Novel and Emerging Therapeutic Strategies in the Management of Select Gastrointestinal Cancers

Philip A Philip, MD, PhD
Kathryn Cramer Endowed Chair in Cancer Research
Professor of Oncology and Pharmacology
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Vice President of Medical Affairs
Karmanos Cancer Institute
Wayne State University
Detroit, Michigan
## Disclosures

<table>
<thead>
<tr>
<th>Advisory Committee</th>
<th>ASLAN Pharmaceuticals, BioLineRx, Caris Life Sciences, Celgene Corporation, Eisai Inc, Erytech Pharma, Halozyme Inc, Ipsen Biopharmaceuticals Inc, Merck, TriSalus Life Sciences</th>
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<tr>
<td>Consulting Agreements</td>
<td>AbbVie Inc, Merck, Rafael Pharmaceuticals Inc, TriSalus Life Sciences</td>
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<td>Contracted Research</td>
<td>Astellas Pharma Global Development Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeiGene, BioLineRx, Boston Biomedical Inc, Bristol-Myers Squibb Company, Caris Life Sciences, Celgene Corporation, Halozyme Inc, Incyte Corporation, Lilly, Novartis, Novocure, QED Therapeutics, Rafael Pharmaceuticals Inc, Roche Laboratories Inc, Taiho Oncology Inc</td>
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<td>Data and Safety Monitoring Board/Committee</td>
<td>ASLAN Pharmaceuticals, Blueprint Medicines, Erytech Pharma, Lexicon Pharmaceuticals Inc</td>
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<tr>
<td>Speakers Bureau</td>
<td>Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Celgene Corporation, Ipsen Biopharmaceuticals Inc, Merck</td>
</tr>
</tbody>
</table>
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Division of Medical Oncology  
Associate Director for  
Translational Research  
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**Philip A Philip, MD, PhD**  
Kathryn Cramer Endowed Chair in Cancer Research  
Professor of Oncology and Pharmacology  
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Vice President of Medical Affairs  
Karmanos Cancer Institute  
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Winthrop Rockefeller Chair in Medical Oncology  
Section Head, Hepatopancreatobiliary/Neuroendocrine Cancers  
Gastrointestinal Oncology Service  
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Attending Physician, Member  
Memorial Sloan Kettering Cancer Center  
Professor of Medicine  
Weill Cornell Medical College  
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The Madden Family Distinguished Professor of Medical Oncology and Translational Research
Shorenstein Associate Director
Program Development
Helen Diller Family Comprehensive Cancer Center
University of California, San Francisco
San Francisco, California

Project Chair
Neil Love, MD
Research To Practice
Miami, Florida
Which of the following best represents your clinical background?

1. Medical oncologist/hematologic oncologist
2. Radiation oncologist
3. Radiologist
4. Surgical oncologist or surgeon
5. Other MD
6. Nurse practitioner or physician assistant
7. Nurse
8. Researcher
9. Other healthcare professional
Module 1: Colorectal Cancer

• Primary tumor sidedness and selection of first-line therapy
• Sequencing of available therapies in the second line and beyond
• Novel targeted approaches

Module 2: Hepatocellular Carcinoma

• First-line systemic treatment: Sorafenib versus lenvatinib
• Beyond first-line therapy: Cabozantinib, ramucirumab, regorafenib and anti-PD-1/PD-L1 antibodies

Module 3: Pancreatic Cancer

• Neoadjuvant and adjuvant therapy approaches
• Management of metastatic disease and integration of nanoliposomal irinotecan
• BRCA mutations and PARP inhibition

Module 4: Gastric/Gastroesophageal Junction (GEJ)/Esophageal Cancer

• Pembrolizumab for the treatment of recurrent or advanced gastric, GEJ and esophageal cancer
• Efficacy and safety of TAS-102 for recurrent metastatic gastric or GEJ adenocarcinoma
What is your usual first-line treatment strategy for a 65-year-old patient with left-sided, microsatellite-stable (MSS), pan-RAS wild-type metastatic colorectal cancer (mCRC)?

1. Chemotherapy + bevacizumab
2. Chemotherapy + EGFR antibody
3. Chemotherapy
4. Other
What is your usual first-line treatment strategy for a 65-year-old patient with left-sided, microsatellite-stable (MSS), pan-RAS wild-type metastatic colorectal cancer (mCRC)?

<table>
<thead>
<tr>
<th>Doctor</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>TANIOS BEKAI-II SAAB, MD</td>
<td>FOLFIRI + bevacizumab</td>
</tr>
<tr>
<td>JOHANNA BENDELL, MD</td>
<td>FOLFIRI + EGFR antibody</td>
</tr>
<tr>
<td>HOWARD S HOCHSTER, MD</td>
<td>FOLFOX + bevacizumab</td>
</tr>
<tr>
<td>JOHN L MARSHALL, MD</td>
<td>CAPOX + bevacizumab</td>
</tr>
<tr>
<td>EILEEN M O'REILLY, MD</td>
<td>FOLFOXIRI + bevacizumab</td>
</tr>
<tr>
<td>PHILIP A PHILIP, MD, PHD</td>
<td>Chemotherapy + bevacizumab</td>
</tr>
<tr>
<td>ALAN P VENOOK, MD</td>
<td>FOLFIRI or FOLFOXIRI ± bevacizumab</td>
</tr>
</tbody>
</table>
How would you compare the global antitumor efficacy of chemotherapy/bevacizumab and chemotherapy/EGFR antibody as first-line therapy for left-sided, MSS, pan-RAS wild-type mCRC?

Do you administer EGFR antibodies to patients with right-sided mCRC?

<table>
<thead>
<tr>
<th>Name</th>
<th>Efficacy of chemo/bev vs chemo/EGFR Ab</th>
<th>EGFR Ab for right-sided mCRC?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanios Bekaïi-Saab, MD</td>
<td>Chemo/EGFR Ab somewhat more efficacious</td>
<td>Yes, 3rd line and beyond</td>
</tr>
<tr>
<td>Johanna Bendell, MD</td>
<td>Chemo/EGFR Ab somewhat more efficacious</td>
<td>Yes, 3rd line and beyond</td>
</tr>
<tr>
<td>Howard S Hochster, MD</td>
<td>Efficacy about the same</td>
<td>No</td>
</tr>
<tr>
<td>John L Marshall, MD</td>
<td>Chemo/EGFR Ab somewhat more efficacious</td>
<td>Yes, 3rd line and beyond</td>
</tr>
<tr>
<td>Eileen M O'Reilly, MD</td>
<td>Chemo/EGFR Ab somewhat more efficacious</td>
<td>Yes, 3rd line and beyond</td>
</tr>
<tr>
<td>Philip A Philip, MD, PhD</td>
<td>Chemo/EGFR Ab somewhat more efficacious</td>
<td>Yes, 2nd line</td>
</tr>
<tr>
<td>Alan P Venook, MD</td>
<td>Chemo/EGFR Ab somewhat more efficacious</td>
<td>No</td>
</tr>
</tbody>
</table>
Tumor Sidedness Associated with Genetic Alterations

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CALGB/SWOG-80405: Overall Survival by Biologic Agent and Primary Tumor Sidedness

### Left-sided primary

<table>
<thead>
<tr>
<th>Agent</th>
<th>N</th>
<th>Median</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bev</td>
<td>356</td>
<td>31.4 mo</td>
<td>0.817</td>
<td>0.018</td>
</tr>
<tr>
<td>Cetux</td>
<td>376</td>
<td>36.0 mo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Right-sided primary

<table>
<thead>
<tr>
<th>Agent</th>
<th>N</th>
<th>Median</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bev</td>
<td>150</td>
<td>24.2 mo</td>
<td>1.269</td>
<td>0.065</td>
</tr>
<tr>
<td>Cetux</td>
<td>143</td>
<td>16.7 mo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For a younger, otherwise healthy patient with MSI-high mCRC for whom you are planning to administer immune checkpoint inhibitor therapy, which agent or regimen would you most likely recommend?

