Best of SWOG Update: GI Oncology
Fall Meeting, October 2014

Howard S. Hochster, MD
GI Committee Chair
Thanks to the Chief!

To Chuck Blanke
GI Committee Leadership

- Colon: Anthony F. Shields, Philip Gold
- Rectal: Cathy Eng, Lisa Kachnic
- Gastroesophageal: Larry Leishman, Syma Iqbal
- Pancreas: Philip Philip
- Hepato-Biliary: Tony El-Khouiery, Abby Siegel
- Translational Med: Heinz-Josef Lenz, Wells Messersmith
- Statistics: Katherine Gutherie
- Support: Kimberle Kaberle

MANY THANKS!
Colon Cancer

Chuck Blanke

H-J Lenz

Tony Shields

Phil Gold
CALGB/SWOG 80405: Phase III trial of FOLFIRI or FOLFOX with Bevacizumab or Cetuximab for patients w/ KRAS *wild type* untreated metastatic adenocarcinoma of the colon or rectum

A Venook, D Niedzwiecki, HJ Lenz, F Innocenti, M Mahoney, B O’Neil, J Shaw, B Polite, H Hochster, R Goldberg, R Mayer, R Schilsky, M Bertagnolli, C Blanke for the ALLIANCE and SWOG

PRESENTED AT THE 2014 ASCO ANNUAL MEETING. PRESENTED DATA IS THE PROPERTY OF THE AUTHOR.
CALGB/SWOG 80405: FINAL DESIGN

mCRC 1st-line

KRAS wild type (codons 12,13)

STRATA:
FOLFOX/FOLFIRI
Prior adjuvant
Prior XRT

FOLFIRI or FOLFOX
MD choice

Chemo + Cetuximab

Chemo + Bevacizumab

N = 1140 (SWOG = 646)

1° Endpoint: Overall Survival
CALGB/SWOG 80405: Overall Survival

<table>
<thead>
<tr>
<th>Arm</th>
<th>N (Events)</th>
<th>OS (m)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo + Cetux</td>
<td>578 (375)</td>
<td>29.9</td>
<td>27.0-32.9</td>
</tr>
<tr>
<td>Chemo + Bev</td>
<td>559 (371)</td>
<td>29.0</td>
<td>25.7-31.2</td>
</tr>
</tbody>
</table>

P=0.34
HR 0.925 (0.78-1.09)
CALGB/SWOG 80405: Progression-Free Survival (Investigator Determined)

<table>
<thead>
<tr>
<th>Arm</th>
<th>N (Events)</th>
<th>PFS (m) Median</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo + Bev</td>
<td>559 (498)</td>
<td>10.8</td>
<td>9.7-11.4</td>
</tr>
<tr>
<td>Chemo + Cetux</td>
<td>578 (499)</td>
<td>10.4</td>
<td>9.6-11.3</td>
</tr>
</tbody>
</table>

P=0.55
HR 1.04 (0.91 -1.17)
Colorectal Cancer: 20 Years Later
meta-analysis 1992  80405 results

CALGB/SWOG 80405

Median 12 mos  Median 30 mos

Fig 2. Overall survival.  J Clin Oncol, 1992
670/1137 patients (59%) with KRAS codon 12/13 WT tumors evaluable
621/1137 analyzed (55%) analyzed
95/621 (15.3%) patients new ras mutation identified

**KRAS**

<table>
<thead>
<tr>
<th>Exon</th>
<th>Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>1.8%</td>
</tr>
<tr>
<td>4</td>
<td>117</td>
<td>5.9%</td>
</tr>
</tbody>
</table>

**NRAS**

<table>
<thead>
<tr>
<th>Exon</th>
<th>Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2.3%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4.2%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

†Percentages relate to fraction of RAS evaluable patients with mutations in particular exons;

*One patient had a mutation at both NRAS Exon1 codon12 and NRAS Exon3 codon61
## Comparability of RAS subgroups: Efficacy

