Lingering Questions in the Selection and Sequence of Therapy for Patients with mCRC

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Sequencing of chemobiologic agents

- Tumor sidedness and use of EGFR antibodies
- Optimal dosing of regorafenib
- TAS-102: Neutropenia, use in combination with bevacizumab
Sequencing of chemobiologic agents

• Tumor sidedness and use of EGFR antibodies
• Optimal dosing of regorafenib
• TAS-102: Neutropenia, use in combination with bevacizumab

Consider the last patient in your practice who died of mCRC. Did the patient receive...

- Both regorafenib and TAS-102: 14
- Regorafenib: 5
- TAS-102: 1
- Neither regorafenib nor TAS-102: 3

When administering regorafenib to a younger patient with a good performance status, what is your usual starting dose, and do you generally escalate to 160 mg?*

- 40 mg → 160 mg: 1
- 80 mg → 160 mg: 10
- 80 mg → 120 mg: 3
- 120 mg → 160 mg: 6
- 160 mg: 2

*All escalations are as tolerated

Have you or would you use TAS-102 in combination with bevacizumab outside of a clinical trial setting?

- I have: 7
- I have not but would for the right patient: 5
- I have not and would not: 11

Sequential of chemobiologic agents

• Tumor sidedness and use of EGFR antibodies
• Optimal dosing of regorafenib
• TAS-102: Neutropenia, use in combination with bevacizumab
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## Disclosures

<table>
<thead>
<tr>
<th>Advisory Committee, Consulting Agreements and Contracted Research</th>
<th>Amgen Inc, Bayer HealthCare Pharmaceuticals, Caris Life Sciences, Celgene Corporation, Indivumed GmbH, Roche Laboratories Inc, Taiho Oncology Inc</th>
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What influences treatment choices in mCRC?

- Patient characteristics
  - Comorbidities
  - Age
- Prior adjuvant treatment
- Performance status
- Tumor characteristics
  - Tumor burden
  - Resectability
  - Tumor location
- Tumor characteristics
- Molecular characteristics
  - RAS
  - BRAF
  - MSI-high
  - HER2
- Patient preference
  - Quality of life
  - Toxicity profile

Therapy tailored according to individual patient needs
2019: A classical case of mCRC

- **30 months OS**
- **2019: A classical case of mCRC**
- **5 months first-line induction**
- **3 months reintroduction (or treatment beyond progression)**
- **3 months "rechallenge"**
- **3 months break**
- **6 months maintenance**
- **4 months second line**
- **3 months third line**
- **3 months preterminal phase**
- **6 months maintenance**
- **3 months reintroduction (or treatment beyond progression)**

**Right or Left**
- MSI or MSS
- RAS/RAF
- HER2
- Other markers?
- Need for response
- QOL

**FU/Ox/Iri a new standard?**

**OS 30 months**

**Courtesy: Alberto Sobrero**
Refractory Colon Cancer: Many options, new data

- EGFR targeted therapy
- BRAF targeted therapy
- TAS 102
- Regorafenib
- HER2 as a target
- Immune Therapy
- Precision Medicine
- Recycled chemotherapy
- Biologics beyond progression
- Maintenance therapy 1 and sometimes 2 and 3!
Sequence and how to decide

• Do you have to be right?
• Biomarker or not?
• Do you need a response or is stable disease OK?
• Survival benefit proven?
• Likely toxicity
• Patient preferences, includes insurance issues
Basic Rules

• Possible advantage to “induction” chemo but don’t go too long
• Use EGFR therapy when you need a response
  • Only RAS and maybe BRAF WT
  • Only left sided?
• Maintenance therapy helps
• Unclear on stage IV NED
• Don’t leave known survival on the table
Global Randomized Phase III Study
RE COURSE: Refractory Colorectal Cancer Study
(NCT01607957)

- Treatment continuation until progression, intolerant toxicity or patient refusal
- Multicenter, randomized, double-blind, placebo-controlled, phase III
  - Stratification: KRAS status, time from diagnosis of metastatic disease, geographical region
- Sites: 13 countries, 114 sites
- Enrollment: June 2012 to October 2013

Metastatic colorectal cancer (mCRC)
- 2 or more prior regimens
- Refractory / Intolerable
  - fluoropyrimidine
  - irinotecan
  - oxaliplatin
  - bevacizumab
  - anti-EGFR if wild-type KRAS
- ECOG PS 0-1
- Age ≥ 18  
(target sample size: 800)