1. Pembrolizumab
2. Nivolumab
3. Nivolumab/ipilimumab
4. Other
For a younger, otherwise healthy patient with MSI-high mCRC for whom you are planning to administer immune checkpoint inhibitor therapy, which agent or regimen would you most likely recommend?

In which line of therapy would you like to use an anti-PD-1/PD-L1 antibody?

<table>
<thead>
<tr>
<th>Agent or regimen</th>
<th>Preferred line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>First line</td>
</tr>
<tr>
<td>Nivolumab/ipilimumab</td>
<td>First line</td>
</tr>
<tr>
<td>Nivolumab/ipilimumab</td>
<td>Second line</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>First line</td>
</tr>
<tr>
<td>Nivolumab/ipilimumab</td>
<td>First line</td>
</tr>
<tr>
<td>Nivolumab/ipilimumab</td>
<td>First line</td>
</tr>
<tr>
<td>Nivolumab/ipilimumab</td>
<td>Second Line</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Second line</td>
</tr>
</tbody>
</table>
# FDA Approvals and Indications for MSI-H or dMMR Solid Tumors or mCRC

<table>
<thead>
<tr>
<th>Agent, approval date</th>
<th>Indication</th>
<th>Objective response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pembrolizumab</strong>&lt;br&gt;May 23, 2017</td>
<td>Adult and pediatric patients with unresectable or metastatic, MSI-H or dMMR solid tumors that have progressed after treatment who have no satisfactory alternative treatment options OR with MSI-H or dMMR mCRC that has progressed after treatment with a fluoropyrimidine, oxaliplatin and irinotecan</td>
<td>39.6%</td>
</tr>
<tr>
<td><strong>Nivolumab</strong>&lt;br&gt;July 31, 2017</td>
<td>Patients 12 years and older with dMMR and MSI-H mCRC that has progressed after treatment with a fluoropyrimidine, oxaliplatin and irinotecan</td>
<td>28%</td>
</tr>
<tr>
<td><strong>Nivolumab + ipilimumab</strong>&lt;br&gt;July 10, 2018</td>
<td>Patients 12 years and older with dMMR and MSI-H mCRC that has progressed after treatment with a fluoropyrimidine, oxaliplatin and irinotecan</td>
<td>46%</td>
</tr>
</tbody>
</table>

MSI-H = microsatellite instability high; dMMR = deficient mismatch repair

CheckMate 142: Long-Term Follow-Up of Nivolumab + Low-Dose Ipilimumab in Previously Treated dMMR/MSI-H mCRC

Nivo (3 mg/kg) + ipi (1 mg/kg) q3w x 4, then nivo (3 mg/kg) q2w until disease progression
Median duration of follow-up: 25.4 mo

• ORR (n = 119) = 58%
• DCR (≥12 weeks) = 81%

79% of patients had a reduction in tumor burden from baseline with combination therapy

Patients had target lesion at baseline and at least 1 on-treatment tumor assessment.
* Confirmed response per investigator assessment

• Select Grade 3/4 treatment-related AEs:
  - Elevated AST (8%), diarrhea (3%), pruritus (2%), fatigue (2%)

Overman MJ et al. Gastrointestinal Cancers Symposium 2019;Abstract 635.
In general, for a younger patient with mCRC, what is your usual starting dose of regorafenib?

1. 160 mg
2. 120 mg
3. 80 mg
4. 40 mg
5. Other
In general, for a **younger patient** with mCRC, what is your usual starting dose of regorafenib?

<table>
<thead>
<tr>
<th>Name</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>TANIOS BEKAI-Saab, MD</td>
<td>80 mg</td>
</tr>
<tr>
<td>JOHANNA BENDELL, MD</td>
<td>120 mg</td>
</tr>
<tr>
<td>HOWARD S HOCHSTER, MD</td>
<td>80 mg</td>
</tr>
<tr>
<td>JOHN L MARSHALL, MD</td>
<td>80 mg</td>
</tr>
<tr>
<td>EILEEN M O'REILLY, MD</td>
<td>120 mg</td>
</tr>
<tr>
<td>PHILIP A PHILIP, MD, PHD</td>
<td>120 mg</td>
</tr>
<tr>
<td>ALAN P VENOOK, MD</td>
<td>120 mg</td>
</tr>
</tbody>
</table>
What would be your third-line treatment recommendation for a 65-year-old patient with right-sided, MSS, pan-RAS wild-type mCRC who is experiencing disease progression after first-line FOLFOX/bev and second-line FOLFIRI/bev (PS 0)?

If the patient had a RAS mutation and PS 0 or PS 1-2?

<table>
<thead>
<tr>
<th>Pan-RAS WT, PS 0</th>
<th>RAS mutation, PS 0</th>
<th>RAS mutation, PS 1-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>TANIOS BEKAI- SAAB, MD</td>
<td>Regorafenib</td>
<td>Regorafenib or TAS 102 – coin flip</td>
</tr>
<tr>
<td>JOHANNA BENDELL, MD</td>
<td>Regorafenib</td>
<td>TAS-102</td>
</tr>
<tr>
<td>HOWARD S HOCHSTER, MD</td>
<td>Regorafenib or TAS 102 – coin flip</td>
<td>TAS-102</td>
</tr>
<tr>
<td>JOHN L MARSHALL, MD</td>
<td>Irinotecan + panitumumab</td>
<td>Regorafenib or TAS 102 – coin flip</td>
</tr>
<tr>
<td>EILEEN M O’REILLY, MD</td>
<td>Regorafenib</td>
<td>Regorafenib or TAS 102 – coin flip</td>
</tr>
<tr>
<td>PHILIP A PHILIP, MD, PHD</td>
<td>Irinotecan + panitumumab</td>
<td>Regorafenib or TAS 102 – coin flip</td>
</tr>
<tr>
<td>ALAN P VENOOK, MD</td>
<td>Irinotecan + panitumumab</td>
<td>Regorafenib or TAS 102 – coin flip</td>
</tr>
</tbody>
</table>
Regorafenib Dose Optimization Study (ReDOS): A Phase II Trial to Evaluate Dosing of Regorafenib for Refractory mCRC

Survival Esc dose (n = 54) Std dose (n = 62) HR p-value
Median OS 9.8 mo 6.0 mo 0.72 0.12
Median PFS 2.8 mo 2.0 mo 0.84 0.38

• Multiple QoL parameters were favorable with the escalating dose versus standard dose strategy primarily at week 2 of cycle 1

Reduced Dose (RD) Regorafenib 120 mg/day 3w on/1w off

Regorafenib 160 mg/day 3w on/1w off

Intermittent Dose (ID) Regorafenib 160 mg/day 1w on/1w off

Eligibility

- Stage IV CRC
- Progression on/after approved standard therapies, which must include fluoropyrimidine, oxaliplatin, irinotecan, an anti-VEGF and an anti-EGFR (if RAS WT)

Argiles G et al. Proc ESMO World Congress GI 2019;Abstract O-026.
REVERCE: Overall Survival with Regorafenib Followed by Cetuximab versus the Reverse Sequence


N = 101 pts with mCRC and disease progression on fluoropyrimidine, oxaliplatin and irinotecan

Median OS
- R-C arm: 17.4 mo
- C-R arm: 11.6 mo
HR: 0.61
p = 0.029
REGONIVO: A Phase Ib Study of Regorafenib with Nivolumab for CRC or Advanced Gastric Cancer (GC)

- Dose of regorafenib reduced to 80 mg due to skin toxicities
- Select Grade ≥3 treatment-related AEs (TRAEs) in all patients: 40%
- Select Grade ≥3 TRAEs in patients given regorafenib 80 mg: 27%
  - Proteinuria (9%)
  - Liver dysfunction (9%)
- One treatment-related death due to diabetic ketoacidosis