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Chemo + BV N</th>
<th>Chemo + CET N</th>
<th>Response Rate (%)&lt;sup&gt;*&lt;/sup&gt; BV vs CET p-value</th>
<th>PFS time Hazard ratio 95% CI p-value</th>
<th>OS time Hazard ratio 95% CI p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KRAS codon 12/13 wild-type</strong></td>
<td>559</td>
<td>578</td>
<td>57.2 vs 65.6 p=0.02</td>
<td>10.8 vs 10.4† 1.04 0.91–1.17 p=0.55</td>
<td>29.0 vs 29.9† 0.92 0.78–1.09 p=0.34</td>
</tr>
<tr>
<td><strong>RAS evaluable†‡</strong></td>
<td>324</td>
<td>346</td>
<td>56.0 vs 68.8 p&lt;0.01</td>
<td>11.4 vs 10.9† 1.10 0.90–1.30 p=0.31</td>
<td>30.3 vs 30.8† 0.90 0.70–1.10 p=0.40</td>
</tr>
</tbody>
</table>

<sup>*</sup>733 KRAS codon 12/13 WT and 406 RAS evaluable patients are evaluable for response

†Median, months;

‡Patients with KRAS codon 12/13 wild-type tumors for which tumor DNA samples were evaluable for other RAS mutations
Overall Survival By Arm
(All RAS Wild Type Patients)

<table>
<thead>
<tr>
<th>Arm</th>
<th>N (Events)</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo</td>
<td>256</td>
<td>31.2 (26.9-34.3)</td>
<td>0.9 (0.7-1.1)</td>
<td>0.40</td>
</tr>
<tr>
<td>+ Bev</td>
<td>178</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemo</td>
<td>270</td>
<td>32.0 (27.6-38.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ Cetux</td>
<td>177</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

% Event Free

Months From Study Entry

# At Risk

Chemo: 256 199 147 77 35 16 5 2
Bev: 270 205 164 88 41 24 7 1
Cetux: 270 205 164 88 41 24 7 1
### Progression Free Survival By Arm

*(All RAS Wild Type Patients)*

<table>
<thead>
<tr>
<th>Arm</th>
<th>N (Events)</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo</td>
<td>256</td>
<td>11.3</td>
<td>1.1 (0.9-1.3)</td>
<td>0.31</td>
</tr>
<tr>
<td>+ Bev</td>
<td>221</td>
<td>(10.3-12.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemo</td>
<td>270</td>
<td>11.4</td>
<td>1.1 (0.9-1.3)</td>
<td>0.31</td>
</tr>
<tr>
<td>+ Cetux</td>
<td>241</td>
<td>(9.6-12.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Graph:**
- % Event Free vs. Months From Study Entry.
- Two lines representing different arms.
- # At Risk:
  - Chemo: 256, 112
  - Chemo + Bev: 221, 137
  - Chemo + Cetux: 241, 126
CALGB/SWOG C80702 for Stage III Colon Cancer

Resected Stage III Colon Cancer

N =1855/2500 Sep, 2014

Celecoxib starts concurrently with FOLFOX and continue for 3 years

IDEA International collaboration: 6 prospective studies with >12,000 patients to test non-inferiority of 3 months of therapy. Interim Analysis May, 2014- study to continue as boundary not crossed. Final Analysis expected Fall, 2016
**COLLABORATION WITH SWOG CANCER PREVENTION COMMITTEE:**

**S0820:** A Double Blind Placebo-Controlled Trial of Eflornithine and Sulindac to Prevent Recurrence of High Risk Adenomas and Second Primary Colorectal Cancers in Patients with Stage 0-III Colon Cancer, Phase III (PACES)

**Baseline data collection:**
- audiogram
- blood
- urine
- CT-scans
- colonoscopy

*Stratification by stage:
- 0 or I
- II (no chemo)
- II (adj. chemo)
- III

**Trial Status:** Activated Jan 2013  n=24/1488

**3-year study intervention**

**5-year follow-up**

**Patients 9 – 15 months post-resection**

**CT and Colonoscopy within 42 days of registration**

**End-of-study audiogram, blood, urine collection**

**Colonoscopy**

**Primary endpoint =** 3-year rate of high risk adenomas or 2nd primary CRCs.
**SWOG 1406:** Dual BRAF and EGFR inhibition in Metastatic Colorectal Cancer

- BRAF mutations occur in 7% of mCRC
  - *Large cooperative group effort needed for screening and enrollment*

- Very poor prognosis and a unique biology
  - Substantial clinical need

- Resistance to BRAF inhibition is through EGFR activation: *Dual inhibition needed*

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**Eligibility:**
1) BRAF \( V600 \) mutation
2) Prior treatment for metastatic disease
3) No more than 2 prior progression on chemotherapy
4) No prior cetuximab

