Treatment of Advanced Colorectal Cancer

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Conflict of Interest:
1. No employment, speaker’s bureaus, stock ownership, royalties, patents, etc
2. Unpaid advisory boards with Bayer, Genentech, Pfizer
3. PI or Local PI of clinical trials by Genentech/Roche, GSK, Pfizer, Millenium/Takeda, Bayer, Onconova, Immunomedics, and NIH/CTEP.
4. I serve on DSMB’s for OncoMed, Immunomedics.

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No exam questions will be disclosed in my presentation.
**Advanced CRC: Treatment**

**Outline:**
1. Introduction: Colorectal Cancer
2. Biomarkers/treatment in colorectal cancer
3. Future directions

**Colorectal Cancer (CRC) Facts**
- 3rd most common cancer in the U.S.
- 5-year survival ~11% in the metastatic setting
- Current options for metastatic CRC (mCRC)
  - 5-FU/leucovorin, capcitabine, oxaliplatin, irinotecan, bevacizumab, ziv-aflibercept (approved 8/12), regorafenib (9/12), ramucirumab (4/2015), TAS-102 (9/2015)
  - Cetuximab or panitumumab if KRAS/NRAS wild-type (both approved in first line metastatic setting)
- Numerous gaps in understanding the disease
  - e.g., why don’t biologics work in adjuvant setting?
  - What are predictive biomarkers for VEGFR inhibitors?
- Additional treatment options are needed
- Additional prevention options are needed
- Most treatment decisions not based on biomarkers

**General Themes in mCRC Treatment**
- Chemotherapy backbones appear to be interchangeable (FOLFOX vs CAPOX vs FOLFIRI)
  - There may be differences in combinations with biologics
- Some patients with stage IV disease are cured using multidisciplinary approaches (surgery, chemo, etc)
- Combination therapy is generally well-tolerated, but sequential therapy is also reasonable
- Biologics have added incremental (and somewhat disappointing) benefit
- Era of personalized therapy began with KRAS

## Drugs for Colorectal Cancer

<table>
<thead>
<tr>
<th>“Cytotoxics”</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 5-Fluorouracil (5-FU)</td>
<td>pyrimidine analog</td>
</tr>
<tr>
<td>2. capecitabine</td>
<td>oral 5-FU pro-drug</td>
</tr>
<tr>
<td>3. TAS-102</td>
<td>5-FU drug with metabolism inhibitor</td>
</tr>
<tr>
<td>4. irinotecan</td>
<td>topoisomerase I inhibitor</td>
</tr>
<tr>
<td>5. oxaliplatin</td>
<td>3rd generation platinum</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>“Biologics/Targeted”</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. cetuximab</td>
<td>antibody against EGFR</td>
</tr>
<tr>
<td>2. panitumumab</td>
<td>antibody against EGFR</td>
</tr>
<tr>
<td>3. bevacizumab</td>
<td>antibody against VEGF</td>
</tr>
<tr>
<td>4. ziv-aflibercept</td>
<td>dummy VEGF receptor</td>
</tr>
<tr>
<td>5. regorafenib</td>
<td>tyrosine kinase inhibitor</td>
</tr>
<tr>
<td>6. ramucirumab</td>
<td>antibody against VEGFR2</td>
</tr>
</tbody>
</table>

**VEGF** = Vascular Endothelial Growth Factor; **EGFR** = Epidermal Growth Factor Receptor

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### How are we going to pay for this?