Fukuoka S et al. ASCO 2019;Abstract 2522.
TAS-102 with Bevacizumab for Chemorefractory mCRC

- Randomized study with N = 93 patients with chemorefractory mCRC

<table>
<thead>
<tr>
<th></th>
<th>TAS-102/bevacizumab</th>
<th>TAS-102</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>4.6 mo</td>
<td>2.6 mo</td>
<td>0.45</td>
<td>0.001</td>
</tr>
<tr>
<td>Median OS</td>
<td>9.4 mo</td>
<td>6.7 mo</td>
<td>0.55</td>
<td>0.03</td>
</tr>
</tbody>
</table>

- Adverse events were as expected
- Grade 3 or 4 neutropenia (TAS-102/bev vs TAS-102): 67% vs 38% (p < 0.05)
- Serious adverse events (TAS-102/bev vs TAS-102): 19 patients vs 21 patients

Pfeiffer P et al. Proc ESMO World Congress GI 2019;Abstract O-014.
In addition to pan-RAS status, which of the following items do you routinely assess in patients with mCRC?

<table>
<thead>
<tr>
<th>Name</th>
<th>Assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>TANIOS BEKAI-SAAB, MD</td>
<td>HER2 status, BRAF status, MSI, multigene panel (NGS)</td>
</tr>
<tr>
<td>JOHANNA BENDELL, MD</td>
<td>HER2 status, BRAF status, MSI, multigene panel (NGS)</td>
</tr>
<tr>
<td>HOWARD S HOCSTER, MD</td>
<td>HER2 status, BRAF status, MSI</td>
</tr>
<tr>
<td>JOHN L MARSHALL, MD</td>
<td>HER2 status, BRAF status, MSI, multigene panel (NGS)</td>
</tr>
<tr>
<td>EILEEN M O'REILLY, MD</td>
<td>HER2 status, BRAF status, MSI, multigene panel (NGS)</td>
</tr>
<tr>
<td>PHILIP A PHILIP, MD, PHD</td>
<td>Multigene panel (next-generation sequencing)</td>
</tr>
<tr>
<td>ALAN P VENOOK, MD</td>
<td>HER2 status, BRAF status, MSI</td>
</tr>
</tbody>
</table>

MSI = microsatellite instability; NGS = next-generation sequencing
Prevalence of Molecular Alterations in Colorectal Cancer (CRC)

- **RAS mut +/- PIK3CA/PTEN mut** (45%)
- **PIK3CA/PTEN mut** (8%)
- **Wild-type** (26%)
- **BRAF V600E** (8%)
- **BRAF non-V600** (8%)
- **HER2 ampl** (2%)
- **MET ampl** (2%)
- **POLE mut** (1%)
- **Gene fusion** (1%)
- **MSI** (2%)
- **MSI + other** (2%)
- **Gene fusion** (1%)

Reimbursement and regulatory issues aside, what would be your most likely second-line treatment recommendation for a 65-year-old patient with left-sided, MSS, pan-RAS wild-type mCRC with a BRAF V600E mutation who received first-line FOLFOXIRI/bevacizumab and experienced disease progression 8 months later (PS 0)?

1. Continue bevacizumab and switch chemotherapy
2. Chemotherapy + EGFR antibody
3. Irinotecan + vemurafenib + EGFR antibody
4. Dabrafenib + trametinib + EGFR antibody
5. Encorafenib + binimetinib + EGFR antibody
6. Other
Continue bevacizumab and switch chemotherapy

Chemotherapy + EGFR antibody

Irinotecan + vemurafenib + EGFR antibody

Dabrafenib + trametinib + EGFR antibody

Encorafenib + binimetinib + EGFR antibody

Other
Reimbursement and regulatory issues aside, what would be your most likely second-line treatment recommendation for a 65-year-old patient with left-sided, MSS, pan-RAS wild-type mCRC with a BRAF V600E mutation who received first-line FOLFOXIRI/bevacizumab and experienced disease progression 8 months later (PS 0)?

<table>
<thead>
<tr>
<th>Name</th>
<th>Treatment Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>TANIOS BEKAIJ-Saab, MD</td>
<td>Encorafenib + binimetinib + EGFR antibody</td>
</tr>
<tr>
<td>Johanna Bendell, MD</td>
<td>Encorafenib + binimetinib + EGFR antibody</td>
</tr>
<tr>
<td>Howard S Hochster, MD</td>
<td>Encorafenib + binimetinib + EGFR antibody</td>
</tr>
<tr>
<td>John L Marshall, MD</td>
<td>Encorafenib + binimetinib + EGFR antibody</td>
</tr>
<tr>
<td>Eileen M O’Reilly, MD</td>
<td>Encorafenib + binimetinib + EGFR antibody</td>
</tr>
<tr>
<td>Philip A Philip, MD, PhD</td>
<td>Encorafenib + binimetinib + EGFR antibody</td>
</tr>
<tr>
<td>Alan P Venook, MD</td>
<td>Encorafenib + binimetinib + EGFR antibody</td>
</tr>
</tbody>
</table>
BEACON CRC: A Phase III Trial of Encorafenib and Cetuximab with or without Binimetinib for mCRC with BRAF V600E Mutation

**Eligibility**
- Histologically or cytologically confirmed metastatic CRC
- Disease progression after 1 or 2 regimens in the metastatic setting
- BRAF V600E mutation in tumor tissue as previously determined by a local assay at any time prior to screening or by the central laboratory

**Primary endpoint:** OS and ORR (by blinded central review) comparing the triplet to the control arm.

BEACON CRC: Encorafenib and Cetuximab with or without Binimetinib for mCRC with BRAF V600E Mutation

<table>
<thead>
<tr>
<th></th>
<th>ENCO/CETUX/BINI (n = 224)</th>
<th>ENCO/CETUX (n = 220)</th>
<th>Control – Irinotecan or FOLFIRI + cetuximab (n = 221)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR</td>
<td>26%</td>
<td>20%</td>
<td>2%*</td>
</tr>
<tr>
<td>Median OS</td>
<td>9.0 mo</td>
<td>8.4 mo</td>
<td>5.4 mo</td>
</tr>
<tr>
<td>Hazard ratio (p-value)</td>
<td>0.52 (&lt;0.001)</td>
<td>0.60 (&lt;0.001)</td>
<td>Ref</td>
</tr>
</tbody>
</table>

*p < 0.001

Adverse events were as anticipated based on prior trials with each combination.

Module 1: Colorectal Cancer
- Primary tumor sidedness and selection of first-line therapy
- Sequencing of available therapies in the second line and beyond
- Novel targeted approaches

Module 2: Hepatocellular Carcinoma
- First-line systemic treatment: Sorafenib versus lenvatinib
- Beyond first-line therapy: Cabozantinib, ramucirumab, regorafenib and anti-PD-1/PD-L1 antibodies

Module 3: Pancreatic Cancer
- Neoadjuvant and adjuvant therapy approaches
- Management of metastatic disease and integration of nanoliposomal irinotecan
- BRCA mutations and PARP inhibition

Module 4: Gastric/Gastroesophageal Junction (GEJ)/Esophageal Cancer
- Pembrolizumab for the treatment of recurrent or advanced gastric, GEJ and esophageal cancer
- Efficacy and safety of TAS-102 for recurrent metastatic gastric or GEJ adenocarcinoma
What would be your most likely first-line systemic treatment for a 65-year-old patient with hepatocellular carcinoma (HCC), a Child-Pugh A score and a PS of 0?

