WEEK 11, LECTURE 1:
SYSTEMIC TREATMENT OF CANCER:
DRUGS, BIOLOGICALS AND IMMUNOTHERAPIES

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Cancer as a Complex Adaptive System: Emergent Phenomena and Tumor Progression (System State Shifts)

- Escape From Controls for Normal Tissue Architecture
- Genome Instability and Emergence of Clonal Variants
- Evasion of Detection/Destruction by Host Immune System
- Use of Host Systems to Promote Progression
- Invasion and Metastasis
- Emergence of Drug-Resistant Clones
Implications of Cancer as a Complex Adaptive System for the Development of More Effective Diagnostics and Therapies

- current treatment practices and limitations
- confronting the tumor cell heterogeneity problem
- emerging treatment strategies and the particular promise of immunotherapy
- the time, cost and technical challenges of development of new diagnostics and therapies to achieve FDA approval and marketing

Weeks 11 and 14
Meeting The Cancer Challenge

The Ideal

- prevention
- cure
US Cancer Deaths 2012

577,000
Progress in Reducing Disease Burden
Mortality 1970 – 2008*

- cerebrovascular disease: 74% ↓
- heart disease: 63% ↓
- accidents: 33% ↓
- cancer: 12% ↓ (largely since 1990)

*S. Soneji et al (2014) JCO 32, 444
# US Cancer Prevalence Estimates 2010 and 2020

<table>
<thead>
<tr>
<th>Site</th>
<th># People (thousands)</th>
<th>% change</th>
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<tbody>
<tr>
<td></td>
<td>2010</td>
<td>2020</td>
</tr>
<tr>
<td>Breast</td>
<td>3461</td>
<td>4538</td>
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<td>Prostate</td>
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<td>3265</td>
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<tr>
<td>Colorectal</td>
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<td>Uterus</td>
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<td>672</td>
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<td>Bladder</td>
<td>514</td>
<td>629</td>
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<tr>
<td>Lung</td>
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<td>457</td>
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<tr>
<td>Kidney</td>
<td>308</td>
<td>426</td>
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<tr>
<td>Leukemia</td>
<td>263</td>
<td>240</td>
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<tr>
<td>All Sites</td>
<td>13,772</td>
<td>18,071</td>
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</table>

The Thin Line Between Hype and Hope
- celebrity populism and delusional belief that more money will solve everything

- fundamental reassessment of why therapeutic success for metastatic solid tumors remains so elusive

- implications of cancer as a complex adaptive system

- clonal heterogeneity and evolutionary clonal dynamics during tumor progression as the major obstacle to effective therapy
The Principal Challenges in Cancer Treatment

- Tumor cell heterogeneity and Rx effectiveness
- Disseminated disease (metastasis)
- Drug-resistance (intrinsic or acquired)
- Treatment toxicities and complex clinical care
- Treatment cost
- Quality-of-life (in-treatment; post-treatment)
- Timing of recommendation for palliative care versus interventional care
- End-of-life care
Ensuring That the Patient’s Voice is Heard

- what is my prognosis?
- what are the treatment options?
- what is the toxicity of the treatment?
- how will treatment impact my quality-of-life?
- what is likely course of my disease if I don’t take treatment?
Aspirations for Improved Cancer Diagnosis and Treatment

Better Approaches to Early Stage Disease

- earlier detection of subclinical disease
- earlier detection of clinical disease before metastasis occurs (surgery = cure)
- better methods to assess metastatic risk from primary tumor to evaluate need for exposure to adjuvant therapy
  - can tumors with metastatic potential be identified versus tumors that have low/no probability of metastatic spread?
Aspirations for Improved Cancer Diagnosis and Treatment

Improved Outcomes

- maximize the efficacy and safety of Rx interventions against advanced (metastatic) disease
  - circumventing variability in tumor cell clones to the selected Rx regimen (overcoming the heterogeneity problem)
  - dynamic monitoring of changing clonal dynamics during treatment for faster detection of drug-resistant clones
Clinical Standard-of-Care (SOC) Guidelines