**Stratified:**
1) Prior treatment with irinotecan

**PFS**

<table>
<thead>
<tr>
<th>Arm A</th>
<th>Control + Irinotecan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm B</td>
<td>Vemurafenib + Cetuximab + Irinotecan</td>
</tr>
</tbody>
</table>

**PDX Model**
- Embedded patient-derived xenografts

**Patient**
- Baseline vs Treated

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SWOG Hope Funding, Jackson Lab Collaboration
Kopetz (PI), Hochster; Mao et al CCR ‘12, Prahallad et al Nature ‘12
SWOG COLON SUBCOMMITTEE FUTURE PLANS:

SWOG 1406: Randomized Phase II of Dual BRAF + EGFR Inhibition in BRAF\textsuperscript{mut} Metastatic Colorectal Cancer (Scott Kopetz, PI)

Eligibility:
1) BRAF V600 mutation
2) Prior treatment for metastatic disease
3) No more than 2 prior progression on chemotherapy
4) No prior cetuximab

Stratified:
1) Prior treatment with Irinotecan

N=78
Primary endpoint: PFS
Arm A may cross-over at progression
ECOG/SWOG E7208: Irino-Cetuximab + Ramucirumab in 2nd line therapy of KRAS wt CRC (Hochster, PI)

Eligibility: metastatic or advanced CRC, K-RAS wild-type, first line therapy with Oxaliplatin-containing chemotherapy and Bevacizumab; Stop-and-Go or Maintenance allowed Recent progression; Registration within 42 days of documented disease progression and at least 28 days since last bevacizumab dose.

Stratify:
1) PS (0 vs 1-2)
2) Discontinuation of Oxaliplatin first-line Therapy Prior to progression (Yes vs No)
3) Time since last Bevacizumab (≤6 vs. > 6 months)

Primary endpoint: PFS; 85% power to detect difference between 4.5 months for control vs. 7.65 months for experimental arm (α = 0.10, β = 0.10); N = 100

Irinotecan 150 mg/m2 iv +
Cetuximab 500 mg/m2 iv q2 weeks*

Irinotecan 180 mg/m2 iv +
Cetuximab 500 mg/m2 iv q2 weeks *

mICR

Ramucirumab 6 mg/kg iv q2 weeks *
ASSIGN DESIGN

Metastatic Colorectal Cancer: Second-line trial molecular targeted

Progression on First-line Treatment of Metastatic Colorectal Cancer

Analysis of metastatic tumor specimen

Marker Defined Sub-Groups (potential options)

- RAS
- BRAF
- PIK3CA
- AKT
- Both RAS and PI3K
- Not RAS Not PI3K

Targeted therapy Control arm*

*Standard chemotherapy-containing regimen

Phase II with PFS as the end point, plan HR = 0.65 will require about 130 patients per arm
Rectal Cancer

Cathy Eng

Lisa Kachnic
Subcommittee Aims:

• Unmet needs:
  – No paradigm change in locally advanced rectal cancer for the past decade
  – No established regimen in metastatic anal cancer

• Mission:
  – Creation and conduct of novel trials using new agents or approaches for the treatment of anal and rectal cancer
  – Mentorship of junior faculty
Study Portfolio

• Completed: S0713: Phase II XELOX/C + XRT (KRAS WT) - Leichman
  – N=82 (73 are evaluable)
  – Final results: Pending

• Ongoing: PROSPECT N0148 (Shrag)
  – Randomized Phase II/III: mid-high lying rectal cancer
  – Objective: $R_0$ resection rate
  – Aim: To determine if selective use of chemoXRT is non-inferior to standard neoadjuvant treatment
  – N= 215/1000 (phase II = 366)
  – Potentially paradigm changing
Trials Under Development:

- Phase II: Low rectal “Watch and Wait” – ECOG/SWOG? (Sigurdson/Kennecke)
  - T1-T3N0 pts
    - ≤4 cm from anal verge
    - Induction FOLFOX
      - CR/PR: Transanal excision
        » CR: observe, PR: chemoXRT

- Phase II: Role of adjuvant FOLFOXIRI (Kennecke)
  - ypT4 or N2-3 disease
  - Further discussion

- Met anal cancer (ECOG 2133) - Eng
  - First trial to be conducted in this patient population.
  - Randomized phase II study of carboplatin/taxol vs. 5-FU/Cisplatin (HIV+ eligible),
    - 7/80 enrolled in the UK
    - Pending approval by NCI
Pancreatic Cancer

