WEEK 11, LECTURE 1:
SYSTEMIC TREATMENT OF CANCER:
PHARMACOLOGIC, BIOLOGICAL AND
IMMUNOTHERAPEUTIC TREATMENTS

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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

Weeks 11 and 12

- current treatment practices and limitations
- confronting the tumor cell heterogeneity problem
- emerging treatment strategies to overcome tumor cell heterogeneity and rapid emergence of therapeutic resistance
Meeting The Cancer Challenge

The Ideal

- prevention
- cure
US Cancer Deaths 2014

580,000
The Biological Complexity of Cancer and the Design of Future Treatment Strategies

- successful surgical removal of primary tumor assumed (except brain tumors)

- targeting metastatic disease and circumventing Rx resistance
  - subclinical (adjuvant Rx)
  - advanced clinically evident metastases
  - minimal residual disease and tumor dormancy
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?
The Extravagant Landscape of Genomic Alterations in Cancer (Cell 2012, 150, 1107 and 1121)

- “malignant snowflakes”: each cancer carries multiple unique mutations and other genome perturbations
- disturbing implications for development of new Rx
Zonal Heterogeneity in Expression of Carbonic Anhydrase X in Renal Cell Carcinoma

Intratumor Genetic Heterogeneity in Multiple Regions of Primary Clear Cell Tumor and Three Metastases (Perinephric and Chest Wall) in RCC

From: M. Gerlinger et al. (2012) NEJM 366, 883
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
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?
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)
Drug Classes
Therapeutics

- small (heterocyclic) molecules <1500 Daltons Mw
- biologicals
  - recombinant (r)proteins, antibodies (natural/engineered)
  - nucleic acids: antisense, miRNAs, aptamers
- gene therapy (and delivery vectors)
- cell therapy
- vaccines
  - prophylactic, therapeutic
- novel drug formulations/drug delivery systems
(Bio) Pharmaceutical R&D

- small molecules (M_r typically <500 Daltons)
  - proprietary drugs (on patent) and generic versions (off-patent)
- biologicals (nucleic acids, genes, proteins, monoclonal antibodies, cells, vaccines)
  - proprietary biologicals (on-patent) and biosimilars (off patent)
## FDA-Approved Anti-Cancer Drugs

### DNA Damaging Agents

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Approved Indication</th>
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</thead>
<tbody>
<tr>
<td>altretamine</td>
<td>Hexalen</td>
<td>ovarian cancer</td>
</tr>
<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>
</tr>
<tr>
<td>busulfan</td>
<td>Myleran, Busulfex</td>
<td>certain leukemias</td>
</tr>
<tr>
<td>carboplatin</td>
<td>Paraplatin, Paraplat</td>
<td>breast, lung and ovarian cancers</td>
</tr>
<tr>
<td>carmustine</td>
<td>BiCNU</td>
<td>brain tumors, certain lymphomas</td>
</tr>
<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>
</tr>
<tr>
<td>doxorubicin hydrochloride</td>
<td>Adriamycin PFS,</td>
<td>multiple cancers</td>
</tr>
<tr>
<td></td>
<td>AdriamycinRDF</td>
<td></td>
</tr>
<tr>
<td>epirubicin hydrochloride</td>
<td>Ellence</td>
<td>certain leukemias, breast and stomach cancers</td>
</tr>
</tbody>
</table>
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)
- immune cells with engineered anti-tumor activities
Cancer Predisposition Genes

**Retinoblastoma (RB)**

**Adenomatosis Polyposis Coli (APC)**
## Inherited Cancer Risk

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Syndrome</th>
<th>Associated Gene</th>
</tr>
</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>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>Hereditary pancreatitis/familial pancreatitis</td>
<td>PRSS1, SPINK1</td>
</tr>
<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>
</tr>
<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>

AACR Cancer Progress Report 2013, pg31
BRCA 1 and 2 as Tumor Suppressor Genes: Different Mutations May Confer Different Risks

- substantially increased lifetime risks of breast and ovarian cancers but only small risk of increased pancreatic cancer
- loss-of-function mutations in central gene region confer higher risk of ovarian cancer versus breast cancer than mutations at gene end regions
Screening and Cancer Prevention in Individuals with Inherited Germline Mutations in Cancer Predisposing Genes