- adjuvant therapy
  - (post-surgery/radiation)
- neoadjuvant therapy
  - (pre-surgery/radiation)
- palliative therapy
  - (non-curative Rx for advanced disease)
- end-of-life care
  - (last six months but more typically last month: ICU, hospice, in-home)
Therapeutics

- small (heterocyclic) molecules <1500 Daltons Mw
- biologicals
  - recombinant (r)proteins, antibodies (natural/engineered)
  - nucleic acids: antisense, miRNAs, aptamers
- gene therapy (and delivery vectors)
- vaccines
  - prophylactic, therapeutic
- novel drug formulations/drug delivery systems
# FDA-Approved Anti-Cancer Drugs

## DNA Damaging Agents

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<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Approved Indication</th>
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<tr>
<td>altretamine</td>
<td>Hexalen</td>
<td>ovarian cancer</td>
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<tr>
<td>arsenic trioxide</td>
<td>Trisenox</td>
<td>certain leukemias</td>
</tr>
<tr>
<td>bendamustine</td>
<td>Treanda</td>
<td>multiple cancers</td>
</tr>
<tr>
<td>bleomycin sulfate</td>
<td>Blenoxane</td>
<td>certain lymphomas, squamous cell and testicular cancers</td>
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<tr>
<td>busulfan</td>
<td>Myleran, Busulfex</td>
<td>certain leukemias</td>
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<tr>
<td>carboplatin</td>
<td>Paraplatin, Paraplat</td>
<td>breast, lung and ovarian cancers</td>
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<tr>
<td>carmustine</td>
<td>BiCNU</td>
<td>brain tumors, certain lymphomas</td>
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<tr>
<td>chlorambucil</td>
<td>Leukeran</td>
<td>multiple cancers</td>
</tr>
<tr>
<td>cisplatin</td>
<td>Platinol-AQ</td>
<td>multiple cancers</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td>Cytoxan</td>
<td>multiple cancers</td>
</tr>
<tr>
<td>dacarbazine</td>
<td>DTIC-Dome</td>
<td>melanoma, certain brain cancers</td>
</tr>
<tr>
<td>dactinomycin</td>
<td>Cosmegen</td>
<td>multiple cancers</td>
</tr>
<tr>
<td>daunorubicin, daunomycin</td>
<td>Cerubidine</td>
<td>certain leukemias</td>
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<tr>
<td>doxorubicin hydrochloride</td>
<td>Adriamycin PFS, AdriamycinRDF</td>
<td>multiple cancers</td>
</tr>
<tr>
<td>epirubicin hydrochloride</td>
<td>Ellence</td>
<td>certain leukemias, breast and stomach cancers</td>
</tr>
</tbody>
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BIO 302:
APRIL 1, 2014

WEEK 11, LECTURE 1:
SUPPLEMENTAL MATERIALS

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Categories of Cancer Therapeutics

- expected to know different modes of action of anti-cancer drugs
- long lists of drugs posted on blackboard for reference only for those who want more information (no exam question on individual drugs)
Categories of Anti-Cancer Therapeutics

**Cytotoxic Chemotherapy**
- DNA synthesis inhibitors (anti-metabolites)
- DNA damaging agents
- Cytoskeleton (microtubule) modifying agents

**Hormonal Agents**
- Hormones (agonists)
- Hormone blockers (antagonists)
Categories of Anti-Cancer Therapeutics

Targeted Chemotherapy

- small molecule cell signaling inhibitors
  - largely tyrosine kinase inhibitors (TKi’s)
- angiogenesis inhibitors
  - again largely kinase inhibitors
- monoclonal antibodies
  - block growth factor receptors on tumor cells
  - induce tumor cell death
  - promote destruction by host defense cells
    (antibody dependent cellular cytotoxicity: ADCC)
Categories of Anti-Cancer Therapeutics

- **Epigenetic Modulators**
  - modify histones and gene expression

- **Proteasome Inhibitors**

- **Cell Differentiation Agents**
  - induce terminal differentiation to non-replicating state (leukemias/lymphomas but not solid tumors to date)
Categories of Anti-Cancer Therapeutics

- anti-tumor monoclonal antibodies
- immune checkpoint modulators (overcome tumor-induced suppression of host defenses)
- immunomodulators (stimulate immune system)
- anti-cancer vaccines (prophylactic or therapeutic)
### Inherited Cancer Risk

