THE CROSSROADS: Drug Development, Biomarkers, and Colorectal Cancer

SANJAY GOEL, M.D., M.S.
PROFESSOR OF MEDICINE
ALBERT EINSTEIN COLLEGE OF MEDICINE
MONTEFIORE MEDICAL CENTER
DEPT. OF ONCOLOGY
JUN 22, 2018
Objectives:

After attending this activity, participants will be able to:

• Appreciate the role that genetics plays in the therapy and pathogenesis of colorectal cancer including the latest therapy option
• Understand the concept of drug development in oncology, with a special emphasis on colorectal cancer
• Develop a basic understanding on screening, diagnosis, and management of colorectal cancer
Estimated New Cancer Cases* in the US in 2018

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>856,370</td>
<td>878,980</td>
<td>1735,350</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>14%</td>
<td>30%</td>
<td>44%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td>7%</td>
<td>16%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>7%</td>
<td>7%</td>
<td>14%</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>6%</td>
<td>5%</td>
<td>11%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>5%</td>
<td>4%</td>
<td>9%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>5%</td>
<td>4%</td>
<td>9%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>4%</td>
<td>3%</td>
<td>7%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td>3%</td>
<td>7%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>4%</td>
<td>3%</td>
<td>7%</td>
</tr>
<tr>
<td>All other sites</td>
<td>22%</td>
<td>21%</td>
<td>43%</td>
</tr>
</tbody>
</table>

*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.
## Estimated Cancer Deaths in the US in 2018

<table>
<thead>
<tr>
<th></th>
<th>Males 323,630</th>
<th>Females 286,010</th>
<th>Total 50,630</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>26%</td>
<td>25%</td>
<td>27,390</td>
</tr>
<tr>
<td>Prostate</td>
<td>9%</td>
<td>14%</td>
<td>23,240</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>8%</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>7%</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>6%</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>4%</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>All other sites</td>
<td>24%</td>
<td>24%</td>
<td>24%</td>
</tr>
</tbody>
</table>
### Trends in Five-year Relative Survival Rates (%), 1975-2013

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>49</td>
<td>55</td>
<td>69</td>
</tr>
<tr>
<td>Breast (female)</td>
<td>75</td>
<td>84</td>
<td>91</td>
</tr>
<tr>
<td>Colorectum</td>
<td>50</td>
<td>60</td>
<td>66</td>
</tr>
<tr>
<td>Leukemia</td>
<td>34</td>
<td>43</td>
<td>64</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>12</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>82</td>
<td>88</td>
<td>94</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>47</td>
<td>51</td>
<td>73</td>
</tr>
<tr>
<td>Ovary</td>
<td>36</td>
<td>38</td>
<td>47</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Prostate</td>
<td>68</td>
<td>83</td>
<td>99</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>72</td>
<td>79</td>
<td>78</td>
</tr>
</tbody>
</table>


Source: Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute, 2017.
Risk Factors for Colorectal Cancer

- Aging
- Personal history of CRC or adenomas
- High-fat, low-fiber diet
- Inflammatory bowel disease
- Family history of CRC
- Hereditary colon cancer syndromes
Comprehensive molecular characterization of human colon and rectal cancer

The Cancer Genome Atlas Network*

To characterize somatic alterations in colorectal carcinoma, we conducted a genome-scale analysis of 276 samples, analysing exome sequence, DNA copy number, promoter methylation and messenger RNA and microRNA expression. A subset of these samples (97) underwent low-depth-of-coverage whole-genome sequencing. In total, 16% of colorectal carcinomas were found to be hypermutated: three-quarters of these had the expected high microsatellite instability, usually with hypermethylation and MLH1 silencing, and one-quarter had somatic mismatch-repair gene and polymerase ε (POLE) mutations. Excluding the hypermutated cancers, colon and rectum cancers were found to have considerably similar patterns of genomic alteration. Twenty-four genes were significantly mutated, and in addition to the expected APC, TP53, SMAD4, PIK3CA and KRAS mutations, we found frequent mutations in ARID1A, SOX9 and FAM123B. Recurrent copy-number alterations include potentially drug-targetable amplifications of ERBB2 and newly discovered amplification of IGF2. Recurrent chromosomal translocations include the fusion of NAV2 and WNT pathway member TCF7L1. Integrative analyses suggest new markers for aggressive colorectal carcinoma and an important role for MYC-directed transcriptional activation and repression.
Three Genetic pathways to colorectal carcinoma.

