Evolving Targeting Therapy for BRAF-mutated Colorectal Cancer

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Classic Mechanisms of Carcinogenesis in Colorectal Cancer

**Chromosomal Instability Pathway**
- del 5q, 1p
- del 12p
- LOH 17p
- LOH 18q
- APC
- COX2
- K-ras
- Smad2,4
- p53

**Normal mucosa** → **Early adenoma** → **Intermediate adenoma** → **Late adenoma** → **Carcinoma**

**Mutator Pathway**
- β-catenin
- BAX
- TCF-4
- p16\(^{N\_K\_A}\)
- IGF-II
- TGF-βRII
- MLH1
- MSH2
- MSH6
- Microsatellite Instability
- CIMP Hypermethylation

**Serrated Adenoma Pathway**
- B-Raf mutation
- EPHB2 loss
- Methylation of MGMT
- HIF1 overexpression
- CIMP Hypermethylation
- Methylation of MLH1
- Microsatellite Instability
Serrated Adenoma / BRAF\textsuperscript{mut} Subgroup

- BRAF mutations reflect a unique subset of CRC
  - Vast majority are BRAF V600E
  - Unique precursor lesion: Sessile serrated adenoma
  - Prognostic importance in early and late stage

Bollag et al, Nature ‘10
Clinical Utility of $\text{BRAF}^{\text{mut}}$ in Standard of Care for CRC

- Determining Sporadic vs Familial MSI-H
  - Part of the recommended algorithm.
- Prognosis for Stage II / III
  - Yes, likely. Not yet in guidelines.
- Prognosis for Stage IV
  - Yes, in guidelines
- Predictive for EGFR Inhibitor sensitivity
  - Mixed data
Unique BRAF\textsuperscript{mut} Clinical Behavior: Metastatic Colorectal Cancer

Very short overall survival

Hazard Ratio of 10.6 for OS
Less than 1 year OS

Atypical patterns of metastases

Morris et al, Clin Colorectal Cancer '13  Tran, Kopetz, et al, Cancer 2011
Limited Benefit of Standard of Care for BRAF\textsuperscript{mut} CRC Patients

BRAF mutation and EGFR inhibition

<table>
<thead>
<tr>
<th>Subgroup study</th>
<th>Sample size of Tx groups</th>
<th>PFS hazard ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cmab/pmab</td>
<td>Comparator</td>
</tr>
<tr>
<td>RAS WT / BRAF WT</td>
<td></td>
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<tr>
<td>PRIME</td>
<td>228</td>
<td>218</td>
</tr>
<tr>
<td>CRYSTAL and OPUS</td>
<td>349</td>
<td>381</td>
</tr>
<tr>
<td>CO.17</td>
<td>101</td>
<td>97</td>
</tr>
<tr>
<td>20020408</td>
<td>63</td>
<td>52</td>
</tr>
<tr>
<td>PICCOLO</td>
<td>183</td>
<td>188</td>
</tr>
<tr>
<td>20050181</td>
<td>186</td>
<td>190</td>
</tr>
<tr>
<td>COIN</td>
<td>292</td>
<td>289</td>
</tr>
<tr>
<td>Summary:</td>
<td>1402</td>
<td>1415</td>
</tr>
<tr>
<td>Test for effect: $P &lt; 0.001$</td>
<td></td>
<td></td>
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<tr>
<td>Heterogeneity: $I^2 = 82%$, $P &lt; 0.001$</td>
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</tr>
</tbody>
</table>

| RAS WT / BRAF mut |          |                |                  |
| RAS WT / BRAF mut |          |                |                  |
| PRIME            | 24       | 29             | 0.58 [0.29, 1.15] |
| CRYSTAL and OPUS | 32       | 38             | 0.67 [0.34, 1.29] |
| CO.17            | 4        | 6              | 0.76 [0.19, 3.08] |
| 20020408         | 9        | 6              | 0.34 [0.09, 1.24] |
| PICCOLO          | 37       | 31             | 1.40 [0.82, 2.39] |
| 20050181         | 22       | 23             | 0.69 [0.32, 1.49] |
| COIN             | 40       | 50             | 1.25 [0.81, 1.94] |
| Summary:         | 168      | 183            | 0.86 [0.61, 1.21] |
| Test for effect: $P = 0.38$ |
| Heterogeneity: $I^2 = 39\%$, $P = 0.13$ |
Why BRAF in CRC provides an example for discussion