Philip Philip
Randomized Phase II Clinical Trial of AZD6244 (Selumetinib) and MK2206 vs. mFOLFOX in Patients with Metastatic Pancreatic Cancer after Prior Chemotherapy

SWOG 1115

Dr. Vincent Chung
City of Hope
Young Investigator
Overcoming challenges of feedback and cross-talk with dual blockade of AKT and MEK

RTKs

PI3K → Akt → FOXO

PTEN

PDK1 → PI3K

Ras

Raf → MEK → ERK

RSK

TORC1/TORC2

Grb10, S6K, 4EBP1

Survival, proliferation, metabolism, angiogenesis
SWOG 1115: Dual Blockade of MEK and Akt After Failure on Gemcitabine

Patients who failed on gemcitabine-based therapy (N = 120) → R → Selumetinib + MK2206 → mFOLFOX6

ACCRRUAL COMPLETED

Vincent Chung, City of Hope,
Hyaluronan overexpression in >80% of pancreatic cancers

Tumors that accumulate hyaluronan develop high interstitial fluid pressure and drug resistance

Hyaluronan is associated with disease progression and poor prognosis
**S1313 Study Design**\(^1\)

**Phase 1b (run-in)**

- **mFOLFIRINOX**
- + PEGPH20 3 mcg/kg

**Phase 2**

- **mFOLFIRINOX**
- + PEGPH20 3 mcg/kg

- Metastatic
- ECOG 1/2
- PEGH20 24 hours prior to mFOLFOX6

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Proposed Randomized Ph2: PARP inhibition in 2nd line pancreatic cancer (Chiroean)

Objectives:
- primary: OS
- secondary: RR, PFS, safety, biomarker correlatives

Statistics:
- H₀: OS 6 months
- Hₐ: OS 9 months
- Power 80%
  1-sided alpha 10%
- Accrual 2 yr/FU 1.5yr

Pre-specified subgroup analysis (for HRD ≥ 10)
- Hₐ: OS 12 months

FOLFIRI + ABT888
N=66

FOLFIRI + Placebo
N=66

Tumor Biopsy

- Nr Intrachromosomal breaks (CGH)
- Homologous recombination deficiency test (HRD)
- Topo I, SMAD4, p53, PTEN

Randomize
Rationale

- **Topo I**: - is overexpressed in 58% of pancreatic cancers\(^1\) - is involved in the DNA repair of many cytotoxic drugs\(^2\)
  
  **DPC4/SMAD4 (55%)**: may correlate with irinotecan sensitivity in PC\(^7\)

- **Topo I inhibitors**: induce PARP cleavage, which correlates with apoptosis\(^3\)

- **Multiple DNA Repair Mechanisms in Pancreas Cancer:**
  - **Homologous Recombination (HR)**: BRCA1/BRCA2/PALB2/RAD51/FANCD2
  - **DNA Damage Response Proteins**: ATM/CHK2, ATR/CHK1, p53, PTEN
  - **MMR**: MLH1 (3-15%)

- **PARPi (ABT888, BMN673)** synergize with Irinotecan preclinically \(^4-6,8\)

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Hepato-Biliary Cancer

Anthony El-Khoueiry

Abby Slegel
Led the way for cooperative group biliary trials

• Advanced disease:
  – S0514: Phase II trial of sorafenib in advanced biliary cancer
    • Median PFS 3 mo, OS 9 mo (Invest New Drugs, 2012)
  – S0941: Phase II trial of sorafenib plus erlotinib in advanced biliary cancer
    • Median PFS 2 mo, OS 6 mo (Br J Cancer, 2014)
Adjuvant disease: S0809

– SWOG S0809: Phase II trial of *adjuvant* Cape-Gem followed by concurrent Cape-RT in extrahepatic cholangiocarcinoma and gallbladder carcinoma
– 79 pts, 86% completed planned therapy
– Median OS 34 months (ASCO, 2014)
– Plans for SWOG-led North American randomized follow up trial underway
Current unique randomized second line trial for advanced biliary cancers

- S1310: Phase II trial of trametinib (GSK1120212) vs. 5-fluorouracil or capecitabine
- Novel correlative studies:
  - 16-gene expression panel
  - Evaluate inflammatory cytokines for potential associations with response rate and survival
  - Estimate lean soft tissue and fat mass weight gain as a result of treatment
- Activated 2/15/2014; current accrual: 23 (10/14/2014); no unexpected toxicity signals so far
Next steps: HCC