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Syndrome</th>
<th>Associated Gene</th>
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</thead>
<tbody>
<tr>
<td>Leukemias and lymphomas</td>
<td>Ataxia telangiectasia</td>
<td>ATM</td>
</tr>
<tr>
<td>All cancers</td>
<td>Bloom syndrome</td>
<td>BLM</td>
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<tr>
<td>Breast, ovarian, pancreatic, and prostate cancers</td>
<td>Breast-ovarian cancer syndrome</td>
<td>BRCA1, BRCA2</td>
</tr>
<tr>
<td>Breast, thyroid and endometrial cancers</td>
<td>Cowden syndrome</td>
<td>PTEN</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>Familial adenomatous polyposis (FAP)</td>
<td>APC</td>
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<tr>
<td>Melanoma</td>
<td>Familial atypical multiple mole–melanoma syndrome (FAMM)</td>
<td>CDKN2A</td>
</tr>
<tr>
<td>Retinal cancer</td>
<td>Familial retinoblastoma</td>
<td>RB1</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Fanconi’s anemia</td>
<td>FACC, FACA</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>Hereditary nonpolyposis colorectal cancer/Lynch syndrome</td>
<td>MLH1, MSH2, MSH6, PMS2</td>
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<tr>
<td>Pancreatic cancer</td>
<td>Hereditary pancreatitis/familial pancreatitis</td>
<td>PRSS1, SPINK1</td>
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<tr>
<td>Leukemias, breast, brain and soft tissue cancers</td>
<td>Li-Fraumeni</td>
<td>TP53</td>
</tr>
<tr>
<td>Pancreatic cancers, pituitary adenomas, benign skin and fat tumors</td>
<td>Multiple endocrine neoplasia 1</td>
<td>MEN1</td>
</tr>
<tr>
<td>Thyroid cancer, pheochromacytoma</td>
<td>Multiple endocrine neoplasia 2</td>
<td>RET, NTRK1</td>
</tr>
<tr>
<td>Pancreatic, liver, lung, breast, ovarian, uterine and testicular cancers</td>
<td>Peutz–Jeghers syndrome</td>
<td>STK11/LKB1</td>
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<tr>
<td>Tumors of the spinal cord, cerebellum, retina, adrenals, kidneys</td>
<td>von Hippel-Lindau syndrome</td>
<td>VHL</td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>Wilms’ tumor</td>
<td>WT1</td>
</tr>
<tr>
<td>Skin cancer</td>
<td>Xeroderma pigmentosum</td>
<td>XPD, XPB, XPA</td>
</tr>
</tbody>
</table>
surgical removal of ‘at risk’ organ in high risk patients
  – mastectomy, oophorectomy (BRCA-1/2 carriers)
  – stomach (CDH1 mutation)
  – thyroid (RET mutation)
  – colon (APC mutation)

detection of early cancer and surgical resection
  – elevated catecholamines (phaeochromocytoma)
  – elevated calcitonin (thyroid cancer)
The Current Status of Cancer Care
Flying Blind:
One-Size-Fits All Rx Approaches to Complex Multigenic Diseases
Non-responders to Oncology Therapeutics Are Highly Prevalent and Very Costly
Ignoring The Obvious in Clinical Practice

• diseases are not uniform
• patients are not uniform
• a “one-size fits all” Rx approach cannot continue
• ignores known variation in disease progression and therapeutic responses

• inefficiency and waste caused by empirical Rx
• cost of futile therapy
• risk to patients via AE’s
• first rule of radical ethics: do no harm!
The Path to Precision (Personalized) Therapy
Medical Progress: From Superstitions to Symptoms to Signatures
Understanding Cancer Biology and the Quest for Improvements in Cancer Care

- **Histopathology**
- **Molecular profiling and disease subtyping**
- **Robust biomarkers**
- **New Rx targets and Rx discovery**
- **Rational Rx based on individual patient molecular profile(s)**

- **Anatomic pathology**
- **Molecular pathology**
- **Molecular medicine**
- **Precision (personalized) medicine**
Precision Medicine