- Defines a unique molecular AND clinical subset
  - Substantial clinical need
- Compensatory activity uncovers at least two key drivers: BRAF and EGFR
- Proof of concept is established
  - With strong preclinical rationale established
  - In multiple single arm studies
  - In ongoing randomized CRC trials
- Lessons learned for iterative drug development

BRAF$^{V600E}$ ~6%
Landscape of BRAF\textsuperscript{mut} Colorectal Cancer

- Hypermethylation (CIMP-H)
- BRAF mutation
- Limited chromosomal instability
- Hypermutation, Microsatellite instability
Consensus Molecular Subtypes: CMS1

Guinney et al Nat Med ‘15
How to treat these patients?

BRAF inhibitor

BRAF mutation
Vemurafenib (PLX4032)

**Refractory Melanoma**

81% Response Rate

Flaherty et al NEJM ‘10

**Refractory Colorectal**

5% Response Rate

Kopetz et al ASCO ‘10

Preclinical data fails to demonstrate sufficient MAPK inhibition in CRC, unlike melanoma

Mao, et al CCR ‘14
Persistent MEK activation: Expansion from melanoma concepts

ERK inhibition is incomplete in some CRC cell lines

Colo205  HT29  RKO

\[ \text{pERK1/2} \]

\[ \text{Total ERK} \]

\[ \text{Vinculin} \]

\[ \text{PLX4720 (µM)} \]

0  1  0  1  0  1

Acquired resistance is associated with increased pERK and incomplete inhibition

Mao, et al CCR ‘14
**BRAF resistance through MEK reactivation**

IF the problem is only incomplete MEK inhibition....

Then treat with dual inhibition of BRAF + MEK
BRAF resistance through MEK reactivation

IF the problem is only incomplete MEK inhibition….

Then treat with dual inhibition of BRAF + MEK
Minimal Improved Efficacy with Dual BRAF + MEK Inhibition

BRAF + MEK inhibition

12% Response Rate

GSK212 + GSK436

BRAF inhibition

5% Response Rate

Vemurafenib

Corcoran et al JCO ‘15, Kopetz et al JCO ‘15
Key Finding: Feedback EGFR Signaling

Perhaps the problem isn’t ONLY incomplete MEK inhibition….

Treat with EGFR + BRAF inhibitors

Prahallad et al Nature ’12, Corcoran et al Can Disc ‘12
Unbiased Synthetic Lethality Screen:
EGFR Identified as a Synergistic Partner

HT29 cell line (Sensitive)

EGFR identified

Prahallad et al Nature ’12
Synergy in Murine Models: BRAF + EGFR

Cell line and Patient-derived xenograft models

Kopetz, unpublished; Yang et al Can Res ’11

Prahallad et al Nature ’12; Corcoran et al Can Disc ‘12
Irinotecan combined with EGFR/BRAF inhibition induces regressions

Van Morris, Alex Sorokin
Improved *Survival* with Cetuximab and Vemurafenib combined with Irinotecan

Better outcomes with irinotecan

Fang, et al, Can Res, ‘12
Phase 1B of Cetuximab, Vemurafenib, Irinotecan: High Response Rate

Historical response rate is <10% for cetuximab and irinotecan with PFS of 2 months.

David Hong et al. ASCO, ’15; Morris, CCC, ‘14
Cross-Trial Comparison: Phase 1B vs Historic Control for mBRAF CRC

Progression-free survival

Proportion surviving without progression

Vemurafenib+
Cetuximab + Irinotecan
Irinotecan + Cetuximab
Vemurafenib

Months

Van Morris
SWOG 1406: BRAF + EGFR
with availability through other cooperative groups

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

Results Fall ‘16, Kopetz, PI

Historical response rate is <10% for cetuximab and irinotecan, with PFS of 2.4 months for BRAF\textsuperscript{mut}

Target HR 0.5 for PFS, with 2-sided alpha 5%, power 90%

N= 105 patients
Cross-Study Comparison of Phospho-ERK Modulation

**Response Rate:**
- D+P CRC BRAF mut MEK116833: 13%
- D+T CRC BRAF mut BRF113220: 12%

Chloe Atreya, ASCO ‘15
BRAF resistance through MEK reactivation

IF the problem is only incomplete MEK inhibition....