- Planned first-line randomized phase II trial of rilotumumab (HGF ab) and sorafenib in advanced HCC
- Discussions with CTEP suggested need for more preclinical data
- Correlative studies ongoing with Amgen

- Primary endpoint: PFS
- Secondary endpoints: RR, OS, toxicity
Next steps: Biliary

- Planned randomized phase II trial of SGI-110 (hypomethylating agent) with gemcitabine and cisplatin in first-line advanced biliary cancer
- Based on evidence of synergy of demethylating agents with platins
- Importance of methylation in pathogenesis of hepatobiliary cancers
- Preclinical biliary proposal sent to Astex in anticipation of CTEP review

**SGI-110**
45 mg/m²/day
(d -8 to -3)
Followed by Gem/cis d 1,8

**Gem/cis alone**
d 1, 8 q 21 days

Primary endpoint: PFS
Secondary: OS, RR, methylation biomarkers
Gastro-esophageal Cancer

Lawrence Leichman

Syma Iqbal
S0356: Neoadjuvant Tx for Esophageal Adenoca (Oxali and PVI 5FU + RT) JCO, 29, 4555, 2011

• Assess pCR rate, PFS and OS
  – Goals: pCR rate 40%; median OS>4 years
• Assess frequency and severity of toxicities
• Explore intratumoral parameters thought to be relevant to pCR (ERCC-1, XPA, TS, yGT and yGCS)

• RESULTS: 98 patients enrolled;
  – 6 ineligible
  – 2 did not receive any protocol therapy
• 90 patients are considered in this analysis.
  – 84 men (93%)
  – 6 women
  – Median age: 61.7 years
  – pCR = 28%, med OS = 28m

ERCC1 is part of the nucleotide excision repair complex that repairs platin crosslinks in DNA
S0356: OS and by ERCC-1

Kaplan-Meier curve of overall survival in the Southwest Oncology Group S0356 trial.

Overall survival by ERCC-1 mRNA levels in 53 patients treated with chemoradiotherapy.

Leichman L P et al. JCO 2011;29:4555-4560
SWOG 1201 -- A RANDOMIZED PHASE II PILOT STUDY PROSPECTIVELY EVALUATING TREATMENT FOR PATIENTS BASED ON ERCC1 (EXCISION REPAIR CROSS-COMPLEMENTING 1) FOR ADVANCED/METASTATIC ESOPHAGEAL, GASTRIC OR GASTROESOPHAGEAL JUNCTION (GEJ) CANCER

• Activated 02/08/2012 – 103 pts randomized*
• Multiple Active Drugs
  – Response rates with combination cytotoxics range from 30 to 50%, PFS 3 - 4 months and median survival remains between 6 and 9 months

• Establish ERCC1 as a predictive marker in UGI cancer
Metastatic HER2 neg UGI Trial

- To assess PFS in high-ERCC1 and low ERCC1 patients treated with FOLFOX compared to those treated with irinotecan plus docetaxel.
- To assess PFS for low-ERCC1 vs high-ERCC1 patients treated with FOLFOX.
- Overall survival and toxicities
- To assess the response probability
- Explore ERCC-1 and response
- Bank tissue for molecular studies and SNPs
- N =225; 103 enrolled and randomized
1\textsuperscript{st} and 2\textsuperscript{nd} Line Rx for HER-2 overexpressing gastric/GEJ adenoca: Pertuzumab and TDM1 (Mechanisms of Action)

**Pertuzumab:** June 2012 (monoclonal antibody for the extracellular domain of HER2, binds to a different epitope and inhibits the dimerization with HER3)

**TDM1:** Feb 2013 (trastuzumab and mayteansine, antibody drug conjugate, allows delivery of a microtubule inhibitor to the cell)
For med PFS of 6.7 months in the control arm (FOLFOX + trastuzumab)

250 total for HR = 1.4 (median PFS of 9.4 months) with approximately 81% power.

