62 year-old male with history of HCV cirrhosis (Child-Pugh A), diagnosed with multifocal HCC, s/p multiple TACE procedures.

- 1 yr after dx: Interval CT AP reveals progression of disease with development of adrenal metastasis, lymphadenopathy, rib metastasis.

**Case #1 Question #1:** What is your initial choice for treatment?

A. Sorafenib  
B. Lenvatinib  
C. Nivolumab  
D. ⁹⁰Y selective internal radiotherapy (SIRT)

**Sorafenib (SHARP Trial; Llovet, NEJM 2008)**

- Phase III RCT of 602 patients with advanced HCC, without prior systemic therapy.
- ECOG 0-2
- Child-Pugh Class A
- Life expectancy of 12 weeks
- Adequate marrow, liver, and kidney function.
- Randomized to receive sorafenib 400mg twice daily vs. placebo, continued until progression. Crossover not permitted.
- Primary endpoints: Time to symptomatic progression and overall survival.
**Sorafenib: Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sorafenib</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (months)</td>
<td>10.7</td>
<td>7.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>DCR* (%)</td>
<td>43</td>
<td>32</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*DCR: Disease control rate (CR + PR + SD)*

---

**Lenvatinib (REFLECT; Kudo, Lancet 2018)**

- Phase III RCT of 954 patients with unresectable HCC who had not received prior systemic therapy.
- ECOG 0-1
- Child-Pugh Class A
- BCLC stage B or C
- Adequate marrow, liver, and kidney function.
- Randomized to receive lenvatinib 8-12 mg vs. sorafenib 400mg twice daily, continued until progression.
- Primary endpoint: Overall survival. Non-inferiority threshold: 1.08.

---

**Subsequent Failed Trials in the First-Line Setting**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year</th>
<th>n</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib</td>
<td>2013</td>
<td>1,074</td>
<td>Terminated early due to futility.</td>
</tr>
<tr>
<td>Brivanib</td>
<td>2013</td>
<td>1,155</td>
<td>Non-inferiority could not be shown.</td>
</tr>
<tr>
<td>Linifanib</td>
<td>2015</td>
<td>1,035</td>
<td>Non-inferiority could not be shown.</td>
</tr>
<tr>
<td>Erlotinib + sorafenib</td>
<td>2015</td>
<td>720</td>
<td>Superiority could not be shown.</td>
</tr>
<tr>
<td>Sorafenib + doxorubicin</td>
<td>2017</td>
<td>480</td>
<td>Terminated early due to futility.</td>
</tr>
</tbody>
</table>

### Lenvatinib (REFLECT; Kudo, Lancet 2018)

<table>
<thead>
<tr>
<th>ORR by Measurement Method (%)</th>
<th>Lenvatinib</th>
<th>Sorafenib</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRECIST (independent)</td>
<td>40.6</td>
<td>12.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>mRECIST (investigator)</td>
<td>24.1</td>
<td>9.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RECIST 1.1</td>
<td>18.8</td>
<td>6.5</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

### Adverse Event of Grade ≥3

<table>
<thead>
<tr>
<th></th>
<th>Lenvatinib (%)</th>
<th>Sorafenib (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>23</td>
<td>14</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Weight loss</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

### Case # 1: Subsequent Clinical Course

- The patient was started on sorafenib, with decrease in size of his chest wall metastasis as well as AFP from 15,897 → 27 ng/mL (normal < 10 ng/mL) over the next 6 months.
- 12 months after beginning sorafenib, interval imaging revealed progression of nodal, adrenal, and chest wall lesions, with concurrent AFP rise to a peak of 1145 ng/mL.

**Case #1 Question #2**

What is your choice for second-line treatment?