- 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
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!
Non-responders to Oncology Therapeutics are highly prevalent and very costly.
The Path to Precision (Personalized) Therapy
Medical Progress: From Superstitions to Symptoms to Signatures
Precision (Personalized) Medicine

Mapping the Disruption in Molecular (Information) Signaling Pathways in Disease

Foundation of Improved Diagnostic Accuracy Prognosis and Rational Selection of Rx Choice
Mapping The Molecular Signatures of Disease: The Intellectual Foundation of Rational Diagnosis and Treatment Selection

Genomics

Proteomics

Molecular Pathways and Networks

Network Regulatory Mechanisms

ID of Causal Relationships Between Network Perturbations and Disease

Patient-Specific Signals and Signatures of Disease or Predisposition to Disease
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
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)
The Need for Multiple Molecular Diagnostic Platforms for Comprehensive Profiling of Actionable Drug: Target Associations to Guide Therapeutic Decisions in Oncology

- FISH
  - trastuzumab
  - lapatinib
  - pertuzumab
  - T-DM1
  - everolimus

- CISH
  - afatinib
  - cetuximab
  - erlotinib

- Sequencing (NGS; Sanger)
  - gefitinib
  - imatinib
  - panitumumab

- PCR
  - dabrafenib
  - trametinib
  - vemurafenib

- IHC
  - everolimus
  - hormone therapy
  - lapatinib
  - pertuzumab
  - T-DM1
  - trastuzumab

55 Actionable Drug/Target Associations

- abarelix
- cetuximab
- dacarbazine
- docetaxel
- erlotinib
- gefitinib
- gemcitabine
- irinotecan
- nab-paclitaxel
- oxaliplatin
- paclitaxel
- pertuzumab
- trastuzumab

19 Actionable Drug/Target Associations

- afatinib
- carboplatin
- cetuximab
- cisplatin
- crizotinib
- dabrafenib
- erlotinib
- everolimus
- gefitinib
- irinotecan
- lapatinib
- panitumumab
- trastuzumab
- vemurafenib
Oncogene Addiction and ‘targeted’ Cancer Therapies

- 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)
Heterogeneity of Driver Oncogenes in NSCLC

# Targeted Oncology Therapies in Molecularly Stratified Populations

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Target</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast carcinoma</td>
<td>HER2 amplification</td>
<td>trastuzumab, lapatinib</td>
</tr>
<tr>
<td>NSCLC (adenoCA)</td>
<td>EGFR mutations</td>
<td>EGFR TKIs (erlotinib, gefitinib)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>EML-ALK</td>
<td>ALK inhibitors (crizotinib)</td>
</tr>
<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>
</tr>
<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>
</tr>
</tbody>
</table>
Context:

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

Differential Sensitivity of Glioma-Versus Lung Cancer-Specific EGFR Mutations to EGFR Kinase Inhibitors

- 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
Tumor Cell Heterogeneity: The Omnipresent and Greatest Challenge in Cancer Therapy
The Extravagant Landscape of Genomic Alterations in Cancer (Cell 2012, 150, 1107 and 1121)

- “malignant snowflakes”: each cancer carries multiple unique mutations and other genome perturbations
- disturbing implications for development of new Rx
Cellular (Clonal) Heterogeneity:
A Ubiquitous Feature of Cancer and the Largest Obstacle to Effective Treatment

- between patients (inter-patient heterogeneity)
- within the primary tumor (zonal heterogeneity)
- between different metastases in the same patient (inter-regional heterogeneity)
Tumor Cell Heterogeneity:
The Omnipresent and Greatest Challenge in Cancer Therapy
Tumor Cell Heterogeneity:
The Omnipresent and Greatest Challenge in Cancer Therapy
Drug Resistance:

The Principal Challenge in Cancer Rx Therapy

The Co-existence of Multiple Tumor Cell Clones with Varied Susceptibility to Different-Rx
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)
Targeted Therapeutics and Cancer