#### Chemotherapy for Colorectal Cancer (2 weeks)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Unit Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU (500 mg/m²)</td>
<td>$6</td>
</tr>
<tr>
<td>Leucovorin (500 mg/m²)</td>
<td>$85</td>
</tr>
<tr>
<td>Capecitabine (2000 mg/m²/day)</td>
<td>$3,250 / $1,250</td>
</tr>
<tr>
<td>Irinotecan (180 mg/m²) / generic</td>
<td>$2,300 / $480</td>
</tr>
<tr>
<td>Oxaliplatin (85 mg/m²) / generic</td>
<td>$4,190 / $590</td>
</tr>
<tr>
<td>Bevacizumab (5 mg/kg)</td>
<td>$2,560</td>
</tr>
<tr>
<td>Cetuximab (250 mg/m²)</td>
<td>$5,120</td>
</tr>
<tr>
<td>Panitumumab (6 mg/kg)</td>
<td>$4,360</td>
</tr>
<tr>
<td>Ziv-Aflibercept (4 mg/kg)</td>
<td>$5,380</td>
</tr>
<tr>
<td>Regorafenib (160 mg, 3/1)</td>
<td>$5,650</td>
</tr>
<tr>
<td>Ramucirumab (6 mg/kg)</td>
<td>$7,140</td>
</tr>
</tbody>
</table>

1997: 6 months of 5-FU/LV costs ~$500
2013: 24 months therapy with combinations costs ~$300,000

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### Cancer Genome Atlas - CRC

Genomic changes in 195 primary colorectal cancers.
Hypermutated tumors (top) segregate from others.

TCGA, Nature 2012

Copyright © 2012 MacMillan Publishers Limited
- Complex genetic data is simplified by analysis of pathways.
- Again, hypermutated tumors segregate from others.
- Alterations in pathways identified by mutations, deletions, amplifications, or significant up- or down-regulation of genes.

**Cancer Genome Atlas - CRC**

- WNT signaling
- TGF-β signaling
- ERK signaling
- AKT signaling
- PI3K signaling
- RTK-RAS signaling

- PI3K signaling
- DNA replication stress
- Oncogenic stress
- Proliferation
- Cell survival

- Nuclear, cell survival, transcription

TCGA, Nature 2012

**Advanced CRC: Treatment**

Outline:

1. Introduction: Colorectal Cancer
2. Biomarkers/treatment in colorectal cancer
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Messersmith

**Large Molecule VEGF Inhibitors**

- PIGF
- VEGF-B
- VEGF-A
- Bevacizumab
- VEGF-C
- VEGF-D
- Ramucirumab
- Afiblercept (VEGF Trap)

- Functions
- Migration
- Invasion
- Survival
- Proliferation
- Permeability
- Lymphangiogenesis

- PI GF = placental growth factor.

Copyright © 2012 MacMillan Publishers Limited

TCGA, Nature 2012
### Targeting VEGF

**First-Line bevacizumab in mCRC, Phase III Trials**

<table>
<thead>
<tr>
<th>Trial Regimen</th>
<th>Response rate (%)</th>
<th>Median OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CIR</td>
<td>CIR + Bev</td>
</tr>
<tr>
<td>AVF210fg IFL (n = 411) vs IFL + bev (n = 402)</td>
<td>36</td>
<td>45</td>
</tr>
<tr>
<td>NO16068 FOLFOX-IBOX (n = 701) vs FOLFOX-IBOX + bev (n = 699)</td>
<td>49</td>
<td>47</td>
</tr>
<tr>
<td>BICC-C FOLIFRI (n = 144) vs FOLIFRI + bev (n = 57)</td>
<td>47</td>
<td>58</td>
</tr>
<tr>
<td>BICC-C mIFL (n = 141) vs mIFL + bev (n = 60)</td>
<td>43</td>
<td>53</td>
</tr>
<tr>
<td>AVEX (pT &gt; 70 years) Bev + Cape (n = 140) vs Cape (n = 140)</td>
<td>10%</td>
<td>19%</td>
</tr>
</tbody>
</table>

**CT, chemotherapy; OS, overall survival; Bev, bevacizumab; Cape, capcitabine.**

### VEGF-Targeted Agents in 2nd mCRC

**Modest improvements in PFS and OS, even in patients with prior exposure to bevacizumab.**

Hazard Ratios (HR) for OS are 0.81 (bevacizumab), 0.82 (aflibercept), 0.84 (ramucirumab). Remarkably similar.