65-80% CIN

10-15% MSI

~10% Serrated polyp

De Vita. Cancer principles & Practice of Oncology, 9th ed.
Mismatch Repair (MMR) deficiency and Microsatellite Instability (MSI)

- MMR deficiency leads to MSI and high concordance rate noted
- Microsatellites are mono or dinucleotide repeats
- Single base pair insertion/deletion leads to instability: >1 (high), 1 (low)
- Right sided, poorly differentiated, lymphocyte infiltration, mucinous
- Better prognosis, lower rate of metastases
• Screening
  • Familial CRC
  • Diagnosis and Staging
  • Treatment
    Early stage - surgery
    Intermediate stage - adjuvant chemotherapy
    Advanced stage
  • Use of biomarkers in CRC: towards personalized medicine
  • Drug Development at Montefiore Einstein
### Figure. Screening for Colorectal Cancer: Clinical Summary

<table>
<thead>
<tr>
<th>Population</th>
<th>Adults aged 50 to 75 y</th>
<th>Adults aged 76 to 85 y</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation</strong></td>
<td>Screen for colorectal cancer starting at age 50 y. Grade: A</td>
<td>The decision to screen for colorectal cancer is an individual one. Grade: C</td>
</tr>
</tbody>
</table>

### Risk Assessment
For the vast majority of adults, the most important risk factor for colorectal cancer is older age. Other associated risk factors include family history of colorectal cancer, male sex, and black race.

### Screening Tests
There are numerous screening tests to detect early-stage colorectal cancer, including stool-based tests (gFOBT, FIT, and FIT-DNA), direct visualization tests (flexible sigmoidoscopy, alone or combined with FIT; colonoscopy; and CT colonography), and serology tests (SEPT9 DNA test). The USPSTF found no head-to-head studies demonstrating that any of these screening strategies are more effective than others, although they have varying levels of evidence supporting their effectiveness, as well as different strengths and limitations.

### Starting and Stopping Ages
The USPSTF concluded that the evidence best supports a starting age of 50 y for the general population. The age at which the balance of benefits and harms of colorectal cancer screening becomes less favorable varies based on a patient’s life expectancy, health status, comorbid conditions, and prior screening status. The USPSTF does not recommend routine screening for colorectal cancer in adults 80 y and older.

### Treatment and Interventions
Treatment of early-stage colorectal cancer generally consists of local excision or simple polypectomy for tumors limited to the colonic mucosa or surgical resection (via laparoscopy or open approach) with anastomosis for larger, localized lesions.

### Balance of Benefits and Harms
The USPSTF concludes with high certainty that the net benefit of screening for colorectal cancer is substantial. The USPSTF concludes with moderate certainty that the net benefit of screening for colorectal cancer in adults aged 76 to 85 y who have been previously screened is small. Adults who have never been screened are more likely to benefit. Screening is most appropriate for those healthy enough to undergo treatment and those without comorbid conditions that significantly limit their life expectancy.

### Other Relevant USPSTF Recommendations
The USPSTF has made a recommendation on aspirin use for the primary prevention of cardiovascular disease and colorectal cancer in average-risk adults. This recommendation is available on the USPSTF website ([www.uspreventiveservicestaskforce.org](http://www.uspreventiveservicestaskforce.org)).
**Summary of Screening Options**

<table>
<thead>
<tr>
<th>Test</th>
<th>Type</th>
<th>Involves</th>
<th>Interval</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stool</strong></td>
<td>gFOBT</td>
<td>Kit for blood</td>
<td>1 yr</td>
<td>30-50%</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>FIT</td>
<td>Kit for blood</td>
<td>1 yr</td>
<td>65-70%</td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td>FIT DNA</td>
<td>Kit for DNA</td>
<td>1-3 yr</td>
<td>More</td>
<td>Less</td>
</tr>
<tr>
<td><strong>Direct Visualization</strong></td>
<td>Colonoscopy</td>
<td>Scope</td>
<td>10 yr</td>
<td>95-98%</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>Flex sig</td>
<td>Scope</td>
<td>5 yr</td>
<td>Lower</td>
<td>??</td>
</tr>
<tr>
<td></td>
<td>CT colonography</td>
<td>CT imaging</td>
<td>5 yr</td>
<td>84%</td>
<td>90%</td>
</tr>
<tr>
<td><strong>Combination</strong></td>
<td>Flex sig, FIT</td>
<td></td>
<td>10/1 yr</td>
<td>&lt; c-scope</td>
<td>??</td>
</tr>
</tbody>
</table>