Then treat with triplet inhibition of BRAF + MEK + EGFR
Dabrafenib + Panitumumab +/- Trametinib

**BRAF + EGFR inhibition**
- Maximum % Change from Baseline
- Progressive disease
- Stable disease
- Partial response
- Complete response

**BRAF + MEK + EGFR inhibition**
- Maximum % Change from Baseline
- Progressive disease
- Stable disease
- Partial response
- Complete response

D+P (N=20)
CR+PR: 2 (10%)

D+P+T (N = 35)
CR+PR: 9 (26%)

*Maximum reduction from baseline is 0%*

Atreya et al ASCO ‘15
Cross-Study Comparison of Phospho-ERK Modulation

Response Rate: 13% 12% 40%

Chloe Atreya, ASCO '15
Encorafenib + Cetuximab +/- BLY719

BRAF+EGFR

Dual Combination
PD: 4 (15%)
SD: 14 (54%)
PR: 5 (19%)a
CR: 1 (4%)

BRAF+EGFR+PI3K

Triple Combination
PD: 1 (4%)
SD: 17 (61%)
PR: 9 (32%)b

See survival data update tomorrow (J. Tabernero)

Geel et al ASCO ‘14
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Response</th>
<th>PFS</th>
<th>Citation</th>
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</thead>
<tbody>
<tr>
<td><strong>Single/Doublet RAF/MEK</strong></td>
<td></td>
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<tr>
<td>Vemurafenib</td>
<td>5%</td>
<td>2.1 months</td>
<td>Kopetz, JCO’15</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>11%</td>
<td>NR</td>
<td>Falchook, Lancet ’08</td>
</tr>
<tr>
<td>Encorafenib</td>
<td>16%</td>
<td>NR</td>
<td>Gomez-Roca, ESMO ’14</td>
</tr>
<tr>
<td>Dabr + Tramet</td>
<td>12%</td>
<td>3.5 months</td>
<td>Corcoran, JCO ’15</td>
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<tr>
<td><strong>Doublet with EGFR</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Vem + Panit</td>
<td>13%</td>
<td>3.2 months</td>
<td>Yeager et al CCR ’14</td>
</tr>
<tr>
<td>Vem + Cetux</td>
<td>20%</td>
<td>3.2 months</td>
<td>Tabernero et al ASCO ‘14</td>
</tr>
<tr>
<td>Encoraf + Cetux</td>
<td>23%</td>
<td>3.7 months</td>
<td>Schellen et al AACR ’15</td>
</tr>
<tr>
<td>Dabr + Panit</td>
<td>10%</td>
<td>3.4 months</td>
<td>Atreya, ASCO ‘15</td>
</tr>
<tr>
<td><strong>Triplet with EGFR</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Vem + Cetux + Irino</td>
<td>35%</td>
<td>7.7 months</td>
<td>Hong, ASCO ‘15</td>
</tr>
<tr>
<td>Dabr + Tramet + Panit</td>
<td>26%</td>
<td>4.1 months</td>
<td>Atreya, ASCO ‘15</td>
</tr>
<tr>
<td>Encoraf+Cetux+Alpelisib</td>
<td>32%</td>
<td>4.3 months</td>
<td>Schellen et al AACR ’15</td>
</tr>
</tbody>
</table>
Learning from BRAF Drug Development Story

• Better preclinical models

• Improving interrogation of response

• Beyond paired biopsies… improved options for interrogating biology of patients under therapy
Vemurafenib *in vivo* in colorectal cancer: Too optimistic?