<table>
<thead>
<tr>
<th>TML</th>
<th>VELOR*</th>
<th>RAISE</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, mos</td>
<td>9.8</td>
<td>11.2</td>
</tr>
<tr>
<td>mPFS, mos</td>
<td>4.1</td>
<td>5.7</td>
</tr>
</tbody>
</table>

**PFS = progression-free survival; OS = overall survival**

### Biomarkers for VEGF Inhibitors

**This slide sums up what we know with certainty!**
RAS Genes and Proteins

- The three RAS genes encode highly homologous proteins: HRAS, NRAS, KRAS 4A and KRAS 4B (alternative splicing)\(^1\)
- GTP/GDP-binding proteins (21 kDa) located at inner surface of the plasma membrane; signal transducers
- Somatic point mutations of RAS genes occur in about 30% of all cancers\(^1\)
- Mutations result in amino acid substitutions at codons 12, 13, 61, 146 which favor GTP-bound, active state.
- KRAS mutation is an early event in polyp progression\(^2\);
  high concordance between primary and metastases\(^3\)

\(^1\) Schubbert, Nat Rev Cancer 2007; \(^2\) Fearon and Vogelstein, Cell 1990; \(^3\) Santin, Oncologist 2008

RAS Genes and Human Cancers

| Table 2. Incidence of KRAS Mutations in Three Human Cancers |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| All KRAS | G12C | G12D | G12V | G13D |
| Colorectal | 60,000 | 5,700 | 25,000 | 15,700 | 13,600 |
| Lung | 45,600 | 23,000 | 9,200 | 11,900 | 1,500 |
| Pancreas | 32,200 | 1,000 | 19,500 | 11,500 | 200 |
| Total new cases/year | 137,200 | 29,700 | 53,700 | 39,100 | 15,300 |

Shown are the numbers of new cancer cases per year in the United States that contain the most frequent KRAS mutant alleles. Data are based on estimated new case incidence values from the National Cancer Institute and primary tumor mutation frequency data from COSMIC v.67.

KRAS mutations are common in CRC; one of few with codon 13.

Stephen et al., Cancer Cell 25, March 17, 2014 ©2014 Elsevier Inc.

In reality, many RAS effectors!

NCIC CO.17 Trial

Previously treatedmetastatic colorectal cancer
N=572

Not Prognostic! (BSC patients)

Overall Survival:
Mutant
Wildtype

~50%
~40%
~10%

New RAS mt
Rare KRAS Mutations
NRAS Mutations

In KRAS WT patients, the incidence of other Ras mutations is small, but the numbers add up. We should not spend hundreds of millions of dollars harming patients.
Is Re-Biopsy Necessary?

Answer: No

- >96% concordance between primaries and metastases
- Only 2% clinically relevant

CALGB/SWOG 80405: Which biologic 1st line?

**nCRC 1st-line**
- KRAS wild type (codons 12, 13)
- STRATA: FOLFOX/FOLFIRI
  - Prior adjuvant
  - Prior SRT

**FOLFIRI or FOLFOPX**
- MD choice
- Chemo + cetuximab
- Chemo + bevacizumab

**N = 1140**

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)
**BRAF Background**

- Overall, approximately 8% of all tumors have a BRAF mutation; in CRC it ranges from 5-10%.
- The predominant mutation, similar to melanoma, is a single base substitution of valine by glutamic acid at position 600 (V600E) within the activation segment.
- Signals through MEK/ERK activation pathway.
- BRAF mutation is an early event in CRC and there is a high concordance between primary and metastatic tissue.
- Associated with:
  - R-sided tumors, high grade
  - Older age, female
  - MSI-high (due to epigenetic mechanisms)
  - Serrated (as opposed to tubular) adenoma pathway.

- Due to confounding effect of MSI status in BRAF MT patients, Ogino proposed this strategy for classification. Must split, rather than lump, BRAF MT patients.

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**BRAF Structure and Mutations**

V600E (500-fold greater kinase activity) is most common mutation. BRAF and KRAS mutations appear to be mutually exclusive.
RAS and BRAF do not overlap

KRAS/NRAS and BRAF are usually mutually exclusive; but PIK3CA, others are not. Do not need to test for BRAF and NRAS in a KRAS mutated tumor.

