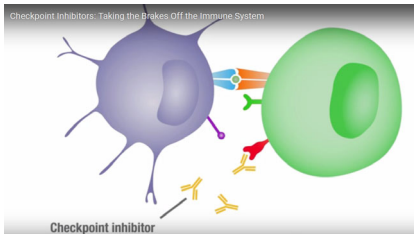
Immunotherapy



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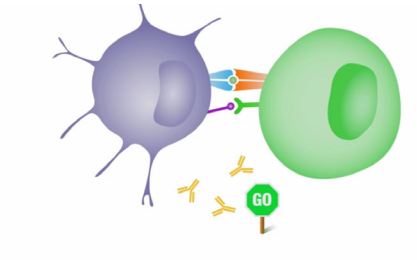
Immunotherapy



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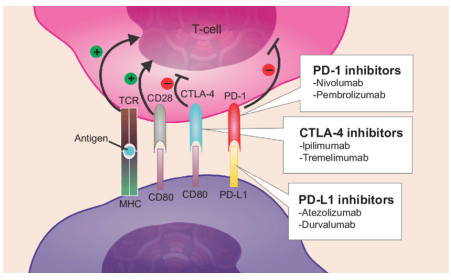

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Side effects of Immuno-therapy

- **Immune mediated side effects**
  - Colitis
  - Pneumonitis
  - Thyroiditis
  - Dermatitis
  - Myocarditis
  - Hepatitis
  - Nephritis
  - Hypopitutiarism
  - Hypoadrenalism
  - Exacerbation of underlying autoimmune diseases

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Pallimedinib

- ❖ Low cost/ cost savings
- ❖ High patient and family satisfaction
- ❖ Improves quality of life
- ❖ Improves pain scores
- ❖ Lowers depression scores
- ❖ decreases 30 day hospital readmission
- ❖ Above all "*improves survival*"

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