Enroll 278 patients to ensure 250 pts

• 1st endpoint PFS for TDM1 after trastuzumab based 1st line Rx
• Assume 60% go on to 2nd line
• N = 150
• If med PFS for TDM-1 = 3 mos, then 87% power to detect HR = 1.5 (4.5 months)
Radiosensitivity Biomarker Validation in INT0116: Trial of Adjuvant Chemoradiation after Gastric Resection for Adenocarcinoma, Phase III

- **Objectives**
  - Retrospective study to determine whether a clinically-validated molecular signature of tumor radiosensitivity can identify gastric cancer patients that benefit (OS-RFS) from adjuvant chemoradiation from INT0116
  - To validate that the signature is specific for radiated patients

- **RSI (Radiosensitivity Index):**
  - The ten genes will be assessed and ranked in order of expression. RSI will be generated using the linear regression algorithm:
    \[
    RSI = -0.0098009\text{AR} + 0.0128283\text{cJun} + 0.0254552\text{STAT1} - 0.0017589\text{PKC} - 0.0038171\text{RelA} + 0.1070213\text{cABL} - 0.0002509\text{SUMO1} - 0.0092431\text{CDK1} - 0.0204469\text{HDAC1} - 0.0441683\text{IRF1}
    \]

- **Definition of RSI-based radiosensitive (RS) and radioresistant (RR) groups:**
  - The 25\textsuperscript{th} percentile for RSI will be utilized to dichotomize patients into radiosensitive (RS) and radioresistant (RR) groups as described

- **2\textsuperscript{nd} objective:** Compare expression profiles of Surgery Alone arm vs Adjuvant Chemo-RT arm to determine resistance genes.
Methodology

• Clinical Assay Development Program
  – Development of an analytically-validated commercial platform for the radiosensitivity signature in RT-PCR/FFPE format
  – The assays will be performed at the MRI Global (CLIA certified Lab), a contractor of Cvergenx.

• RSI (Radiosensitivity Index):
  – This will be performed as previously described. The ten genes will be assessed and ranked in order of expression. RSI will be generated using the linear regression algorithm:
    \[
    \text{RSI} = -0.0098009 \times \text{AR} + 0.0128283 \times \text{cJun} + 0.0254552 \times \text{STAT1} - 0.0017589 \times \text{PKC} - 0.0038171 \times \text{RelA} + 0.1070213 \times \text{cABL} - 0.0002509 \times \text{SUMO1} - 0.0092431 \times \text{CDK1} - 0.0204469 \times \text{HDAC1} - 0.0441683 \times \text{IRF1}
    \]

• Definition of RSI-based radiosensitive (RS) and radioresistant (RR) groups:
  – The 25th percentile for RSI will be utilized to dichotomize patients into radiosensitive (RS) and radioresistant (RR) groups as described
Expertise in GI Committee
(USC, MD Anderson, Yale, Colorado)

- Avatar Models: over 350
- Tumor Samples; over 3000
- Cell lines: over 120
- Molecular Pathways/preclinical Models
  - Wnt, notch, MEK, IGFR1, EphB4, CXCR4/2, GRP78, Demethylation, LMTK, dUTPase, PI3K, aurokinase, ALK/ROS, SCR
Prospective Biomarker Driven Trials

- SWOG 1201 (Iqbal) Gastric Cancer driven by ERCC1
- SWOG 80405 (Lenz) ERCC1, AREG, kras
- SWOG 1310 (El-Khoueiry) : evaluation of MEK inhibition in biliary cancers (whole exome analysis, proinflammatory cytokines) (El-Khoueiry)
- SWOG 1406 (Kopetz): braf driven trial (mouse models)
SWOG 1406 Tumor Model Program with JAX

**Figure 3:** Acquired mutations in a \(BRAF^{mut}\) mCRC PDX after resistance to vemurafenib not seen in untreated/control mice from the same parent tumor.

**Figure 4:** Proposal Schema. In **Specific Aim 1**, outcomes of patients will be compared to the matched PDXs given the same treatment to which the patient is randomized on the S1406 study. In **Specific Aim 2**, cfDNA from patients after progression will be compared to tumor DNA following tumor progression in PDXs treated with the same regimen as the matched patient.
Conclusions:

- Landmark work in all GI cancers
- Plenary session at ASCO and ESMO 2014
- SWOG leading translational efforts in GI Cancer Research
- Innovative trials in process
  - Biomarkers, Molecular triage and Treatment
- Current trials: WE NEED YOUR SUPPORT
- THANKS for the dedication and support
SWOG Group Meeting
Fall 2014

Plenary, Part II

October 24, 2014