Molecular Subtyping and RX Targets

Initial Rx-Response to Targeted Rx

Rx-Resistance via Redundant Molecular Pathways

B = 15 weeks Rx (Zelboraf®)
C = 23 weeks Rx and emergence of MEK1C1215 mutant
(Wagle et al. (2011) JCO 29, 3085)
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)
Point Mutation\(^{\text{M}}\)-Driven Resistance
to Targeted Anticancer Drugs

Evolution of Rx-Resistant Clones During Tumor Progression

- Rx-sensitive Rx1
- Rx-resistant
- Rx-sensitive Rx2
- Rx-resistant
- refractory resistant disease Rx\(^n\)
'Compensatory' Signaling Pathways and Drug Resistance

Linkage (Connections) Between Different Signaling Pathways Offers a Major By-Pass for Cancer Cells to Develop Rx Resistance
Redundancy and Robustness in Molecular Signaling Networks: The Biological Foundation of Rx Resistance

sensitive

sensitive

resistant

sensitive
Drug Resistance Can Arise from Both Mutations in the Drug-Target Plus Use of By-Pass Pathways
Monitoring Treatment Efficacy
### Monitoring Treatment Responses in Cancer Patients

- no, partial (PR) or complete (CR) responses
- 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
Tumor Responses to Crizotinib for Patients with ALK-positive NSCLC

*Partial response patients with 100% change have non-target disease present
Survival estimates are shown for different subtypes of breast cancer. The median survival times are as follows:

- HER2+ with trastuzumab: 12.8 months
- HER2+ without trastuzumab: 4.0 months
- HER2-: 3.4 months

The P-value for the difference in survival estimates is 0.0011.
RECIST (Response Evaluation Criteria In Solid Tumors)

![RECIST Image]

**Topics**
1. RECIST - Definitions
2. Measure the longest in plane diameter
3. Target Measurement Rules
4. Selecting Target Lesions
5. Importance of Imaging Consistency
6. Importance of IV-Contrast
7. Importance of IV-Contrast and proper timing, scanning delay
8. Imaging: Anatomy for CT/MRI
9. Target Measurement Rules at Follow-up
10. Progression by Non-Targets only
11. Reappearing Lesion
12. Splitting Lesions
13. Merging Lesions
14. Merging lesions example
15. Variable Enhancement
16. Lung Lesion develops cavity
17. Lymph Node Measurements, CT
18. Lymph Node Measurements, MRI
19. Bone mets
20. MRI
21. PET
22. Overview: RECIST vs. RECIST 1.1

**Topic 16**
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

**RECIST**

- **Response Evaluation Criteria In Solid Tumors**
- Imaging of size and volume of tumor metastases
- Not sufficiently sensitive to detect emergence of treatment-resistant tumor cell clones in solid tumors
The Urgent Need for New Diagnostics and Molecular Profiling Tools for Improved Monitoring of Tumor Progression

From ‘Static Snap Shot’ at Initial Diagnosis to Dynamic Monitoring of Clonal Population Dynamics
Tumor Profiling and Optimum Treatment Selection

- initial diagnosis ('static snapshot')

- longitudinal profiling during treatment for earlier detection of emergence of drug-resistant clones

- more agile shifts in Rx regimen to reflect changing clonal dynamics driven by Rx selection pressure(s)
Anticipation-Based Chemotherapy in CLL

Fine Needle Aspiration (FNA) Biopsy

Minimally-Invasive Profiling (Blood/Other Body Fluids)
Detection of Tumor-Associated Biomarkers in Blood: ‘The Liquid Biopsy’

- cell-free nucleic acids
  - DNA, miRNAs
- circulating tumor cells (CTC)
- exosomes
Gallery of representative HD-CTCs found in cancer patients. Each HD-CTC is cytokeratin positive (red), CD45 negative (green), contains a DAPI nucleus (blue), and is morphologically distinct from surrounding WBCs.

Liquid Biopsy:
Identifies Type of Cancer from Blood Draw
Lab on a Chip
From: He, Mei et al. (2014)
The Royal Society of Chemistry
Human plasma Carisome™ cMV isolated via Caris proprietary method captured on bead with anti-CD63 antibody
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