*Guaiac fecal occult blood test

*Fecal immunochemical test

**USPSTF, JAMA 315: 2564, 2016**

**JNCCN 14:1033, 2016**
• Screening

• **Familial CRC**
  • Diagnosis and Staging
  • Treatment
  Early stage - surgery
  Intermediate stage - adjuvant chemotherapy
  Advanced stage
• Use of biomarkers in CRC: towards personalized medicine
• Drug Development for CRC at MECC
**FAP**

- Germline APC mutation
- Autosomal Dominant
- Penetrance 100%
- > 100 adenomas
- Rectosigmoid dominant
- Risk of extracolonic tumors (upper GI, desmoid, osteoma, thyroid, brain, other)
- Screen at age 10-12

---

**HNPPCC**

- Germline MMR mutation
- Autosomal Dominant
- Penetrance 60-80%
- Impressive Family history
- Proximal colon dominant
- Extracolonic cancers: (endometrium, ovary, stomach, urinary tract, small bowel, bile ducts, sebaceous skin tumors)
- Screen at age 20-25
Proposed algorithm for systematic evaluation for Lynch syndrome in patients with colorectal cancer

Fay Kastrinos, and Sapna Syngal JCO 2012;30:1024-1027
Cancer Screening for Lynch affected patients

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Recommendation</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy</td>
<td>Every 1–2 y beginning at age 20–25 y or 2–5 y younger than youngest age at diagnosis of CRC in family if diagnosis before age 25 y. Considerations: Start at age 30 y in MSH6 and 35 in PMS2 families. Annual colonoscopy in MMR mutation carriers.</td>
<td>Strong recommendation: Level of evidence (III): well-designed and conducted cohort or case-controlled studies from more than 1 group with cancer. GRADE rating: moderate.</td>
</tr>
<tr>
<td>EGD with biopsy of the gastric antrum</td>
<td>Beginning at age 30–35 y and subsequent surveillance every 2–3 y can be considered based on patient risk factors.</td>
<td>Offer to patient: Level of evidence (V): expert consensus. GRADE rating: low.</td>
</tr>
</tbody>
</table>

EGD, esophagastroduodenoscopy; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation.

Management of Lynch affected patients

Table 12. Guidelines for management of affected persons with Lynch syndrome

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Recommendation</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colectomy with ileorectal anastomosis</td>
<td>Patients with colon cancer or colorectal neoplasia not removable by endoscopy</td>
<td>Strong recommendation: Level of evidence (III): well-designed and conducted cohort or case-controlled studies from more than 1 group with cancer. GRADE rating: moderate</td>
</tr>
<tr>
<td></td>
<td>Consideration for less extensive surgery in patients older than age 60–65 y</td>
<td></td>
</tr>
<tr>
<td>Hysterectomy and bilateral salpingo-oophorectomy</td>
<td>After childbearing or age 40 y</td>
<td>Recommendation: Level of evidence (IV): observation study. GRADE rating: moderate</td>
</tr>
<tr>
<td>Daily aspirin</td>
<td>Treatment of an individual patient with aspirin is a consideration after discussion of patient-specific risks, benefits, and uncertainties of treatment is conducted</td>
<td>Consideration: Level of evidence (I): randomized controlled study. GRADE rating: moderate</td>
</tr>
</tbody>
</table>

• Screening
• Familial CRC

**Diagnosis and Staging**

• Treatment
  Early stage - surgery
  Intermediate stage - adjuvant chemotherapy
  Advanced stage

• Use of biomarkers in CRC: towards personalized medicine

• Drug Development for CRC at MECC
Diagnosis of CRC

“Tissue is the issue”

“No meat, no treat”

Core biopsy on endoscopy or metastatic site – lung or liver or LN

FNA from metastatic site
Staging

T - The extent of invasion of the intestinal wall
T0 - no evidence of tumor
Tis - cancer in situ (intraepithelial or lamina propria)
T1 - invades submucosa
T2 - invades muscularis propria
T3 - invades through the muscularis propria into pericolorectal tissues
T4 - invasion completely through the wall of the colon  
  T4a - penetrates visceral peritoneum
  T4b - invades or adherent to surrounding organs

