Progress towards an individualized approach to therapy: colorectal cancer

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GIST: PET change after 4 weeks imatinib

Multiple liver and upper abdominal ¹⁸FDG-accumulating metastases
A marked decrease in ¹⁸FDG uptake 4 weeks after starting imatinib

Overall Survival by Genotype
(Kaplan-Meier Estimate)

Von Mehren, ASCO, 2008
Personalized decision-making: predicting risk/benefit

Breast cancer oncologist envy—can there be the oncotype DX for other malignancies?

$3820 \rightarrow \text{RNA extraction} \rightarrow \text{algorithmic analysis} \rightarrow \text{RT PCR (21 genes)} \rightarrow \text{recurrence score, chemotherapy benefit}

Towards Personalized Therapy: Colorectal Cancer

- Tumor genetic profiling
  - Stage II colon cancer
  - Stage IV colorectal cancer
- Pharmacogenetics
  - Oxaliplatin efficacy
  - Irinotecan - UGT1A1
- Therapeutic Drug Monitoring

Colorectal Cancer: TNM Staging System

- Extent of invasion through bowel wall (T)
- Extent of LN metastases (N)
- Presence of distant metastases (M)
“Predictive” vs. “Prognostic”

- Predictive: response to treatment
- Prognostic: independent of treatment

Variables: host (germline) tumor
Colorectal Cancer Predictors: Microsatellite Instability (MSI)

- Defective DNA mismatch repair
- Different genetic mechanism for tumorigenesis
- Associated with HNPCC
- Appears to reflect improved prognosis
**E5202 – Stage II Colon Cancer**

- **Tumor block risk assessed based on Biology (18q/MSI)**
- **OBSERVATION**
  - High-risk (MSS and 18q LOH)
  - mFOLFOX6 v.
  - mFOLFOX6 + Bevacizumab qow
  - mFOLFOX6
  - LOH 18q
  - MSI + or no loss 18q

- **Accrual Goal: 3,125**

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**PETACC III: Correlative findings**

Tejpar & Roth, ASCO, 2009

- **MSI strong prognostic factor for RFS / OS in stage II**
- **Prognostic effect**
  - retained for RFS and OS despite treatment with SFU
  - LOH 18q not prognostic
- **Predictive:**
  - no evidence for an effect of the addition of irinotecan in MSI-H
- **Discordances with previous studies**
  - Biomarker studies may be confounded small size studies, retrospective studies, pooled analysis
  - Biology: Confounded by molecular heterogeneity
**E5202: High Risk Stage II**

**Planned accrual: 3610 patients**

- High Risk
- MSS or Hig LOH
- MSI-L + TLR LOH
- mFOLFOX6
- mFOLFOX6 + bevacizumab

**Really low risk?**

**Real-time RT-PCR for RNA Quantification from Fixed Paraffin-Embedded Tumor Tissue**

**QUASAR: Pre-Specified Primary Endpoint: Recurrence Risk**

Is there a significant relationship between the risk of recurrence and the pre-specified continuous Recurrence Score in stage II colon cancer patients randomized to surgery alone?
QUASAR Results: Colon Cancer Recurrence Score Predicts Recurrence Following Surgery

Prospectively-Defined Primary Analysis in Stage II Colon Cancer (n=711)

\[ p=0.004 \]

QUASAR Results: Recurrence Score, T Stage, and MMR Deficiency are Key Independent Predictors of Recurrence in Stage II Colon Cancer

NB: 17 patients had both T4 and MMR deficient tumors and had recurrence risks that were similar to those for patients with T3 and MMR proficient tumors and were not included in the plot.