1. Sorafenib
2. Lenvatinib
3. Sorafenib or lenvatinib — coin flip
4. Chemotherapy
5. Other
Sorafenib 0%

Lenvatinib 0%

Sorafenib or lenvatinib — coin flip 0%

Chemotherapy 0%

Other 0%
What would be your most likely first-line systemic treatment for a 65-year-old patient with...

<table>
<thead>
<tr>
<th></th>
<th>Child-Pugh A HCC</th>
<th>Child-Pugh B7 HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PS 0</td>
<td>Painful bone mets</td>
</tr>
<tr>
<td>TANIOS BEKAI-L-SAAB, MD</td>
<td>Sorafenib</td>
<td>Lenvatinib</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>JOHANNA BENDELL, MD</td>
<td>Lenvatinib</td>
<td>Lenvatinib</td>
</tr>
<tr>
<td>HOWARD S HOCHSTER, MD</td>
<td>Sorafenib or</td>
<td>Sorafenib or</td>
</tr>
<tr>
<td></td>
<td>lenvatinib – coin flip</td>
<td>lenvatinib – coin flip</td>
</tr>
<tr>
<td>JOHN L MARSHALL, MD</td>
<td>Sorafenib</td>
<td>Lenvatinib</td>
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</tr>
<tr>
<td>EILEEN M O'REILLY, MD</td>
<td>Lenvatinib</td>
<td>Lenvatinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHILIP A PHILIP, MD, PHD</td>
<td>Lenvatinib</td>
<td>Lenvatinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALAN P VENOOK, MD</td>
<td>Sorafenib or</td>
<td>Sorafenib or</td>
</tr>
<tr>
<td></td>
<td>lenvatinib – coin flip</td>
<td>lenvatinib – coin flip</td>
</tr>
</tbody>
</table>
Based on current clinical trial data and your personal experience, how would you compare the global antitumor efficacy and tolerability profile of sorafenib and lenvatinib as first-line therapy for HCC?

<table>
<thead>
<tr>
<th></th>
<th>Efficacy</th>
<th>Tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>TANIOS BEKAI-Saab, MD</td>
<td>About the same</td>
<td>Sorafenib has somewhat more toxicity</td>
</tr>
<tr>
<td>JOHANNA BENDELL, MD</td>
<td>Lenvatinib is somewhat more efficacious</td>
<td>Sorafenib has somewhat more toxicity</td>
</tr>
<tr>
<td>HOWARD S HOCHSTER, MD</td>
<td>About the same</td>
<td>About the same</td>
</tr>
<tr>
<td>JOHN L MARSHALL, MD</td>
<td>Lenvatinib is somewhat more efficacious</td>
<td>Lenvatinib has somewhat more toxicity</td>
</tr>
<tr>
<td>EILEEN M O'REILLY, MD</td>
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<td>About the same</td>
</tr>
<tr>
<td>PHILIP A PHILIP, MD, PHD</td>
<td>Lenvatinib is somewhat more efficacious</td>
<td>Lenvatinib has somewhat more toxicity</td>
</tr>
<tr>
<td>ALAN P VENOOK, MD</td>
<td>About the same</td>
<td>About the same</td>
</tr>
</tbody>
</table>
REFLECT: A Phase III Trial of Lenvatinib versus Sorafenib as First-Line Treatment for Unresectable HCC

### Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Lenvatinib (n = 478)</th>
<th>Sorafenib (n = 476)</th>
<th>HR or OR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>7.4 mo</td>
<td>3.7 mo</td>
<td>HR 0.66</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median time to progression</td>
<td>8.9 mo</td>
<td>3.7 mo</td>
<td>HR 0.63</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Objective response rate</td>
<td>24.1%</td>
<td>9.2%</td>
<td>OR 3.13</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

HR = hazard ratio; OR = odds ratio

The safety and tolerability profiles of lenvatinib were consistent with those previously observed.

## REFLECT: Select Treatment-Emergent AEs

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Lenvatinib (n = 476)</th>
<th>Sorafenib (n = 475)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>201 (42)</td>
<td>111 (23)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>184 (39)</td>
<td>20 (4)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>162 (34)</td>
<td>22 (5)</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>147 (31)</td>
<td>36 (8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>141 (30)</td>
<td>18 (4)</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia</td>
<td>128 (27)</td>
<td>14 (3)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>117 (25)</td>
<td>27 (6)</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>113 (24)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>93 (20)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Decreased platelet count</td>
<td>87 (18)</td>
<td>26 (6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>77 (16)</td>
<td>6 (1)</td>
</tr>
</tbody>
</table>

What would be your most likely second-line systemic therapy for a 65-year-old patient with HCC, a Child-Pugh A score and a PS of 0 who received first-line standard-dose sorafenib with minimal toxicity, had stable disease for 14 months and then experienced disease progression (alpha-fetoprotein [AFP] 2,500 ng/mL)?

1. Lenvatinib
2. Regorafenib
3. Ramucirumab
4. Chemotherapy
5. Nivolumab
6. Pembrolizumab
7. Cabozantinib
8. Palliative care
9. Other
What would be your most likely second-line systemic therapy for a 65-year-old patient with HCC who received first-line standard-dose sorafenib with minimal toxicity, had stable disease for 14 months and then experienced disease progression?

<table>
<thead>
<tr>
<th></th>
<th>Child-Pugh A, PS 0</th>
<th>Child-Pugh B7, PS 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AFP 2,500 ng/mL</td>
<td>AFP 300 ng/mL</td>
</tr>
<tr>
<td>AFP 2,500 ng/mL</td>
<td>Regorafenib</td>
<td>Regorafenib</td>
</tr>
<tr>
<td>AFP 300 ng/mL</td>
<td>Regorafenib</td>
<td>Ramucirumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pembrolizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TANIOS BEKAI-Saab, MD</td>
<td>Regorafenib</td>
<td>Ramucirumab</td>
</tr>
<tr>
<td>JOHANNA BENDELL, MD</td>
<td>Cabozantinib</td>
<td>Cabozantinib</td>
</tr>
<tr>
<td>HOWARD S HOCHSTER, MD</td>
<td>Regorafenib</td>
<td>Cabozantinib</td>
</tr>
<tr>
<td>JOHN L MARSHALL, MD</td>
<td>Regorafenib</td>
<td>Cabozantinib</td>
</tr>
<tr>
<td>EILEEN M O'REILLY, MD</td>
<td>Regorafenib</td>
<td>Nivolumab</td>
</tr>
<tr>
<td>PHILIP A PHILIP, MD, PHD</td>
<td>Regorafenib</td>
<td>Ramucirumab</td>
</tr>
<tr>
<td>ALAN P VENOOK, MD</td>
<td>Nivolumab</td>
<td>Nivolumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pembrolizumab</td>
</tr>
<tr>
<td>Regorafenib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regorafenib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regorafenib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regorafenib or nivolumab</td>
<td>Regorafenib</td>
<td>Nivolumab</td>
</tr>
<tr>
<td>Regorafenib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regorafenib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regorafenib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Research To Practice®
What would be your most likely **second-line systemic therapy** for a 65-year-old patient with HCC who received **first-line sorafenib** and required a dose reduction to 400 mg daily, had stable disease for 5 months and then experienced disease progression?