"CRYSTAL" Trial: 1st line chemo/cetuximab

BRAF mutation is a negative prognostic factor

Preclinical studies show lack of benefit from single-agent vemurafenib in CRC cell lines

Phase I study of vemurafenib in BRAF mutant CRC is not as effective as seen in melanoma (one response)
Targeting BRAF with Combinations
Update from ASCO 2014 and 2015: Hope!

Small Molecule Combinations
- BRAF+MEK (Corcoran) with 12% response rate

EGFR mAb combinations
- BRAF+MEK+EGFR (Bendell) with 40% response rate (this arm will be in FOCUS4 trial in UK)
- BRAF+EGFR (van Geel), with 29% response rate
- BRAF+EGFR+Irino (Hong), with 50% response rate

PI3K Pathway as a Target
PI3K (phosphoinositide 3-kinases) is a family of lipid kinases which activate a signal transduction cascade promoting cancer growth and survival.

Discovered in 1980’s, probably the most commonly activated pathway in human cancers.

Multiple PI3K effectors (via phospholipids)
- AKT (AK-transforming)
- Non-AKT
  - BTK (Bruton tyrosine kinase)
  - SGK’s (serum/glucocorticoid kinases)
  - Tec (nonreceptor tyrosine kinase)

PI3K Mutations
(Samuels, Science 2004)

High Frequency of Mutations of the PIK3CA Gene in Human Cancers
- Functionally important
  - Nontruncating
  - Nonsynonymous
  - Conserved residues
  - Higher PI3K activity

- Colorectal and gastric cancers frequently harbor mutations.
- Not found in 76 polyps (except two >5cm tubulovillous adenomas)
- Co-existent with KRAS and BRAF mutations (distinct pathway)
**Signaling Pathway Target: PI3K**

- **Ligand**
  - PTEN
  - PI3K
  - PIP
- **Growth Factor**
  - PI3K inhibitors (XL147, GDC-0941, PX-866, SF1126, BEZ235)
- **PI3K**
  - p85, p110
- **PI3K inhibitors**
  - AKT inhibitors (MK-2206, GSK2141795, SR13668, XL418, GSK690693)
- **AKT**
  - PIK3CA mutations and aspirin
  - mTOR inhibitors (sirolimus, temsirolimus, everolimus, AP23573, AZD8055, OSI-027, palomid 529)

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**PIK3CA mutations and aspirin**


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**Possible Mechanism?**

- **COX2 expression**
  - PI3K signal transduction pathways regulate COX-2 expression and PGE2 synthesis.
- **PGE2**
  - PD = PD098059 (MAPK inhibitor)
  - LY = LY294002 (PI3K inhibitor)

Di Popolo et al., Oncogene 2000
Microsatellite Unstable Tumors

Germline: “HNPCC” or Lynch Syndrome
- Due to mutations in one of the mismatch repair genes: MLH1, MSH2, MSH6, PMS2, and/or EPCAM
- Increased lifetime risk of colorectal, endometrial, stomach, ovarian, urothelial, and other cancers

Acquired MSI
- Most due to hypermethylation of the MLH1 promoter and epigenetic silencing of MLH1
- Can also have “double somatic” MSI caused by mutations in MMR genes

Two methods for testing
- PCR-based microsatellite instability (MSI) testing to identify variation in genomic repeats
- Immunohistochemistry (IHC) for loss of expression of one or more of the MMR proteins

Type, Density, and Location of Immune Cells Within Human Colorectal Tumors Predict Clinical Outcome

Galon, et al. Science 2006;313,5785
1969 - 1964

Immunosurveillance Hypothesis
Lack of lymphocytes = poor prognosis
MSI-H carries a better prognosis
Forrest plot of studies on MSI-H subgroup

MSI-H patients do better!