Randomization

TAS-102 + BSC  
(n = 534)  
35 mg/m² b.i.d. p.o.  
d1-5, 8-12 q4wks

Placebo + BSC  
(n = 266)  
d1-5, 8-12 q4wks

Endpoints Primary: OS  
Secondary: PFS, Safety,  
Tolerability, TTF, ORR, DCR,  
DoR, Subgroup by KRAS (OS and PFS)
Overall Survival

TAS-102  
N=534  
Placebo  
N=266  

Events # (%):  
TAS-102: 364 (68)  
Placebo: 210 (79)  

HR (95% CI):  
0.68 (0.58-0.81)  

Stratified Log-rank test: p<0.0001  

Median OS, months:  
TAS-102: 7.1  
Placebo: 5.3  

Median follow-up: 8.4 months  

Alive at, %:  
6 months: 58  
12 months: 27  

Mayer et al., NEJM 2015
Progression-free Survival

**Events # (%)**
- TAS-102: 472 (88)
- Placebo: 251 (94)

**HR (95% CI)**
- TAS-102: 0.48 (0.41-0.57)

**Stratified Log-rank test**
- p<0.0001

**Median PFS, months**
- TAS-102: 2.0
- Placebo: 1.7

Tumor assessments performed every 8 weeks

Mayer et al., NEJM 2015
Refractory mCRC: TASCO-1

Multicenter, randomized, open-label Phase II study

- Median PFS was 9.2 months TT/B vs 7.8 months
  - (HR) of 0.71 (95% confidence interval [CI] 0.48-1.06)
- Preliminary median OS was 18 months TT/B vs 16.2 months C-B
  - HR of 0.56 (95% CI, 0.32-0.98)

What comes next if this is 1L?


BID, twice daily; CI, confidence interval; DCR, disease control rate; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, by mouth

TT-B (35 mg/m² po bid d1–5 + 8–12 [TT]; 5 mg/kg d1 + 15 [B]) q28d

TT/B, trifluridine/tipiracil + bevacizumab

C-B (1250 or 1000 mg/m² bid d1–14 [C]; 7.5 mg/kg d1 [B]) q21d

C-B, capecitabine + bevacizumab

Primary endpoint
- PFS

Secondary endpoints
- OS, ORR, DCR, tumor response
- Safety, tolerability
Phase I Study of Trifluridine/Tipiracil Plus Irinotecan and Bevacizumab in Advanced Gastrointestinal Tumors

Clin Cancer Res. 2020 Jan 10. [Epub ahead of print]
Varghese AM1, Cardin DB2, Hersch J3, Benson A4, Hochster HS5, Makris L6, Hamada K7, Berlin J8, Saltz LB9.
CORRECT study design

- Multicenter, randomized, double-blind, placebo-controlled, phase III
  - 2:1 randomization
  - Strat. factors: prior anti-VEGF therapy, time from diagnosis of mCRC, geographical region
- Global trial: 16 countries, 114 active centers
  - 1,052 patients screened, 760 patients randomized within 10 months
- Secondary endpoints: PFS, ORR, DCR
- Tertiary endpoints: duration of response / stable disease, QOL, pharmacokinetics, biomarkers

Grothey et al., Lancet 2012
Overall survival (primary endpoint)

Primary endpoint met prespecified stopping criteria at interim analysis
(1-sided p<0.009279 at approximately 74% of events required for final analysis)

Survival distribution function

<table>
<thead>
<tr>
<th></th>
<th>Regorafenib</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>Median</td>
<td>6.4 mos</td>
<td>5.0 mos</td>
</tr>
<tr>
<td>95% CI</td>
<td>5.9–7.3</td>
<td>4.4–5.8</td>
</tr>
</tbody>
</table>

Hazard ratio: 0.77 (95% CI: 0.64–0.94)
1-sided p-value: 0.0052

Grothey et al. Lancet 2012
### ReDOS design

**Randomization**

1:1:1:1  
(Progression on previous standard therapy, including EGFRi if KRAS WT)

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<table>
<thead>
<tr>
<th>WEEK of C1</th>
<th>DOSE</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Starting dose C1 80 mg</td>
</tr>
<tr>
<td>2</td>
<td>120 mg</td>
</tr>
<tr>
<td>3</td>
<td>End dose C1 160 mg</td>
</tr>
<tr>
<td>4</td>
<td>off</td>
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<table>
<thead>
<tr>
<th>WEEK of C2+</th>
<th>DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dose from C1</td>
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**Arm A**