<table>
<thead>
<tr>
<th></th>
<th>Child-Pugh A, PS 0</th>
<th>Child-Pugh B7, PS 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AFP 2,500 ng/mL</td>
<td>AFP 2,500 ng/mL</td>
</tr>
<tr>
<td></td>
<td>AFP 300 ng/mL</td>
<td>AFP 300 ng/mL</td>
</tr>
<tr>
<td><strong>TANIOS BEKAI-Saab, MD</strong></td>
<td>Cabozantinib</td>
<td>Ramucirumab</td>
</tr>
<tr>
<td><strong>JOHANNA BENDELL, MD</strong></td>
<td>Ramucirumab</td>
<td>Ramucirumab</td>
</tr>
<tr>
<td><strong>HOWARD S HOCHSTER, MD</strong></td>
<td>Regorafenib</td>
<td>Ramucirumab</td>
</tr>
<tr>
<td><strong>JOHN L MARSHALL, MD</strong></td>
<td>Pembrolizumab</td>
<td>Pembrolizumab</td>
</tr>
<tr>
<td><strong>EILEEN M O'REILLY, MD</strong></td>
<td>Nivolumab</td>
<td>Nivolumab</td>
</tr>
<tr>
<td><strong>PHILIP A PHILIP, MD, PhD</strong></td>
<td>Ramucirumab</td>
<td>Ramucirumab</td>
</tr>
<tr>
<td><strong>ALAN P VENOOK, MD</strong></td>
<td>Nivolumab</td>
<td>Nivolumab</td>
</tr>
</tbody>
</table>
CELESTIAL: A Phase III Trial of Cabozantinib versus Placebo for Advanced HCC

<table>
<thead>
<tr>
<th></th>
<th>Cabozantinib (n = 470)</th>
<th>Placebo (n = 237)</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>0.76</td>
<td>0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median OS</td>
<td>10.2 mo</td>
<td>8.0 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior sorafenib only</td>
<td>0.70</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median OS</td>
<td>11.3 mo</td>
<td>7.2 mo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* ≥20% decrease in AFP level from baseline at week 8

<table>
<thead>
<tr>
<th>OS in cabozantinib group by AFP response*2</th>
<th>Median OS</th>
<th>No. of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP response (N = 117)</td>
<td>16.1 mo</td>
<td>81</td>
</tr>
<tr>
<td>No AFP response (N = 119)</td>
<td>9.1 mo</td>
<td>85</td>
</tr>
</tbody>
</table>

FDA Grants Approval to Ramucirumab for HCC
Press Release – May 10, 2019

“The Food and Drug Administration approved ramucirumab as a single agent for hepatocellular carcinoma (HCC) in patients who have an alpha fetoprotein (AFP) of ≥400 ng/mL and have been previously treated with sorafenib.

Approval was based on REACH-2 (NCT02435433), a multinational, randomized, double-blind, placebo-controlled, multicenter study in 292 patients with advanced HCC with AFP ≥400 ng/mL who had disease progression on or after sorafenib or who were intolerant.”

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ramucirumab-hepatocellular-carcinoma
REACH-2: A Phase III Trial of Ramucirumab After Sorafenib for Patients with Advanced HCC and Increased AFP

<table>
<thead>
<tr>
<th></th>
<th>Ramucirumab (n = 197)</th>
<th>Placebo (n = 95)</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>8.5 mo</td>
<td>7.3 mo</td>
<td>0.710</td>
<td>0.0199</td>
</tr>
</tbody>
</table>

Median durations of follow-up were 7.9 months for ramucirumab, 6.6 months for placebo.

<table>
<thead>
<tr>
<th></th>
<th>Ramucirumab (n = 197)</th>
<th>Placebo (n = 95)</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>2.8 mo</td>
<td>1.6 mo</td>
<td>0.452</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Grade ≥3 AEs associated with ramucirumab included hypertension and hyponatremia.

**RESORCE: A Phase III Trial of Regorafenib for Patients with HCC Who Experienced Disease Progression on Sorafenib**

<table>
<thead>
<tr>
<th></th>
<th>Regorafenib (n = 379)</th>
<th>Placebo (n = 194)</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS(^1)</td>
<td>3.1 mo</td>
<td>1.5 mo</td>
<td>0.46</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median OS (primary analysis)(^1)</td>
<td>10.6 mo</td>
<td>7.8 mo</td>
<td>0.63</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median OS (updated analysis)(^2,3)</td>
<td>10.7 mo</td>
<td>7.9 mo</td>
<td>0.62</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ORR (mRECIST)(^1)</td>
<td>11%</td>
<td>4%</td>
<td></td>
<td>0.0047</td>
</tr>
<tr>
<td>Disease control rate(^1)</td>
<td>65%</td>
<td>36%</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

- Common clinically relevant Grade 3/4 TEAEs: Hypertension (15% vs 5%), hand-foot skin reaction (13% vs 1%), fatigue (9% vs 5%) and diarrhea (3% vs 0)\(^1\)
  - Data cutoff for primary analysis: February 29, 2016
  - Data cutoff for updated OS analysis: January 23, 2017

Efficacy

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>All patients (n = 214)</th>
<th>Uninfected untreated/intolerant (n = 56)</th>
<th>Uninfected progressor (n = 57)</th>
<th>HCV infected (n = 50)</th>
<th>HBV infected (n = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate</td>
<td>20%</td>
<td>23%</td>
<td>21%</td>
<td>20%</td>
<td>14%</td>
</tr>
<tr>
<td>Median DOR</td>
<td>9.9 mo</td>
<td>8.4 mo</td>
<td>NYR</td>
<td>9.9 mo</td>
<td>NYR</td>
</tr>
<tr>
<td>9-mo overall survival</td>
<td>74%</td>
<td>82%</td>
<td>63%</td>
<td>81%</td>
<td>70%</td>
</tr>
</tbody>
</table>

HCV = hepatitis C virus; HBV = hepatitis B virus; DOR = duration of response; NYR = not yet reached

On September 22, 2017, the Food and Drug Administration granted accelerated approval to nivolumab for the treatment of HCC in patients who have previously received sorafenib.
Phase III KEYNOTE-240 Trial: Pembrolizumab versus Best Supportive Care as Second-Line Therapy for Advanced HCC

- Accelerated approval for pembrolizumab granted in 2018 based on Phase II KEYNOTE-224 study
- Confirmatory KEYNOTE-240 trial: Numerical but not statistical advantage in PFS and OS
- Results of Phase III KEYNOTE-394 are pending

**Progression-free survival (%)**

- Pembrolizumab: 19.4%
- Placebo: 6.7%
- Median: 3.0 mo for Pembrolizumab, 2.8 mo for Placebo

**Overall survival (%)**

- Pembrolizumab: 13.9 mo
- Placebo: 10.6 mo
- Median: 10.6 mo for Placebo, 13.9 mo for Pembrolizumab

**PFS final analysis**

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>214</td>
<td>0.718</td>
<td>0.0022</td>
</tr>
<tr>
<td>Placebo</td>
<td>118</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Overall survival**

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>183</td>
<td>0.781</td>
<td>0.0238</td>
</tr>
<tr>
<td>Placebo</td>
<td>101</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# Ongoing Phase III Studies of Checkpoint Inhibitors in Advanced HCC

<table>
<thead>
<tr>
<th>Study identifier</th>
<th>Target accrual</th>
<th>Eligibility</th>
<th>Randomization</th>
</tr>
</thead>
</table>
| LEAP-002 (NCT03713593) | 750 | First line, advanced HCC | • Lenvatinib + Pembrolizumab  
• Lenvatinib |
| IMbrave150 (NCT03434379) | 480 | First line, locally advanced or advanced HCC | • Atezolizumab + Bevacizumab  
• Sorafenib |
| HIMALAYA (NCT03298451) | 1,310 | First line, advanced HCC | • Durvalumab  
• Durvalumab + Tremelimumab (2 regimens)  
• Sorafenib |
| COSMIC-312 (NCT03755791) | 640 (6:3:1) | First line, advanced HCC | • Cabozantinib + Atezolizumab  
• Sorafenib  
• Cabozantinib |

www.clinicaltrials.gov, Accessed July 2019
What would be your most likely third-line systemic therapy recommendation for an otherwise healthy 65-year-old patient with HCC who experienced disease progression on first-line sorafenib and second-line nivolumab (AFP 2,500 ng/mL)? If their AFP was 300 ng/mL?