Activity of PD-1 (pembro) in MSI-H tumors

<table>
<thead>
<tr>
<th>Type of Response</th>
<th>MSI-mismatch Deficient</th>
<th>MSI-mismatch Proficient</th>
<th>MSI-mismatch Deficient</th>
<th>MSI-mismatch Proficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>4 (40%)</td>
<td>0</td>
<td>4 (25%)</td>
<td>0</td>
</tr>
<tr>
<td>Stable disease</td>
<td>9 (90%)</td>
<td>2 (11%)</td>
<td>11 (60%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>1 (10%)</td>
<td>0</td>
<td>11 (60%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Could not be evaluated</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Objective response rate (95% CI)</td>
<td>48 (12-74)</td>
<td>0 (0-10)</td>
<td>71 (29-96)</td>
<td></td>
</tr>
<tr>
<td>Disease control rate (95% CI)</td>
<td>60 (25-98)</td>
<td>11 (1-15)</td>
<td>71 (29-96)</td>
<td></td>
</tr>
<tr>
<td>Median duration of response</td>
<td>4wk</td>
<td>Not reached</td>
<td>Not reached</td>
<td></td>
</tr>
<tr>
<td>Median time to response (range)</td>
<td>28 (1-35)</td>
<td>Not reached</td>
<td>12 (10-13)</td>
<td></td>
</tr>
</tbody>
</table>

1. The patient had a partial response at 12 weeks, which became a complete response at 20 weeks.
2. One patient had a partial response at 12 weeks.
3. Patients could not be evaluated if they did not undergo a scan at 12 weeks because of clinical progression.
4. The rate of disease control was defined as the percentage of patients who had a complete response, partial response, or stable disease for 12 weeks or more.
5. The median time to response was not applicable (NA) because no responses were observed among patients with mismatch-repair proficient colorectal cancer.

Le, NEJM 2015
Responses in MSI-H subgroup

B Radiographic Response

- Mismatch repair-proficient colorectal cancer
- Mismatch repair-deficient colorectal cancer
- Mismatch repair-deficient noncolorectal cancer

IHC showed PD-L1 expression differences
Mutational load correlates with response

![Graph showing mutational load and response](image)

Le, NEJM 2015

Ongoing Anti-PD1 or Anti-PDL1 Clinical Trials with MSI-high CRC Subsets

- NCT01876511: Phase 2 study of MK-3475 in patients with microsatellite unstable (MSI) tumors
  - MSI-high CRC, MSS CRC, MSI-high non-CRC
- NCT02086188: A study of nivolumab and nivolumab plus ipilimumab in recurrent and metastatic colon cancer (CheckMate 142)
  - MSI-high CRC, MSS CRC
- NCT02277676: Evaluate the Efficacy of MEDI4736 in Immunological Subsets of Advanced Colorectal Cancer
  - MSI-high CRC, MSS CRC
- NCT02404411: Phase I/II study of PDR001 in patients with advanced malignancies
  - MSI-high CRC, other tumors
- NCT01633970: A phase 1b study of MPDL3280A (an engineered anti-PDL1 antibody) in combination with bevacizumab and/or chemotherapy in patients with advanced or metastatic solid tumors
  - MSI-high CRC, other tumors
- A phase 1, open-label study of GSK3174998 administered alone and in combination with anticancer agents including Pembrolizumab in subjects with selected advanced solid tumors
  - MSI-high CRC, other tumors

Overman, MDACC

TAS102: RECOURSE

Combination of two agents:
- Trifluridine (FTD), a nucleoside analog activated by thymidine kinase
- Tipiracil hydrochloride (TPI), a thymidine phosphorylase inhibitor which inhibits metabolism of trifluridine; also has anti-angiogenic properties via PDGF inhibition.

RECOURSE trial:
- Global phase III trial conducted in 13 countries at 114 centres
- mCRC refractory to all standard therapies (including EGFR-targeting mAb for KRAS WT patients)
- Randomized 2:1 to TAS-102 (534 patients), 35 mg/m2 BID on Days 1-5 and 8-12 of each 28-day cycle, or placebo (266 patients)
- The primary endpoint was overall survival.