N - the extent of lymphatic node involvement
N0 - no lymph nodes involved
N1 - 1-3 lymph nodes involved (N1a - 1 LN, N1b - 2-3 LN, N1c - mesentric tumor deposits)
N2 - ≥ 4 lymph nodes involved (N2a - 4-6 LN, N2b - ≥ 7 LN)

M - the extent of metastases
M0 - no metastasis
M1 - metastases present (M1a: single organ,; M1b: ≥2 organs; T1c: peritoneal surface)
## Staging and Survival (AJCC v 7)

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>5 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1,2 N0 M0</td>
<td>97%</td>
</tr>
<tr>
<td>IIa</td>
<td>T3 N0 M0</td>
<td>88%</td>
</tr>
<tr>
<td>IIb</td>
<td>T4a N0 M0</td>
<td>80%</td>
</tr>
<tr>
<td>IIc</td>
<td>T4b N0 M0</td>
<td>58%</td>
</tr>
<tr>
<td>IIIa</td>
<td>T1-2 N1 M0</td>
<td>85%</td>
</tr>
<tr>
<td>IIIb</td>
<td>T3 N2 M0</td>
<td>65%</td>
</tr>
<tr>
<td>IIIc</td>
<td>T4 or N2 M0</td>
<td>30%</td>
</tr>
<tr>
<td>IV</td>
<td>T1- 4 N0-2M1</td>
<td>8%</td>
</tr>
</tbody>
</table>
# Staging and Survival (AJCC v 7)

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>5 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1,2 N0 M0</td>
<td>97%</td>
</tr>
<tr>
<td>IIa</td>
<td>T3 N0 M0</td>
<td>88%</td>
</tr>
<tr>
<td>IIb</td>
<td>T4a N0 M0</td>
<td>80%</td>
</tr>
<tr>
<td>IIc</td>
<td>T4b N0 M0</td>
<td>58%</td>
</tr>
<tr>
<td>IIIa</td>
<td>T1-2 N1 M0</td>
<td>85%</td>
</tr>
<tr>
<td>IIIb</td>
<td>T3 N2 M0</td>
<td>65%</td>
</tr>
<tr>
<td>IIIc</td>
<td>T4 or N2 M0</td>
<td>30%</td>
</tr>
<tr>
<td>IV</td>
<td>T1-4 N0-2M1</td>
<td>8%</td>
</tr>
</tbody>
</table>
- Screening
- Familial CRC
- Diagnosis and Staging

**Treatment**

Early stage - surgery
Intermediate stage - adjuvant chemotherapy
Advanced stage

- Use of biomarkers in CRC: towards personalized medicine
- Drug Development for CRC at MECC
TREATMENT DEPENDS ON STAGE

• STAGE I COLON AND RECTUM – SURGERY ONLY

• STAGE II COLON – SURGERY WITH/WITHOUT CHEMOTHERAPY

• STAGE II RECTAL – SURGERY, RADIATION AND CHEMOTHERAPY

• STAGE III COLON – SURGERY WITH CHEMOTHERAPY

• STAGE III RECTAL – SURGERY, RADIATION AND CHEMOTHERAPY

• STAGE IV COLON AND RECTUM – CHEMOTHERAPY ONLY
Principles of Surgery

• Minimally invasive procedure is an option (laparoscopic colectomy)
• All involved lymph nodes to be removed
• Sample at least 12 nodes for complete staging (if < 12, consider therapy as stage III)
• For metastatectomy, of liver or lung, intent should be complete removal, debulking is of no benefit (including removal of primary tumor)
Principles of Adjuvant Therapy

- Goal of adjuvant therapy is cure (delaying relapse is less important)
- Stage II colon cancer – prefer single agent therapy with 5-FU or capecitabine
- Stage III colon cancer – add oxaliplatin
- Stage II and III rectal cancer – add radiation
Chemotherapy/Drug Names (US FDA approved)