Towards Personalized Therapy:

Tumor Genetics

- EGF-R antibodies: yes or no?
  - KRAS
  - BRAF
  - PTEN
- VEGF antibody: yes or no?
CRC: Adenoma-Carcinoma Sequence

DNA-based K-Ras Testing

Single agent cetuximab: N=80

Single agent panitumumab: N=208

K-Ras Mutation

Wild-Type K-Ras

Panitumumab registration trial


CALGB/SWOG 80405 Study Design
Open-label Phase III Study

Unresected advanced or mCRC N=160

Register

Patient

Screen for eligibility

Randomize Patients w/ Wild-type K-Ras tumor

Bevacizumab followed by FOLFOX or FOLFIRI q 2 wks

Cetuximab followed by FOLFOX or FOLFIRI q 2 wks

One cycle=8 weeks
mCRC=metastatic colorectal cancer

Ras: Downstream Signaling

Sebolt-Leopold, J. S. Clin Cancer Res 2008;14:3651-3656

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Clinical Cancer Research
Fig 1. KRAS and BRAF mutations correlate with lack of response to treatment with monoclonal antibodies targeting epidermal growth factor receptor. The dotted line indicates the cutoff for KRAS and BRAF mutations, with KRAS and BRAF mutations defining nonresponders. The dark line represents the 10% cutoff for KRAS and BRAF mutations, with KRAS and BRAF mutations defining nonresponders.

Wong et al, JCO, 2008

Fig 1. KRAS and BRAF mutations correlate with lack of response to treatment with monoclonal antibodies targeting epidermal growth factor receptor. The dotted line indicates the cutoff for KRAS and BRAF mutations, with KRAS and BRAF mutations defining nonresponders. The dark line represents the 10% cutoff for KRAS and BRAF mutations, with KRAS and BRAF mutations defining nonresponders.

Wong et al, JCO, 2008

Potential relationship between KRAS status and response to EGFR monoclonal antibodies, alone or in combination with irinotecan, in chemorefractory patients.

Nonresponder: KRAS wildtype
- Responds to standard dose: 22%
- Responds to increased dose*: 5%

Nonresponder: KRAS mutant
- 40%

Nonresponder: BRAF mutation 16%
- Nonresponder: Loss of PTEN or PI3K mutation % unknown
- Nonresponder: Reason unknown % unknown

Fig 1. Potential relationship between KRAS status and response to epidermal growth factor receptor (EGFR) monoclonal antibodies, alone or in combination with irinotecan, in chemotherapy-refractive patients. Wong et al, JCO, 2008
Patients with a known V600E BRAF mutation appear to be unlikely to benefit from anti-EGFR monoclonal antibodies.

9 Patients with a known V600E BRAF mutation appear to be unlikely to benefit from anti-EGFR monoclonal antibodies.
Recent small studies suggest that patients with wt KRAS and a BRAF mutation are unlikely to respond to therapy with antibodies targeted to the epidermal growth factor receptor.

- Testing for the BRAF V600E mutation can be performed on formalin fixed paraffin embedded tissues. This is usually performed by PCR amplification and direct DNA sequence analysis. This testing should be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA-88) and qualified to perform highly complex clinical laboratory (molecular pathology) testing.

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Although the data are somewhat inconsistent...
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Predicting oxaliplatin efficacy? McLeod et al, ASCO, 2008

- Genomic DNA from 180/238 patients on C80203 (FOLFOX vs. FOLFIRI +/- cetuximab)
- Genotype transporter genes involved in irinotecan and oxaliplatin clearance:
  - ABCC2, ABCC4, ABCG2, SLCO1B1, SLC22A1, SLC22A2
- Association of genotype with response and toxicity
- Result:
  - ABCG2 34 G>A associated with response to FOLFOX, resistance to FOLFIRI but not to toxicity

Irinotecan pathway

- CPT-11 → ABCB1 → CYP3A4 → APC → SN-38G → ADPRT → TDP1 → CDC45L → Cell Death
UGT1A1: promoter polymorphism and toxicity

![Diagram of UGT1A1 gene structure]

Iyer et al 2002

UGT1A1 TA repeat: irinotecan neutropenia/activity

![Bar charts showing percentage of grade 4/5 neutropenia and objective response by UGT1A1 genotype]

N=524

McLeod et al, ASCO 2003

Patients with Reduced UGT1A1 Activity

Individuals who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia following initiation of CAMPTOSAR treatment. A reduced initial dose should be considered for patients known to be homozygous for the UGT1A1*28 allele (see DOSAGE AND ADMINISTRATION). Heterozygous patients (carriers of one variant allele and one wild-type allele which results in intermediate UGT1A1 activity) may be at increased risk for neutropenia; however, clinical results have been variable and such patients have been shown to tolerate normal starting doses.