<table>
<thead>
<tr>
<th></th>
<th>AFP 2,500 ng/mL</th>
<th>AFP 300 ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>TANIOS BEKAI-Saab, MD</td>
<td>Cabozantinib</td>
<td>Cabozantinib</td>
</tr>
<tr>
<td>JOHANNA BENDELL, MD</td>
<td>Cabozantinib</td>
<td>Cabozantinib</td>
</tr>
<tr>
<td>HOWARD S HOCHSTER, MD</td>
<td>Palliative care</td>
<td>Palliative care</td>
</tr>
<tr>
<td>JOHN L MARSHALL, MD</td>
<td>Ramucirumab</td>
<td>Regorafenib</td>
</tr>
<tr>
<td>EILEEN M O'REILLY, MD</td>
<td>Ramucirumab</td>
<td>Cabozantinib</td>
</tr>
<tr>
<td>PHILIP A PHILIP, MD, PHD</td>
<td>Ramucirumab</td>
<td>Cabozantinib</td>
</tr>
<tr>
<td>ALAN P VENOOK, MD</td>
<td>Cabozantinib</td>
<td>Cabozantinib</td>
</tr>
</tbody>
</table>
Module 1: Colorectal Cancer
• Primary tumor sidedness and selection of first-line therapy
• Sequencing of available therapies in the second line and beyond
• Novel targeted approaches

Module 2: Hepatocellular Carcinoma
• First-line systemic treatment: Sorafenib versus lenvatinib
• Beyond first-line therapy: Cabozantinib, ramucirumab, regorafenib and anti-PD-1/PD-L1 antibodies

Module 3: Pancreatic Cancer
• Neoadjuvant and adjuvant therapy approaches
• Management of metastatic disease and integration of nanoliposomal irinotecan
• BRCA mutations and PARP inhibition

Module 4: Gastric/Gastroesophageal Junction (GEJ)/Esophageal Cancer
• Pembrolizumab for the treatment of recurrent or advanced gastric, GEJ and esophageal cancer
• Efficacy and safety of TAS-102 for recurrent metastatic gastric or GEJ adenocarcinoma
Phase II Studies of (Neo)Adjuvant Chemotherapy for Resectable Pancreatic Adenocarcinoma

**NEONAX: Neoadjuvant and adjuvant or adjuvant gemcitabine/nab paclitaxel**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Arm A (n = 25) (perioperative)</th>
<th>Arm B (n = 23) (adjuvant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor resection: Yes</td>
<td>80%</td>
<td>91.3%</td>
</tr>
<tr>
<td>No</td>
<td>20%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Postoperative complications</td>
<td>45%</td>
<td>42.8%</td>
</tr>
</tbody>
</table>

Grade ≥3 adverse events increased in the perioperative arm, but this was manageable and did not result in peri- or postoperative mortality.

**SWOG-S1505: Neoadjuvant mFOLFIRINOX versus gemcitabine/nab paclitaxel**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reached protocol surgery: Yes</td>
<td>77%</td>
</tr>
<tr>
<td>No</td>
<td>23%</td>
</tr>
</tbody>
</table>

Preoperative chemotherapy was safe and feasible.
What is your likely adjuvant systemic therapy recommendation for an otherwise healthy 75-year-old patient after surgical resection of pancreatic cancer?

1. Gemcitabine
2. Gemcitabine/capecitabine
3. Gemcitabine/nab paclitaxel
4. 5-FU/leucovorin (LV)
5. Modified FOLFIRINOX
6. Other
What is your likely adjuvant systemic therapy recommendation for an otherwise healthy 75-year-old patient after surgical resection of pancreatic cancer?

Would you administer *nab* paclitaxel/gemcitabine as adjuvant therapy for a patient with pancreatic cancer?

<table>
<thead>
<tr>
<th>Adjuvant therapy</th>
<th><em>Nab</em> paclitaxel/gemcitabine as adjuvant therapy?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified FOLFIRINOX</td>
<td>No</td>
</tr>
<tr>
<td>Modified FOLFIRINOX</td>
<td>No</td>
</tr>
<tr>
<td>Modified FOLFIRINOX</td>
<td>No</td>
</tr>
<tr>
<td>Modified FOLFIRINOX</td>
<td>No</td>
</tr>
<tr>
<td>Modified FOLFIRINOX</td>
<td>No</td>
</tr>
<tr>
<td>Modified FOLFIRINOX</td>
<td>Not a candidate or refuses FFX Good performance status</td>
</tr>
<tr>
<td>Modified FOLFIRINOX</td>
<td>Yes, patient w/ poor PS or hyperbilirubinemia</td>
</tr>
</tbody>
</table>
PRODIGE 24/CCTG PA.6: Survival and Safety with FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer

**Outcome** | mFOLFIRINOX (n = 247) | Gem (n = 246) | HR | p-value
---|---|---|---|---
Median DFS | 21.6 mo | 12.8 mo | 0.58 | <0.001
Median OS | 54.4 mo | 35.0 mo | 0.64 | 0.003

- Grade 3/4 AEs: mFOLFIRINOX, 75.9%; gemcitabine, 52.9%
- Grade 3/4 AEs higher in mFOLFIRINOX arm: diarrhea, paresthesia, fatigue, peripheral neuropathy, vomiting, abdominal pain, mucositis
- Grade 3/4 AEs higher in the gemcitabine arm: thrombocytopenia

Phase III APACT Trial of Adjuvant Gemcitabine/Nab Paclitaxel for Surgically Resected Pancreatic Adenocarcinoma

Primary Endpoint: Investigator assessed DFS
- The primary endpoint was not met.
- Interim-analysis OS was improved for nab-P + Gem compared to Gem (40.5 mo vs 36.2 mo; HR 0.82, nominal $P = 0.045$).

Probability of DFS, %

- $nab$-P + Gem: 16.6 mo
- Gem: 13.7 mo
  (HR 0.82; 95% CI, 0.694-0.965; nominal $P = 0.0168$)
- Number of events: 571

Months

Tempero M et al. *Proc ASCO* 2019;Abstract 4000;
Reni M et al. *Proc ESMO World Congress GI* 2019;Abstract O-001.
Phase II LAPACT Trial of *Nab* Paclitaxel and Gemcitabine for Unresectable Locally Advanced Pancreatic Cancer: Survival, Response and Safety Results

<table>
<thead>
<tr>
<th>Outcome (all patients)</th>
<th>N = 107</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate</td>
<td>32.7%</td>
</tr>
<tr>
<td>Partial response rate</td>
<td>32.7%</td>
</tr>
<tr>
<td>Disease control rate (SD ≥24 weeks)</td>
<td>65.4%</td>
</tr>
<tr>
<td>Median PFS</td>
<td>10.8 mo</td>
</tr>
<tr>
<td>Estimated 1-y OS (interim analysis)</td>
<td>72%</td>
</tr>
</tbody>
</table>

*Nab* paclitaxel/gemcitabine was tolerable and QoL was maintained for most patients.
What second-line therapy would you recommend to a 75-year-old who is not a candidate for FOLFIRINOX and who receives first-line gemcitabine/nab paclitaxel for metastatic pancreatic cancer and experiences disease progression after 5 months?

1. Nal-IRI + 5-FU/LV
2. FOLFOX
3. FOLFIRI
4. Other
What second-line therapy would you recommend to a 75-year-old who is not a candidate for FOLFIRINOX and who receives first-line gemcitabine/\textit{nab} paclitaxel for metastatic pancreatic cancer and experiences disease progression after 5 months?