- 5-FU (5-Fluorouracil) – cytotoxic, stage II-IV CRC
- Oxaliplatin (Eloxatin) – cytotoxic, stage III-IV CRC
- Irinotecan (Camptosar) – cytotoxic, stage IV CRC
- Capecitabine (Xeloda) – 5-FU pro drug, cytotoxic, stage II-IV CRC
- Bevacizumab (Avastin) – mAb – VEGF, stage IV CRC
- Cetuximab (Erbitux) – mAb – EGFR, stage IV Ras WT CRC
- Panitumumab (Vectibix) – mAb – EGFR, stage IV Ras WT CRC
- Afirbercept (Zaltrap) – fusion protein – VEGF, stage IV CRC
- Ramucirumab (Cyramza) – mAb – VEGF, stage IV CRC
- Regorafenib (Stivarga) – TKI – VEGF, stage IV CRC
- Trifluridine and tipiracil (Lonsurf) – cytotoxic, stage IV CRC
- Pembrolizumab (Keytruda) – anti PD-1, MSI high tumors/ stage IV CRC
- Nivolumab (Opdivo) – anti PD-1, MSI high stage IV CRC
Overall Survival for First-line Combination Regimens

- 5-FU/LV (Saltz)
- 5-FU/LV (Douillard)
- 5-FU/LV (de Gramont)
- IFL (Goldberg)
- IFL (Saltz)
- FOLFIRI (Douillard)
- FOLFOX (de Gramont)
- FOLFOX (Goldberg)
- IFL + Avastin
- FOLFOX/FOLFIRI + MoAbs
• Screening
• Familial CRC
• Diagnosis and Staging
• Treatment
  Early stage - surgery
  Intermediate stage - adjuvant chemotherapy
  Advanced stage

• **Use of biomarkers in CRC: towards personalized medicine**

• Drug Development for CRC at MECC
Why personalized medicine?

• Because everyone is talking about it! and it is the “in” thing!
Why personalized medicine?

- Because everyone is talking about it!? and it is the “in” thing?? – ABSOLUTELY NOT!
- “First do no harm”
- It is the right approach to patients
- Limit toxicity from intervention
- Reduce health care costs
  (a staggering $ 3.4 trillion in 2016)
The EGF-MAPK-PI3K Pathway and anti EGFR agents

- Exclusivity for EGFR
- Prevent binding of EGF or TGF to EGFR and prevents tyrosine kinase activation

Cetuximab is IgG1, chimeric
Panitumumab is IgG3, human

Tumors with Kras and Nras mutations do not respond to these drugs

Typical anti EGFR induced skin rash
MSI as prognostic/predictive marker

Untreated patients
MSI better outcome

Treated patients
5-FU - worse outcome

Sargent DJ, J Clin Oncol 28:3219-26, 2010
MSI as prognostic/predictive marker

Stage II, untreated

Untreated patients
MSI better outcome

Stage II, MSI

Treated patients
5-FU - worse outcome

Remember the Hippocratic oath:
First do no harm !!

Sargent DJ, J Clin Oncol 28:3219-26, 2010
The dawn of immunotherapy: Programmed Death Pathway

Without immune therapy

- T-cell
- PD-1 receptor
- PD-L1
- Antigen

With immune therapy

- T-cell
- PD-1 inhibitor
- PD-L1
- Antigen
Pembrolizumab is an anti PD1 mAb

Immunotherapy in CRC

Le NEJM 372:2509, 2015
Reovirus growth in a Ras activated cell

K-ras WT cell

K-ras mutant cell

Courtesy: Oncolytics
Intravenous administration of Reolysin®, a live replication competent RNA virus is safe in patients with advanced solid tumors

Radharani Gollamudi · Mohammad H. Ghalib · Kavita K. Desai · Imran Chaudhary · Benny Wong · Mark Einstein · Matthew Coffey · George M. Gill · Karl Mettinger · John M. Mariadason · Sridhar Mani · Sanjay Goel

Received: 4 May 2009 / Accepted: 8 June 2009
© Springer Science + Business Media, LLC 2009