Camptosar package insert, May 2005
Towards Personalized Therapy of Colon Cancer: Pharmacogenetics

- Oxaliplatin efficacy
- Rare polymorphism
- Small sample size
- Irinotecan toxicity
  - Regimen dependent
  - Not all or none
- VEGF antibody efficacy
  - Polymorphisms?
- Cetuximab efficacy
  - FCγR polymorphisms?

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**Drug Receptor Genotypes**

<table>
<thead>
<tr>
<th>Drug Receptor Genotypes</th>
<th>Drug Efficacy (%)</th>
<th>Toxicity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>w/t/wt</td>
<td>&gt; 80</td>
</tr>
<tr>
<td></td>
<td>w/t/m</td>
<td>&gt; 80</td>
</tr>
<tr>
<td></td>
<td>m/m</td>
<td>&gt; 80</td>
</tr>
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</table>

**Drug Concentration**

<table>
<thead>
<tr>
<th>Drug Concentration</th>
<th>Time (h)</th>
<th>Efficacy (%)</th>
<th>Toxicity (%)</th>
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<tbody>
<tr>
<td>A</td>
<td>24</td>
<td>75</td>
<td>1</td>
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<td></td>
<td>99</td>
<td>35</td>
<td>1</td>
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<tr>
<td></td>
<td>50</td>
<td>10</td>
<td>1</td>
</tr>
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</table>

**Evans WE and Relling MV, Science 286:487-91, 1999**
Biochemical Pathways of 5-FU Metabolism

Relationship between Systemic Exposure and survival

Monitoring 5FU?

Remaining questions include:
- What is the target therapeutic range?
  - For toxicity
  - For efficacy
  - With oxaliplatin
- When to sample?
- Would clinicians do this?
- Is this important?
What ELSE should I do ??

**Treatment Arms**
*(CALGB -- Adjuvant Study C89803)*

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Dosage</th>
<th>Treatment Duration</th>
</tr>
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<tbody>
<tr>
<td>CPT-11</td>
<td>125 mg/m²/wk × 4 wks, q 6 wks</td>
<td>5 cycles (30 wks of therapy)</td>
</tr>
<tr>
<td>S-5 FU</td>
<td>500 mg/m²/wk × 4 wks, q 6 wks</td>
<td>5 cycles (32 wks of therapy)</td>
</tr>
<tr>
<td>LV</td>
<td>20 mg/m²/wk × 4 wks, q 6 wks</td>
<td>4 cycles (28 wks of therapy)</td>
</tr>
</tbody>
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**Methods**

- Prospective questionnaires during adjuvant therapy & six months after completion
  - Diet, medications and lifestyle
    - 131 food questions, smoking, BMI & wt change
    - Analgesic usage, physical activity
  - 98% completion first, 92% completed second
  - Analysis of patients free of recurrence at 2nd
- ASA use assessed on both
- Metabolic equivalents of exercise on second
Findings

- Exercise DECREASES risk of recurrence
  - Meyerhardt et al, JCO, 2006

- ASA use DECREASES risk of recurrence

- Western diet INCREASES risk of recurrence
  - Meyerhardt et al, JAMA, 2007

CALGB/SWOG 80702: Stage III Colon Cancer

Resected Stage III Colon Cancer

N = 2,500

6 treatments of mFOLFOX6

Celecoxib 400 mg daily

Placebo

12 treatments of mFOLFOX6

Celecoxib starts concurrently with FOLFOX and continue for 3 years

Towards Personalized Therapy: Colorectal Cancer

- Prognostic but not predictive genetic signature for stage II colon cancer
- KRAS and perhaps BRAF mutations predict NON-response to EGFR antibodies
- Need pharmacogenetic data from large studies
- Therapeutic drug monitoring impractical as of now
- Personal choices may matter
  - exercise, diet, ASA, vitamin D