<table>
<thead>
<tr>
<th>Expert</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>TANIOS BEKAII-SAAB, MD</td>
<td>Nal-IRI + 5-FU/LV</td>
</tr>
<tr>
<td>JOHANNA BENDELL, MD</td>
<td>Nal-IRI + 5-FU/LV</td>
</tr>
<tr>
<td>HOWARD S HOCHSTER, MD</td>
<td>FOLFIRI</td>
</tr>
<tr>
<td>JOHN L MARSHALL, MD</td>
<td>Nal-IRI + 5-FU/LV</td>
</tr>
<tr>
<td>EILEEN M O’REILLY, MD</td>
<td>Nal-IRI + 5-FU/LV</td>
</tr>
<tr>
<td>PHILIP A PHILIP, MD, PHD</td>
<td>Nal-IRI + 5-FU/LV</td>
</tr>
<tr>
<td>ALAN P VENOOK, MD</td>
<td>FOLFIRI</td>
</tr>
</tbody>
</table>
NAPOLI-1: Final Overall Survival and Tolerability with Nal-IRI/5-FU/LV vs 5-FU/LV as Second-Line Therapy


- Grade 3 and 4 adverse events with nal-IRI + 5-FU/LV included neutropenia (15.4%), diarrhea (9.4%), vomiting (6.0%) and fatigue (6.8%)
- Health-related quality of life was maintained with nal-IRI + 5-FU/LV

<table>
<thead>
<tr>
<th></th>
<th>6-month survival (%)</th>
<th>1-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>nal-IRI + 5-FU/LV</td>
<td>53</td>
<td>26</td>
</tr>
<tr>
<td>5-FU/LV</td>
<td>38</td>
<td>16</td>
</tr>
</tbody>
</table>

Overall survival

![Graph showing overall survival with time from randomization, months](image-url)
NAPOLI-1: Impact on OS of Dose Modifications or Dose Delays of Nal-IRI + 5-FU/LV

**Impact of Nal-IRI Dose Delay or Dose Reduction on OS by Treatment Arm**

- **nal-IRI + 5-FU/LV, dose reduction (n = 34)**
- **nal-IRI + 5-FU/LV, dose delay (n = 49)**
- **5-FU/LV (n = 105)**

OS was greater with nal-IRI/5-FU/LV vs 5-FU/LV only

**Impact of Nal-IRI Dose Reduction vs No Dose Reduction on OS in the nal-IRI/5-FU/LV Arm**

- **nal-IRI + 5-FU/LV, dose reduction (n = 34)**
- **nal-IRI + 5-FU/LV, no dose reduction (n = 83)**

No significant impact of dose reduction or dose delay on OS in the nal-IRI/5-FU/LV arm

Regulatory and reimbursement issues aside, which treatment would you recommend to a 65-year-old patient who is diagnosed with unresectable metastatic pancreatic cancer with a deleterious germline BRCA2 mutation?

1. Chemotherapy
2. Olaparib
3. Rucaparib
4. Chemotherapy followed by maintenance with a PARP inhibitor
5. Other
Chemotherapy followed by maintenance with a PARP inhibitor
Regulatory and reimbursement issues aside, which treatment would you recommend to a 65-year-old patient who is diagnosed with unresectable metastatic pancreatic cancer with a deleterious germline BRCA2 mutation?

Do you test for germline BRCA mutation status in your patients with metastatic pancreatic cancer and no significant family history of cancer?

<table>
<thead>
<tr>
<th>Tx for de novo mPCa with BRCA mutation</th>
<th>Test for BRCA mutations?</th>
</tr>
</thead>
<tbody>
<tr>
<td>mFOLFIRINOX</td>
<td>Yes (Invitae assay)</td>
</tr>
<tr>
<td>FOLFIRINOX → maintenance olaparib</td>
<td>Yes (Foundation Medicine)</td>
</tr>
<tr>
<td>FOLFIRINOX → maintenance olaparib</td>
<td>No</td>
</tr>
<tr>
<td>FOLFOX → maintenance olaparib</td>
<td>No (somatic and WES)</td>
</tr>
<tr>
<td>mFOLFIRINOX → maintenance olaparib</td>
<td>Yes (multigene panel)</td>
</tr>
<tr>
<td>modified FFX → Olaparib</td>
<td>Yes (germline and NGS)</td>
</tr>
<tr>
<td>FOLFIRINOX</td>
<td>Yes (UCSF500 assay)</td>
</tr>
</tbody>
</table>

WES = whole exome sequencing
DNA Damage Response (DDR) Tumor Mutations in Pancreatic Cancer

- 17%-25% of pancreatic adenocarcinomas harbor mutations in DDR genes, including those involved with homologous recombination

<table>
<thead>
<tr>
<th>Gene (≥1% Detection)</th>
<th>KYT (N = 616)</th>
<th>Caris (N = 833)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>4.5%</td>
<td>3.60%</td>
</tr>
<tr>
<td>BRCA2</td>
<td>2.9%</td>
<td>3.33%</td>
</tr>
<tr>
<td>SMARCA4</td>
<td>1.6%</td>
<td>NR</td>
</tr>
<tr>
<td>BAP1</td>
<td>1.3%</td>
<td>0.48%</td>
</tr>
<tr>
<td>BRCA1</td>
<td>1.3%</td>
<td>1.41%</td>
</tr>
<tr>
<td>BRIP1</td>
<td>1.0%</td>
<td>0.48%</td>
</tr>
<tr>
<td>PALB2</td>
<td>0.8%</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

Know Your Tumor® (KYT) Data Set; Caris Database Review

Adapted from Michael Pishvaian, MD, PhD
**POLO: A Phase III Trial of Maintenance Olaparib for Metastatic Adenocarcinoma of the Pancreas**

Eligibility (N = 154)

- Metastatic pancreatic cancer
- Deleterious or suspected deleterious germline BRCA mutation
- No disease progression on first-line platinum-based chemotherapy

**Primary endpoint:** Progression-free survival

**Key secondary endpoints** include overall survival, time to second disease progression, response rate and health-related quality of life, disease control rate

• An interim analysis of overall survival showed no difference between olaparib and placebo (median 18.9 mo vs 18.1 mo, HR 0.91, p 0.68)
• The adverse-effect profile of maintenance olaparib was similar to that observed in other tumor types
Phase II Interim Analysis of Maintenance Rucaparib for Patients with Advanced Pancreatic Cancer and BRCA1/2 or PALB2 Mutations

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n = 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>9.1 mo</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>36.8%</td>
</tr>
<tr>
<td>Disease control rate</td>
<td>89.5%</td>
</tr>
</tbody>
</table>

- Patients with advanced pancreatic cancer and pathogenic germline or somatic mutation in BRCA1/2 or PALB2 were enrolled
- Treatment with rucaparib was well tolerated without dose-limiting toxicities
- Most common adverse events: nausea, dysgeusia, fatigue
Novel and Emerging Therapeutic Strategies in the Management of Select Gastrointestinal Cancers

Module 1: Colorectal Cancer
- Primary tumor sidedness and selection of first-line therapy
- Sequencing of available therapies in the second line and beyond
- Novel targeted approaches

Module 2: Hepatocellular Carcinoma
- First-line systemic treatment: Sorafenib versus lenvatinib
- Beyond first-line therapy: Cabozantinib, ramucirumab, regorafenib and anti-PD-1/PD-L1 antibodies

Module 3: Pancreatic Cancer
- Neoadjuvant and adjuvant therapy approaches
- Management of metastatic disease and integration of nanoliposomal irinotecan
- BRCA mutations and PARP inhibition

Module 4: Gastric/Gastroesophageal Junction (GEJ)/Esophageal Cancer
- Pembrolizumab for the treatment of recurrent or advanced gastric, GEJ and esophageal cancer
- Efficacy and safety of TAS-102 for recurrent metastatic gastric or GEJ adenocarcinoma
Regulatory and reimbursement issues aside, what would you currently recommend as second-line therapy for a patient with metastatic HER2-negative, MSS gastric cancer who has experienced disease progression on first-line FOLFOX?