- right diagnosis and disease classification and subtyping by MDx
- right Rx for right disease subtype (efficacy)
- right Rx for right patient (efficacy and adverse event reduction)
- right dose, duration and timing (efficacy, safety and compliance)
Mapping Causal Perturbations in Molecular Pathways and Networks in Disease: Defining a New Taxonomy for Disease

“Omics” Profiling to Identify Disease Subtypes (+ or - Rx Target)

Altered Network Structure and ID of Molecular Targets for MDx and/or Rx Action
Heterogeneity of Driver Oncogenes in NSCLC

Frequencies of Molecular Alterations in CRC and Responsiveness to Cetuximab or Panitumumab

Oncogene Addiction

- tumor cells become reliant on particular oncogene
- die if addictive oncogene is inhibited
- rationale for ‘targeted’ cancer therapy to selectivity inhibit the relevant oncogene
Biomarkers, Disease Subtyping and Targeted Therapy: Companion Diagnostics – the Right Rx for the Right Disease (Subtype)

Her-2+ (Herceptin) (Perjeta)

EML4-ALK (Xalkori)

KRAS (Erbitux) (Vectibix)

BRAF-V600 (Zelboraf)
### Targeted Oncology Therapies in Molecularly Stratified Populations

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Target</th>
<th>Agent</th>
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<tbody>
<tr>
<td>Breast carcinoma</td>
<td>HER2 amplification</td>
<td>trastuzumab, lapatinib</td>
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<tr>
<td>NSCLC (adenoCA)</td>
<td>EGFR mutations</td>
<td>EGFR TKIs (erlotinib, gefitinib)</td>
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<tr>
<td>NSCLC</td>
<td>EML-ALK</td>
<td>ALK inhibitors (crizotinib)</td>
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<tr>
<td>GIST</td>
<td>KIT and PDGFRA mutations</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Melanoma</td>
<td>BRAF-V600 mutation</td>
<td>BRAF inhibitor (vemurafenib)</td>
</tr>
<tr>
<td>Ewing's sarcoma</td>
<td>EWS-FLI translocation</td>
<td>anti-IGF1R mab (figitumumab)</td>
</tr>
<tr>
<td>Medulloblastoma BCC</td>
<td>PTCH1 or SMO mutations</td>
<td>SMO inhibitors (vismodegib)</td>
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<tr>
<td>Ovarian/ breast CA</td>
<td>BRCA1/BRCA2 mutations</td>
<td>PARP inhibitors (olaparib)</td>
</tr>
<tr>
<td>PRCC</td>
<td>MET mutations</td>
<td>MET TKIs (ARQ197. XL880)</td>
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The Overly Simplistic and Deterministic Dangers of a Genome-Sequence Centric Perspective

Genes For ....
The Over-Simplified Perspective That Whole Exome-and Whole Genome-Sequencing Will Reveal the Full Etiology of Disease Pathogenesis and Transform Treatment Options
Individual Variation, Genome Complexity and the Challenge of Genotype-Phenotype Predictions

Junk No More: Pervasive Transcription
- alternate transcription/transcription/translation/(co)splicing
- SNPs, CNVs
- pseudogenes
- indels, SVs
- ncRNAs
- phasing
- epistasis
- imprinting
- silencing

recognition of the complexity of genome organization and regulation

Cell-specific Molecular Interaction Networks

Perturbed Networks and Disease
Profiling Changes in Biological Signaling Networks in Cancer: Understanding Cancer Requires a Holistic “Systems” Approach

- genome sequence data alone does not provide a sufficiently complete picture for either Dx or Rx decisions
  - need to understand cancer as a complex multi-component process

- mapping disruption in signaling pathways requires profiling of multiple aspects of both genotypic and phenotypic changes
The Need for Multi Molecular Diagnostic Platforms to Maximize the Number of Actionable Drug: Target Associations to Guide Therapeutic Decisions

FISH = fluorescent in situ hybridization
CISH = chronogenic in situ hybridization
IHC = immunohistochemistry