Yoshino, ESMO 2014, #0022
TAS-102: Phase II
Randomized pII study in Japan
N=169, randomized 2:1
Improvement in:
OS (HR=0.56) 9.0 v. 6.6 mos

Yoshino, Lancet Oncol 2012

TAS-102 RECURSSE: PFS

HR = 0.48, p<0.001 (log rank)

Mayer, NEJM 2015

TAS-102 RECURSE: OS

HR = 0.68, p<0.001

Mayer, NEJM 2015
**TAS-102 RE COURSE: Toxicity**

Mayer, NEJM 2015

<table>
<thead>
<tr>
<th>Event</th>
<th>Any Grade</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>256 (8)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>146 (48)</td>
<td>21 (2)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>106 (34)</td>
<td>19 (5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>388 (13)</td>
<td>22 (6)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>113 (37)</td>
<td>15 (4)</td>
</tr>
<tr>
<td>Fever</td>
<td>78 (2)</td>
<td>7 (1)</td>
</tr>
<tr>
<td>Anemia</td>
<td>97 (3)</td>
<td>30 (1)</td>
</tr>
</tbody>
</table>

Events associated with fluoropyrimidine treatment — no. (%)

<table>
<thead>
<tr>
<th>Event</th>
<th>Any Grade</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea and eructation</td>
<td>29 (4)</td>
<td>20 (3)</td>
</tr>
<tr>
<td>Skin toxicity</td>
<td>43 (3)</td>
<td>17 (1)</td>
</tr>
<tr>
<td>Hand-Foot syndrome</td>
<td>1 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cardiac ischemia</td>
<td>2 (1)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Laboratory abnormalities — no. (10%)

<table>
<thead>
<tr>
<th>Event</th>
<th>Any Grade</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>315 (128)</td>
<td>209 (128)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>403 (157)</td>
<td>313 (157)</td>
</tr>
<tr>
<td>Anemia</td>
<td>404 (162)</td>
<td>261 (162)</td>
</tr>
</tbody>
</table>

**Advanced CRC: Treatment**

**Outline:**

1. Introduction: Colorectal Cancer
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Messersmith

**Drug Development Paradigm**
WNT pathway associated with resistance to MEKi

Clinical trial currently enrolling initial cohort with this combination (CTEP/UM1).

Combination MEK/WNT

How are current trial designs being influenced by molecular testing?
CURRENT ASSIGN “PROGRAM”

- Progressive
- First-line Treatment of Metastatic Colorectal Cancer
- Analysis of Tumor Specimen
- Standard of Care Markers

**BRAF**
- Open
- 1340G, Kopez

**MSI**
- In development
- Chemotherapy
- Immunotherapy

**IC**
- In development
- Vemurafenib

**MATCH**
- Hiddincken + Trastuzumab + Pertuzumab

Current Goals of the ASSIGN Therapeutics Committee
1. Continue discussions among academic centers, NCI, FOCR, advocates
2. Monitor the best science for molecular subsets and translational opportunities
3. Facilitate molecularly-driven trials, whether in ASSIGN or not
4. Continue to lay the groundwork for a large molecularly driven CRC study

Enrollment on “Master Protocol”

<table>
<thead>
<tr>
<th>Target</th>
<th>Year</th>
<th>Year</th>
<th>Year</th>
<th>Year</th>
<th>Year</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSS absent</td>
<td>2017</td>
<td>2018</td>
<td>2019</td>
<td>2020</td>
<td>2021</td>
<td>2022</td>
</tr>
<tr>
<td>POLE</td>
<td>2017</td>
<td>2018</td>
<td>2019</td>
<td>2020</td>
<td>2021</td>
<td>2022</td>
</tr>
<tr>
<td>CDX2</td>
<td>2017</td>
<td>2018</td>
<td>2019</td>
<td>2020</td>
<td>2021</td>
<td>2022</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>2017</td>
<td>2018</td>
<td>2019</td>
<td>2020</td>
<td>2021</td>
<td>2022</td>
</tr>
<tr>
<td>Smoking status unknown</td>
<td>2017</td>
<td>2018</td>
<td>2019</td>
<td>2020</td>
<td>2021</td>
<td>2022</td>
</tr>
</tbody>
</table>

- Highly prevalent molecular subtypes need several studies
- Need treatment for unselected subtypes

**Thank you!**

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