1. Ramucirumab
2. Paclitaxel/ramucirumab
3. Other chemotherapy
4. Test for PD-L1 CPS and administer pembrolizumab if 1 or higher
5. Test for PD-L1 CPS and administer pembrolizumab if 10 or higher
6. Pembrolizumab
7. Nivolumab
8. Other
Ramucirumab 0%
Paclitaxel/ramucirumab 0%
Other chemotherapy 0%
Test for PD-L1 CPS and administer pembrolizumab if 1 or higher 0%
Test for PD-L1 CPS and administer pembrolizumab if 10 or higher 0%
Pembrolizumab 0%
Nivolumab 0%
Other 0%
Regulatory and reimbursement issues aside, what would you currently recommend as second-line therapy for a patient with metastatic HER2-negative, MSS gastric cancer who has experienced disease progression on first-line FOLFOX?

<table>
<thead>
<tr>
<th>TANIOS BEKAIJ-SAAB, MD</th>
<th>Test for PD-L1 CPS, administer pembrolizumab if ≥10</th>
</tr>
</thead>
<tbody>
<tr>
<td>JOHANNA BENDELL, MD</td>
<td>Paclitaxel/ramucirumab</td>
</tr>
<tr>
<td>HOWARD S HOCHSTER, MD</td>
<td>Test for PD-L1 CPS, administer pembrolizumab if ≥10</td>
</tr>
<tr>
<td>JOHN L MARSHALL, MD</td>
<td>Paclitaxel/ramucirumab</td>
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<tr>
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<tr>
<td>PHILIP A PHILIP, MD, PHD</td>
<td>Test for PD-L1 CPS, administer pembrolizumab if ≥10</td>
</tr>
<tr>
<td>ALAN P VENOOK, MD</td>
<td>Test for PD-L1 CPS, administer pembrolizumab if ≥1</td>
</tr>
</tbody>
</table>
KEYNOTE-059 Trial Cohort 1: PD-L1 Expression and Combined Positive Score (CPS)

- PD-L1 expression is determined by the CPS

\[ \text{CPS} = \frac{\text{Number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages)}}{\text{Total number of viable tumor cells}} \times 100 \]

- A specimen is considered to have positive PD-L1 expression if CPS ≥1%

Fuchs CS et al. *Proc ASCO* 2017;Abstract 4003.
Pembrolizumab in Advanced Gastric or Gastroesophageal Cancer

- Accelerated approval of pembrolizumab monotherapy as third- or later-line therapy was based on the Phase II KEYNOTE-059 study
  - ORR: 11.6% (all patients); 15.5% (PD-L1-positive); 57% (MSI-high)
- Phase III KEYNOTE-061 trial of pembrolizumab versus paclitaxel as second-line therapy did not meet its primary endpoint of OS in patients with CPS ≥1
  - Median OS: Pembrolizumab 9.1 mo, paclitaxel 8.3 mo (HR 0.82; \( p = 0.042 \))
- Phase III KEYNOTE-062 trial evaluates pembrolizumab with or without chemotherapy versus chemotherapy as first-line therapy

KEYNOTE-062: A Phase III Trial of Pembrolizumab with and without Chemotherapy as First-Line Treatment for Advanced Gastric or GEJ Adenocarcinoma

<table>
<thead>
<tr>
<th>CPS ≥1</th>
<th>Pembro + chemo (n = 257)</th>
<th>Pembro (n = 256)</th>
<th>Chemo (n = 250)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>12.5 mo</td>
<td>10.6 mo</td>
<td>11.1 mo</td>
</tr>
<tr>
<td>HR, p-value</td>
<td>0.85, 0.046</td>
<td>0.91, 0.91</td>
<td>Ref</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MSI-H</th>
<th>Pembro + chemo (n = 17)</th>
<th>Pembro (n = 14)</th>
<th>Chemo (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>Not reached</td>
<td>Not reached</td>
<td>8.5 mo</td>
</tr>
<tr>
<td>HR</td>
<td>0.37</td>
<td>0.29</td>
<td>Ref</td>
</tr>
</tbody>
</table>

- Pembrolizumab was noninferior to chemotherapy for OS in patients with CPS ≥1, and a clinically meaningful improvement in OS was reported with pembro versus chemo for patients with CPS ≥10 (17.4 mo vs 10.8 mo, HR 0.69)
- Pembrolizumab + chemotherapy did not show superior OS or PFS for patients with CPS ≥1 or OS for CPS ≥10.

Shitara K et al. *Proc ESMO* 2019;Abstract LBA44.
Pembrolizumab Approved as Monotherapy for Recurrent Locally Advanced or Metastatic Squamous Cell Carcinoma of the Esophagus
Press Release – July 31, 2019

“The US Food and Drug Administration has approved pembrolizumab as monotherapy for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 (Combined Positive Score [CPS] ≥10) as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.

The approval was based on data from KEYNOTE-181, a multicenter, randomized, open-label, active-controlled trial [for] patients with recurrent locally advanced or metastatic esophageal cancer who progressed on or after one prior line of systemic treatment for advanced disease.”

KEYNOTE-181: A Phase III Trial of Second-Line Pembrolizumab Compared to Chemotherapy for Advanced Esophageal Cancer

- ORR higher with pembrolizumab than with chemotherapy for patients with CPS ≥10 (21.5% vs 6.1%)
- Lower frequency of Grade 3-5 treatment-related adverse events with pembrolizumab than with chemotherapy (18.2% vs 40.9%); no new safety signals observed

Kojima T et al. Gastrointestinal Cancers Symposium 2019;Abstract 2;
What is your usual third-line treatment for a patient with metastatic HER2-negative, MSS gastric cancer (PD-L1 CPS lower than 1) who has experienced disease progression on FOLFOX and paclitaxel/ramucirumab?

1. TAS-102
2. Other chemotherapy
3. Nivolumab
4. Palliative care
5. Other
What is your usual third-line treatment for a patient with metastatic HER2-negative, MSS gastric cancer (PD-L1 CPS lower than 1) who has experienced disease progression on FOLFOX and paclitaxel/ramucirumab?

<table>
<thead>
<tr>
<th>Name</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanios Bekaii-Saab, MD</td>
<td>TAS-102</td>
</tr>
<tr>
<td>Johanna Bendell, MD</td>
<td>Irinotecan</td>
</tr>
<tr>
<td>Howard S Hochster, MD</td>
<td>TAS-102</td>
</tr>
<tr>
<td>John L Marshall, MD</td>
<td>TAS-102</td>
</tr>
<tr>
<td>Eileen M O'Reilly, MD</td>
<td>Nivolumab</td>
</tr>
<tr>
<td>Philip A Philip, MD, PhD</td>
<td>FOLFIRI</td>
</tr>
<tr>
<td>Alan P Venook, MD</td>
<td>TAS-102</td>
</tr>
</tbody>
</table>
Phase III TAGS Trial of Trifluridine/Tipiracil for Patients with Heavily Pretreated Metastatic Gastric Cancer: Outcome Summary


**Median OS**
- Trifluridine/tipiracil: 5.7 mo
- Placebo: 3.6 mo

**Clinical variable**
<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>Trifluridine/tipiracil</th>
<th>Placebo</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>2.0 mo</td>
<td>1.8 mo</td>
<td>0.57</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ORR</td>
<td>4.0%</td>
<td>2.0%</td>
<td>—</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Hazard ratio 0.69
One-sided $p = 0.00029$; two-sided $p = 0.00058$
Questions?

To view the slides please visit
www.ResearchToPractice.com/Meetings/Slides
Novel and Emerging Therapeutic Strategies in the Management of Select Gastrointestinal Cancers

Philip A Philip, MD, PhD
Kathryn Cramer Endowed Chair in Cancer Research
Professor of Oncology and Pharmacology
Leader, GI and Neuroendocrine Oncology
Vice President of Medical Affairs
Karmanos Cancer Institute
Wayne State University
Detroit, Michigan