Dabrafenib
Trametinib
Vemurafenib

Afatinib
Gefitinib
Imatinib
Panitumumab

Cetuximab
Erlotinib
Geftinib
Imatinib
Panitumumab

Everolimus
Hormone therapy
Lapatinib
Pertuzumab
T-DM1
Trastuzumab

Afinitor
Tirelizostat
Erlotinib
Gefitinib
Imatinib
Panitumumab

Crizotinib
Everolimus
Lapatinib
Trastuzumab

Sequencing
(Next-Gen Sanger)
Alteration of Rx Target in One Cancer Cell Type May Not Always Translate to Rx Efficacy in Cancers Arising in Different Cell Types
Expression of Same Mutation in Cancers Arising in Different Cell Lineages but with Different Response to Same Targeted Therapy

**Melanoma**
BRAF-V600

- positive response to vemurafenib

**Colorectal Cancer**
BRAF-V600

- 10% patients carry mutation but unresponsive to vemurafenib due to compensatory activation of EGFR
EGFR Mutations in Different Structural Domains

EGFR mutations in lung cancer reside in the intracellular kinase domain

EGFR mutations in glioblastoma multiforme (GBM) cluster in the extracellular domain

- poor clinical results in GBM with erlotinib, gefitinib
The Three Most Dangerous Phenotypes in Tumor Cell Clones: metastasis; immunoevasion; and drug resistance

Dynamic Heterogeneity

Emergence and Adaptive Evolution of Different Tumor Clones and Subclones During Tumor Progression
Drug Resistance: The Principal Challenge in Cancer Rx Therapy
Tumor Cell Heterogeneity: The Omnipresent and Greatest Challenge in Cancer Therapy
Tumor Cell Heterogeneity: The Omnipresent and Greatest Challenge in Cancer Therapy
Tumor Cell Heterogeneity: The Omnipresent and Greatest Challenge in Cancer Therapy
Emergence of Drug-Resistance Mutations in Tumor Progression

- “intrinsic resistance” to specific Rx
- exist prior to Rx

- “acquired resistance” to specific Rx
- Rx as selective pressure (cf. antibiotic resistance in bacteria)
Point Mutation\(^{(M)}\)-Driven Resistance to Targeted Anticancer Drugs

Evolution of Rx-Resistant Clones During Tumor Progression

- Rx-sensitive
- Rx-resistant
- Rx-sensitive
- Rx-resistant
- refractory resistant disease
## Mutations Responsible for Acquired Resistance to Targeted Therapies

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genetic aberration</th>
<th>Tumor type</th>
<th>Acquired drug resistance</th>
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<tbody>
<tr>
<td>EGFR</td>
<td>T790M</td>
<td>Advanced NSCLC</td>
<td>Gefitinib, Erlotinib</td>
</tr>
<tr>
<td>KRAS</td>
<td>Codon 12, 13 and 61</td>
<td>Colorectal cancer</td>
<td>Cetuximab</td>
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<tr>
<td>KIT</td>
<td>T670I</td>
<td>GIST</td>
<td>Imatinib</td>
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<td>PIK3CA</td>
<td>NS</td>
<td>NSCLC</td>
<td>Erlotinib, Gefitinib</td>
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<td>ALK</td>
<td>C1156Y L1196M</td>
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<td>Crizotinib</td>
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<td>MEK1</td>
<td>C121S</td>
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<td>Vemurafenib</td>
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<td>BRAF</td>
<td>Amplification</td>
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<td>Vemurafenib</td>
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<tr>
<td>NRAS</td>
<td>Q61K</td>
<td>Melanoma</td>
<td>Vemurafenib</td>
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Mutation Profiling of 23 Glioma Patients and Hypermutation in Temozolomide (TMZ) Treated Patients

From: B. E. Johnson et al. (2014) Science 343, 189
Emergence of Drug Resistance to Targeted Therapy in Melanoma

Initial Rx-Response to Targeted Rx

Rx-Resistance via Alternate Molecular Signaling Pathway (Network Redundancy)

Circumvention of Rx-Resistance Requires Multi-site Blockade of Connected Signaling Pathways

B = 15 weeks Rx (Zelboraf®)
C = 23 weeks Rx and emergence of MEK1C1215 mutant (Wagle et al. (2011) JCO 29, 3085)
‘Compensatory’ Signaling Pathways and Drug Resistance

