Advances in the Treatment of Colorectal Cancer

University of Colorado
Gastrointestinal Malignancies Program
November 2, 2013
Objectives

- What is the current state of treatment for colorectal cancer?

- What are some of the limitations of the current treatments for colorectal cancer?

- The next generation of treatments for colorectal cancer
Colon Cancer At-A-Glance*

- Colon cancer is the second leading cause of cancer-related death in the U.S.
- On average, your risk is about 1 in 20, although this varies widely according to individual risk factors.
- 90% of new cases occur in people 50 or older.
- People with a first-degree relative (parent, sibling, or offspring) who has colon cancer have two to three times the risk of developing the disease.
- There are currently more than one million colon cancer survivors in the U.S.

*Source: American Cancer Society
Advances in screening


*Rates are per 100,000 persons and are age-adjusted to the 2000 U.S. standard population (19 age groups - Census P25-1130)

Images from ACS
Advances in colorectal cancer

5-year-survival rates
(all stages)

Relative Survival (%)

Period of Diagnosis


Male
Female

Colorectal Cancer in 1997 versus Today

Treatment: 5-fluorouracil

- **Response rate = 10-15%**
- **Overall survival = 8-12 months**

Treatment: 5-fluorouracil
Oxaliplatin
Irinotecan
Bevacizumab/Ziv-aflibercept
Cetuximab/Panitumumab
Regorafenib

- **Response rate = 55-60%**
- **Overall survival has more than doubled!**
Chemotherapy for Colorectal Cancer

• **Marked Improvements in the Last Decade**
  – 8 new drugs approved since 1998 (ziv-aflibercept approved 08/2012, regorafenib approved 09/2012)
  – Overall survival has doubled compared to 5-fluorouracil alone
  – Response rates in large trials have surpassed 60%
  – KRAS testing opened an era of “targeted” patients

• **But . . . Many Negative Studies Since 2008**
  – Combining EGFR/VEGFR inhibition – failed
  – Adjuvant cetuximab, bevacizumab – failed

Advances in Understanding the Genetic Landscape of Colorectal Cancer

- On average, there are 90 genes mutated per cancer
- However, < 20 pathways will actually drive cancer development
- Most mutations are harmless

• Some patients with stage IV disease are cured using multi-disciplinary approaches (surgery, chemo, etc)

• Combination therapy is generally well-tolerated

• Biologics have added incremental (but sometimes limited) benefit

• Era of personalized therapy began with KRAS
Treatment for metastatic colorectal cancer has improved, but . . .

- No active drug: ~4-6 mo
- 5-FU/LV: 12-14 mo
- IFL: ~15-16 mo
- FOLFOX4: ~20 mo
- IFL + bevacizumab: 20.3 mo
- FOLFOX/FOLFIRI: 21.5 mo
- FOLFOX/FOLFIRI + double biologics: ~?

Are we hitting a wall with current drugs?

Courtesy of Wells Messersmith, MD
Colorectal cancer is expensive!

- 5-FU (500 mg/m²): $6
- Leucovorin (500 mg/m²): $85
- Capecitabine (2000 mg/m²/day): $3,250
- Irinotecan (180 mg/m²) / generic: $2,300 / $480
- Oxaliplatin (85 mg/m²) / generic: $4,190 / $590
- Bevacizumab (5 mg/kg): $2,560
- Cetuximab (250 mg/m²): $5,120
- Panitumumab (6 mg/kg): $4,360
- Afiblercept (4 mg/kg): $5,380
- Regorafenib (160 mg, 3/1): $5,650

1997: 6 months of 5-FU/LV costs ~$500
2012: 24 months therapy with combinations costs >$300,000

Courtesy of Lisa Thompson, PharmD
Current Cancer Treatment Strategy: One-size-fits-all

Gene Mutations

University of Colorado Anschutz Medical Campus
We want to find the right drugs for the right patient!
BRAF inhibition in Melanoma
BRAF Inhibition in Melanoma
Unfortunately, colorectal cancer is complex
Our Strategy here at CU

- Develop better therapies for colon cancer
- Find ways to select the right patient for these treatments
- Identify “rational combinations” for cancer treatment
- Convert the disease into a chronic medical illness rather than a terminal disease until we prevent/cure colon cancer
Roadmap of Precision Oncology