Representative Cell Line Model

Fang, et al, Can Res, ‘12
Co-clinical trials: BRAF+MEKi Study

A

PDX response

Change in volume

Control
Trametinib + Dabrafenib

B

Patient response

SUV 9.5
SUV 2.3
SUV 11
SUV 4
SUV 14

Corcoran, Atreya et al JCO '15
Prospective PDX Clinical Trial Integration:
S1406: BRAF + EGFR Inhibition in mCRC

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

Arm A
Cetuximab + Irinotecan

Arm B
Vemurafenib + Cetuximab + Irinotecan

Cetuximab + Irinotecan + Vemurafenib
Optional cross-over
N= 105 patients

Embedded Patient-Derived Xenograft Co-Clinical Trial
- On study biopsies to derive PDXs, serial cfDNA
- Co-clinical trial to interrogate pharmacodynamics and mechanisms of resistance, and correlate outcomes

SWOG Hope, NIH R01 Funding, JAX Collaboration
MDACC, UCSF, USC, UCSD, U Colorado, Yale
Resistance to vemurafenib + cetuximab is associated with MAPK pathway mutation

Classically, KRAS and BRAF mutations are mutually exclusive.
So where are these rare clones coming from?

Kopetz, et al JCO ‘15
Rare $\text{KRAS}^{\text{mut}}$ Cells Exist in $\text{BRAF}^{\text{mut}}$ Colorectal Tumors

Jayesh Desai
Kopetz, et al JCO '15
Acquired RAS after BRAF+EGFR

- Baseline mutation analysis
  - Hotspots in AKT1, AKT2, BRAF, CDK, EGFR, ERBB2, FGFR1, FGFR3, FLT3, HRAS, JAK2, KIT, KRAS, MET, NRAS, PDGFRα, PIK3CA, RET
  - **BRAF V600E**

- Start study treatment:
  - cetuximab+ encorafenib
  - confirmed PR after 10 weeks
  - After 4 months of therapy: New progressive lesion

- Mutation analysis new lesion (same gene panel):
  - **BRAF V600E** and **KRAS G12R**

Schellens et al AACR ‘15
Post-progression cfDNA demonstrates clones that reactivate MAPK

If this is the case, then MEK inhibition may reverse resistance to EGFR/BRAF
But may not substantially improve initial activity

Identified in cfDNA
- PTEN I122N
- MEK1 C121S
- GNAS R201C
- EGFR L93I
- ARAF S490T

Gabi Tarnic, Novellus
Resistance to BRAF +/- EGFR

EGFR pathway activation

RAS mutations

MEK mutations

MAPK pathway reactivation

EGFR, KRAS amplifications

ARAF, PTEN, GNAS mutations

Another example of **convergent evolution** in colorectal cancer resistance to targeted therapy

Misale et al Nat Comm ‘15
PDX model: \( \text{BRAF}^{V600E}/\text{KRAS}^{\text{mut}} \): BRAF+EGFR vs MEK+EGFR inhibition

\[ \text{BRAF}^{V600E}/\text{KRAS}^{G12R} \]

\[ \text{BRAF}^{V600E}/\text{KRAS}^{G12D} \]

MEK inhibition reverses resistance to BRAF/EGFR

Van Morris
Encorafenib + Cetuximab ± Binimetinib

Phase 3 BRAF$^{\text{mut}}$ Colorectal Cancer Study Design

**Primary Endpoint:** Overall survival (OS) of the triplet therapy compared to the control arm.

**Secondary Endpoints:** Address efficacy of the doublet therapy compared to the control arm, and the triplet therapy compared to the doublet therapy.

Patient enrollment is expected to be completed in 2018.
Consensus Molecular Subtypes: CMS1

CMS1
MSI Immune

- MSI, CIMP high
- Hypermutation
- BRAF mutations
- Immune infiltration and activation

Guinney et al Nat Med '15
“BRAF\textsuperscript{mut} biology” is more than a mutated kinase

Sequencing data from NHS/HP Study (Giannakos, et al Cell Report ‘16)
BRAF and MSI share similar gene expression signatures

Role for immunotherapy in CMS1/BRAF mutated context?
Conclusions

- Testing for BRAF mutation is standard of care
  - Strong prognostic information that is useful for clinical management
- Patients with $\text{BRAF}^{\text{mut}}$ CRC have distinct biology and limited benefit with standard therapy
- Patients should be enrolled in clinical trials when available:
  - $\text{BRAF}+\text{EGFR}+\text{irinotecan}$ or $\text{BRAF}+\text{EGFR}+\text{MEK}$ appear most promising
  - Immunotherapy studies may be particularly relevant for patients with $\text{BRAF}^{\text{mut}}$ CRC (with or without MSI-H)
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