Linkage (Connections) Between Different Signaling Pathways Offers a Major By-Pass for Cancer Cells to Develop Rx Resistance
Network Pharmacology and Emergence of Drug-Resistant Cells

**Rx-sensitive pathway blockade and cell death**

1. **Rx-sensitive**
2. **activation of downstream pathway component(s)**
3. **Rx-resistance**
4. **activation of downstream pathway components via by-pass signaling from other pathways**
Drug Resistance Can Arise from Both Mutations in the Drug-Target Plus Use of By-Pass Pathways
Resistance to TKIs in EGFR-Mutant Lung Adenocarcinomas*

- Development of resistance to gefitinib or erlotinib in c.40% patients after one year
- Resistance via additional mutations
  - Second-site resistance EGFR mutations (>50%)
- Resistance via downstream or other by-pass pathways
  - Amplification of MET receptor gene (5-10%)
  - Mutations in PIK3CA encoding PI10α subunit of downstream lipid kinase PI3K (<5%)
- Histologic transformation: EMT or small lung cancer (<5%)

* K. Ohashi et al. (2012) PNAS 109, 12282
Monitoring Treatment Efficacy
Monitoring Treatment Responses in Cancer Patients

- no, partial or complete response
- progression-free survival (interval) (PFS)
- progressive disease
- chronic, stable disease
- regulatory parameters: PFS and overall survival (OS)
- recurrent disease in patients previously viewed as having no or minimal residual disease
- terminal disease
Lung Lesion develops cavity

Continue measuring target lesions in their longest diameter, even when they develop central cavities or necrosis.

If the sum of diameters does not accurately reflect the patient's response assessment, a different assessment may be provided, accompanied by explanatory comments justifying so.
Monitoring Treatment Responses in Cancer

- **Response Evaluation Criteria In Solid Tumors (RECIST)**
  - imaging of size and volume of tumor metastases
  - not sufficiently sensitive to detect emergence of treatment-resistant tumor cell clones in solid tumors
Monitoring Treatment Responses in Cancer

- earlier detection of lack of Rx efficacy
  - switch Rx regimen

- earlier detection of emergence of treatment-resistant clones
  - agile, anticipatory treatment to hit new resistant clones
  - greater current feasibility with ‘liquid’ hematopoietic tumors (leukemias, lymphomas) than solid tumors
given the high frequency (inevitability?) of emergence of Rx-resistant clones (intrinsic or acquired resistance) how can their emergence be best monitored?
Fine Needle Aspiration (FNA) Biopsy

Minimally-Invasive Profiling (Blood/Other Body Fluids)
“Liquid Biopsy”
Monitoring of Changing Clonal Dynamics by Monitoring Tumor Specific Biomarkers in CRC

At diagnosis = APC and KRAS (Wild Type)
emergence = KRAS and NRAS mutations and MET amplification clones

Mapping the Dynamics of Clonal Diversification in Tumor Progression

- urgent need for new technologies for minimally invasive profiling of the full spectrum of clones present in a patient and changes occurring over time with treatment
- difficult to sample (biopsy) multiple metastases in solid tumors
- the quest to create a ‘liquid biopsy’ for profiling clonal dynamics for solid tumor profiling from analysis of blood samples
  - exosomes
  - circulating tumor cells
  - cell-free (cf) DNA or miRNAs from tumor cells
Mapping the Dynamics of Clonal Diversification in Tumor Progression

- urgent need for new technologies for minimally invasive profiling of spectrum of clones present in a patient and changes over time with treatment
- inability to sample (biopsy) multiple metastases in solid tumors
- the quest to create a ‘liquid biopsy’ for tumor profiling from analysis of blood samples

Lecture in Week 14 on Drug Development
- cancer as a complex adaptive system
- dynamics of clonal evolution during tumor progression and treatment
- clonal evolutionary dynamics as a complex interplay between tumor (evasion) and host (detection/destruction) activities
- the evolution of clonal heterogeneity is the core problem in effective therapy
Lecture 2: Cancer Treatment

- rethinking current chemotherapeutic approaches
- the promise of immunotherapy
- post-treatment clinical challenges for cancer survivors
- the impact of advanced cancer on body function and quality-of-life
- palliative care (non-curative)
- end-of-life care