- Colorado Molecular Correlates Laboratory
  - KRAS
  - BRAF
  - MSI

- Hereditary Cancers Clinic
  - Familial Risk
Roadmap of Precision Oncology

1. Patient
   - Inform consent
   - Acquire samples

2. Omic Profiling
   - Comprehensive characterization of the tumor by cutting-edge and emerging technologies

3. Bioinformatics & Data Interpretation
   - Integrative analysis for finding "actionable" mutations or pathways
   - Link mutations with therapeutics
   - Generate mutational and treatment report

4. Omics-driven Treatment
   - Multi-disciplinary Molecular Tumor Board
   - Evaluate report from bioinformatics
   - Hypothesis-driven Phase I trials
   - Mechanism-based clinical studies

5. Clinical Response?
   - Registry studies
   - Pharmacodynamic analyses
   - Update database with new data

6. Drug Resistance?
   - Molecular mechanisms/correlations
   - Link new mutations with therapeutics
   - Guide preclinical studies

7. Salvage or New Therapy?
   - Inform novel therapeutics trials
   - Perform novel combination trials
Feasibility Study of Genomic Sequencing to Find Potential Targets for Personalized Therapy

This study is currently recruiting participants.
Verified May 2013 by University of Colorado, Denver

Sponsor:
University of Colorado, Denver

Collaborator:
University of Colorado Hospital

Information provided by (Responsible Party):
University of Colorado, Denver

ClinicalTrials.gov identifier:
NCT01869218
First received: May 28, 2013
Last updated: May 30, 2013
Last verified: May 2013

Purpose
This study is aimed to determine the feasibility of obtaining and molecularly characterizing pre-treatment tumor biopsies, to determine the feasibility of obtaining and molecularly characterizing archival and post-treatment tumor biopsies, to assess molecular expression changes between archival and baseline tumor samples, and to assess molecular expression changes between tumor samples obtained at baseline and at the time of disease progression.

<table>
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<th>Condition</th>
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<td>Hematologic Neoplasms</td>
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Study Type: Observational
Study Design:
- Observational Modal: Case-Only
- Time Perspective: Cross-Sectional

Official Title: Feasibility Study of Genomic Sequencing to Find Potential Targets for Personalized Therapy in Patients With Advanced Malignancies
KRAS Mutant Colorectal Cancer
The KRAS Pathway
Cetuximab
Panitumumab

The KRAS Pathway

Tumor Growth and Spread
The KRAS Pathway

Cetuximab
Panitumumab

Mutated KRAS

ERK

Tumor Growth and Spread

University of Colorado Anschutz Medical Campus
Ongoing Trials in KRAS Mutant CRC

- **AZD6244 + Irinotecan**
  - MEK inhibitor

- **MSC1936369B + FOLFIRI**
  - MEK inhibitor

- **AZD6244 + MK 2206**
  - MEK inhibitor + Akt inhibitor

- **PF-04691502 + PF-05212384**
  - PI3K + mTOR

- **Regorafenib + FOLFIRI**
  - c-kit, VEGFR2, BRAF

- **BIBW2992 (afatinib)**
  - EGFR, Her2 inhibitor

- **Sorafenib + Irinotecan**
  - RAF, kit, FLT-3, VEGFR-2,3, PDGFR

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Bench to Bedside Research in KRAS Mutant CRC

**CUCRC006**

- Vehicle
- Selumetinib
- CsA
- Combo
- Selumetinib+CsA
- CsA+selumetinib

**CRC007**

- Vehicle
- Selumetinib
- CsA
- Combo
- Selumetinib+CsA
- CsA+selumetinib

Percent day 1 vs. Days

Single agents vs. combo
Combos vs. vehicle
Clinical trial of selumetinib in combination with cyclosporine A in patients with metastatic KRAS mutant colorectal cancer approved by the National Cancer Institute Cancer Therapy Evaluation Program

Trial has been approved (even with the recent government shutdown)!
Help us fight colorectal cancer!

• Treatment for colorectal cancer is changing dramatically

• Research being performed will change the way we think about and treat colorectal cancer

• Clinical Trials are critical to do things better than we have in the past
Childhood ALL: Improvements in Survival

Slide courtesy of Lia Gore, MD
Questions