Summary Background Reolysin® is reovirus serotype 3-Dearing strain, a double-stranded replication-competent RNA non-enveloped icosahedral virus. It induces cytopathic and anti-cancer effects in cells with an activated ras pathway due to inhibition of the dsRNA-activated protein kinase. Methods This was a single center dose escalation trial of Reolysin administered intravenously every 4 weeks in doses ranging from $1 \times 10^8$ to $3 \times 10^{10}$ tissue culture infective dose (TCID)$_{50}$. Serum for neutralizing antibody, and serum, stool, saliva, and urine for viral shedding were collected. Tumor samples were analyzed for activating mutations in the ras and braf oncogenes. Results Eighteen patients received 27 doses of Reolysin in 6 dose cohorts accomplishing a 300 fold dose escalation without a protocol-defined dose limiting toxicity. Drug related grade 2 toxicities included fatigue and fever (1 patient each). All patients developed neutralizing antibody during the course of the study. Viral shedding was observed in 6 patients. One patient with anthracycline and taxane refractory breast cancer experienced a partial response (PR) and her tumor had a ras G12A mutation. Biopsy from her chest wall mass showed evidence of necrosis and viral replication by electron microscopy. Overall clinical benefit (1 PR + 7 stable disease) rate was 45%, and appeared higher in patients with viral shedding (67%) than those without (33%). Conclusion


Radharani Gollamudi and Mohammad H. Ghalib contributed equally to the paper.
Fig. 2 Biopsy taken from a chest wall mass of a 60 year old woman with anthracycline and taxane pre treated breast cancer. The biopsy was taken 93 days after the first dose of Reolysin, (48 h after the third dose). Panel 2a: Pharmacodynamic Effect: Hematoxylin and Eosin stain of the biopsy showing extensive necrosis (also seen in 2b) of the tumor suggestive of anti-tumor activity. Panel 2b: Virokinetics: Electron Microscopy of the same biopsy specimen showing viral replication and remnant capsids/ghosts, typical of findings after prolonged interval between viral exposure and tissue collection, and with evidence of tissue necrosis.
Oncolytic reovirus preferentially induces apoptosis in KRAS mutant colorectal cancer cells, and synergizes with irinotecan

Radhashree Maitra¹, Raviraja Seetharam¹, Lydia Tesfa², Titto A. Augustine², Lidija Klampfer¹,²,⁵, Matthew C. Coffey³, John M. Mariadason⁴, and Sanjay Goel¹,²

Maitra et al, Oncotarget, 2014
Time to and duration of response as assessed per RECIST v1.1

Time to response = time to BEST overall response
Duration of response = time from BEST overall response till PD or last tumor measurement (withdrawal of consent, off study)

Goel et al. ESMO 2017

Dose Cohorts

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Reovirus</th>
<th>Irinotecan</th>
<th># patients</th>
<th>Prior FOLFIRI</th>
<th>Bevacizumab</th>
<th>DLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$1 \times 10^{10}$ TCID$_{50}$</td>
<td>150 mg/m²</td>
<td>3</td>
<td>Yes</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>$3 \times 10^{10}$ TCID$_{50}$</td>
<td>150 mg/m²</td>
<td>12</td>
<td>Yes</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>$3 \times 10^{10}$ TCID$_{50}$</td>
<td>180 mg/m²</td>
<td>6</td>
<td>Yes</td>
<td>No</td>
<td>2**</td>
</tr>
<tr>
<td>2 (new)</td>
<td>$3 \times 10^{10}$ TCID$_{50}$</td>
<td>150 mg/m²</td>
<td>7</td>
<td>No</td>
<td>Yes</td>
<td>0</td>
</tr>
<tr>
<td>3 (new)</td>
<td>$3 \times 10^{10}$ TCID$_{50}$</td>
<td>180 mg/m²</td>
<td>8</td>
<td>No</td>
<td>Yes</td>
<td>0</td>
</tr>
</tbody>
</table>

DLT = dose limited toxicity

** = DLT was grade 4 thrombocytopenia in a heavily pretreated patient (incl FOLFIRI)
** = DLT was urosepsis in a patient with prior FOLFIRI treatment
Acknowledgements

Mentors

- Sridhar Mani, MD
- John Mariadason, PhD
- Roman Perez-Soler, MD

the bench

- Titto Augustine, PhD
- Radhashree Maitra, PhD
- Raviraja Seetharam, PhD

the bedside

- Imran Chaudhary, MBBS
- Mohammad Ghalib, MBBS
- Umang Shah, MD
- Umang Swami, MD

$\$\$ - the real stuff!!

CONQUER CANCER FOUNDATION
of the American Society of Clinical Oncology

NATIONAL INSTITUTES
OF HEALTH

Patients who made this possible