1. **Arm A 1**
   - Regorafenib Start low*
   - + pre-emptive strategy for Palmar-plantar erythrodysesthesia syndrome (PPES)

2. **Arm A 2**
   - Regorafenib Start low dose*
   - + reactive strategy for Palmar-plantar erythrodysesthesia syndrome (PPES)

**Arm B**

1. **Arm B 1**
   - Regorafenib 160 mg PO daily for 21 days
   - + pre-emptive strategy for Palmar-plantar erythrodysesthesia syndrome (PPES)

2. **Arm B 2**
   - Regorafenib 160 mg PO daily for 21 days
   - + reactive strategy for Palmar-plantar erythrodysesthesia syndrome (PPES)

---

**Eary endpoint**: proportion of patients who complete 2 cycles of protocol treatment and initiate cycle 3 in arm A and arm B

**2ary endpoints**: OS, PFS, TTP
Phase II ReDOS Study: OS (secondary endpoint)

**Figure 2B. Overall Survival Arms A & B**

<table>
<thead>
<tr>
<th>Arm</th>
<th>Events/Total</th>
<th>Median (95% CI)</th>
<th>Time-Point</th>
<th>KM Est (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>29/54</td>
<td>9.0 (6.8-13.4)</td>
<td>6 Months</td>
<td>66.5 (53.8-82.2%)</td>
<td>0.65 (0.39-1.08)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12 Months</td>
<td>34.4 (21.5-55.2%)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>34/62</td>
<td>5.9 (5.3-12.4)</td>
<td>6 Months</td>
<td>49.8 (37.2-66.8%)</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12 Months</td>
<td>26.7 (14.0-51.1%)</td>
<td></td>
</tr>
</tbody>
</table>

Logrank P-value: 0.0943

HR, hazard ratio; KM est, Kaplan-Meier estimate; OS, overall survival.

Data on File, ACCRU.
Alternative Regorafenib Dosing

REARRANGE Study Design

Primary endpoint:
- Safety: % of patients having G3/G4 AEs during the entire course of the treatment

Secondary endpoints:
- OS
- PFS
- % of Patients starting C3 on each arm
- Dose intensity
- DCR

Secondary Endpoints

OS Months by Treatment Arm

PFS Months by Treatment Arm

N=299 patients

DCR = disease control rate; IC/EC = inclusion criteria/exclusion criteria; PD = progressive disease

Napabucasin, First-in-Class Cancer Stemness Inhibitor

Courtesy J. Bendell
GI ESMO 2017

Why Target Cancer Cell Stemness?

Cancer Stem Cells & Cancer Stemness

- Highly tumorigenic
- Fundamentally responsible for continued malignant growth
- Initiators (seeds) of metastases
- Resistant to chemotherapy and current targeted therapies

Cancer Stem Cells
Cancer Cells with Stemness
Bulk Cancer Cells

Cancer Stemness Inhibitor

Chemotherapy
Radiotherapy
Targeted therapy

Relapse with resistance
STAT3: A Target for CSC Inhibition

**STAT3**
- Key regulator of cancer stemness
- STAT3 plays a key role in the survival and proliferation of PDAC cancer stem cells\(^1,2,3\)

**Napabucasin**
- Oral inhibitor of STAT3
- Blocks CSC self renewal
- Kills CSC and cancer cells

Signs of Anti-Cancer Activity

Best Response in pts treated with Napabucasin and FOLFIRI +/- bev

Percentage change in Target Lesions

FOLFIRI Naïve
FOLFIRI Exposed
FOLFIRI + Bevacizumab

Patient #

Courtesy J. Bendell
GI ESMO 2017
CanStem303C: Global Phase III Study

Adult Patients with metastatic CRC previously treated with FOLFOX or XELOX (with bevacizumab if appropriate)

Open Label

1:1

Napabucasin orally, twice daily
plus
FOLFIRI* (l-LV 400 mg/m², Irinotecan 180 mg/m², 5-FU 400 mg/m² → 2400 mg/m²)

FOLFIRI* (l-LV 400 mg/m², Irinotecan 180 mg/m², 5-FU 400 mg/m² → 2400 mg/m²)

Disease Progression based on RECIST or unacceptable toxicity

Death

*Addition of bevacizumab to the FOLFIRI regimen, per investigator choice, will be permissible.

Primary Endpoints
- OS

Secondary Endpoints
- PFS
- ORR
- DCR
- Safety
- QoL

 Courtesy J. Bendell
 GI ESMO 2017