A. Cabozantinib  
B. Regorafenib  
C. Ramucirumab  
D. Immune checkpoint inhibition  

**Bar Chart**

- Cabozantinib: 67%
- Regorafenib: 17%
- Ramucirumab: 13%
- Immune checkpoint inhibition: 4%
**19th Multidisciplinary Management of Cancers: A Case-based Approach**

**Subsequent Treatment of mHCC: Recent FDA Approvals**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESORCE¹</td>
<td>2nd-line only: Progressed through sorafenib (must have tolerated ≥400 mg daily).</td>
<td>Regorafenib vs. placebo (2:1)</td>
<td>ORR 7% vs. 3%* Median PFS 3.1 vs. 1.5 mo. (HR 0.46) Median OS 10.6 vs. 7.8 mo. (HR 0.63)</td>
</tr>
<tr>
<td>CheckMate 040 (Phase 1/2)²²</td>
<td>Progressed through, intolerant to, or refused sorafenib.</td>
<td>Nivolumab 3 mg/kg every 2 weeks</td>
<td>ORR 20%* Median PFS 4 mo. Median OS NR</td>
</tr>
<tr>
<td>CELESTIAL¹</td>
<td>Progressed through sorafenib, and up to 2 total lines of prior therapy.</td>
<td>Cabozantinib vs. placebo (2:1)</td>
<td>ORR 4% vs. &lt; 1%* Median PFS 5.2 vs. 1.9 mo. (HR 0.44) Median OS 10.2 vs. 8 mo. (HR 0.76)</td>
</tr>
<tr>
<td>REACH-2²²</td>
<td>2nd-line only: Progressed through sorafenib + AFP ≥ 400 ng/mL.</td>
<td>Ramucirumab vs. placebo (2:1)</td>
<td>ORR 5 vs. 1%* Median PFS 2.8 vs. 1.6 mo. (HR 0.45) Median OS 8.5 vs. 7.3 mo. (HR 0.71)</td>
</tr>
<tr>
<td>KEYNOTE-224 (Phase 2)³³</td>
<td>2nd-line only: Progressed through, or intolerant to sorafenib.</td>
<td>Pembrolizumab 200mg every 3 weeks</td>
<td>ORR 17%* Median PFS 4.9 mo. Median OS 12.9 mo.</td>
</tr>
</tbody>
</table>

* According to RECIST 1.1 criteria | ^ Conditional FDA approval.

**Pembrolizumab in advanced HCC: KEYNOTE-240**

- Randomized, double-blind phase III trial comparing pembrolizumab 200mg IV every 3 weeks + BSC vs. BSC alone in 413 patients with advanced HCC progressing on, or intolerant to sorafenib.

- Primary endpoints: PFS and OS
  - PFS: HR=0.78 [95% CI, 0.61-0.99]; p=0.0209*
  - OS: HR=0.78 [95% CI, 0.611-0.998]; p=0.0238*

* Did not meet pre-specified thresholds for significance

**Case #1 Conclusion**

- Patient started on 2nd-line cabozantinib 60mg daily, eventually dose-reduced to 40mg daily due to development of hand-foot syndrome.

- Serial CT imaging demonstrated objective tumor shrinkage, and AFP declined to a nadir of 194 ng/mL.

- Patient’s duration of response was ~13 months, at which time his disease progressed and cabozantinib was discontinued.
Case #1 Conclusion

6/2016: R adrenal metastasis 4.6 x 4.1 cm; aortocaval lymphadenopathy up to 3.1 x 3.3 cm (not shown).

4/2017: Minor regression R adrenal metastasis 4.0 x 3.5 cm; aortocaval lymphadenopathy up to 3.0 cm (not shown).

Case #1 Take Home Points

- First-line therapy options in advanced HCC include sorafenib or lenvatinib.
- Since 2017, the FDA has granted approval for the use of regorafenib and cabozantinib following progression on sorafenib.
- The FDA also granted conditional approval to nivolumab and pembrolizumab in patients intolerant to, or following progression on sorafenib. However, the confirmatory KEYNOTE-240 trial failed to demonstrate a benefit for pembrolizumab over best supportive care.
- Ramucirumab is an additional agent that has demonstrated a survival benefit in this setting, and is awaiting FDA approval.

Ongoing Clinical Trials: Advanced HCC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Setting</th>
<th>Intervention</th>
<th>Study Site</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03695250</td>
<td>1/2</td>
<td>1st-line</td>
<td>BMS-986205 (IDO inhibitor) + nivolumab</td>
<td>UC Davis</td>
<td>Open</td>
</tr>
<tr>
<td>NCT03439891</td>
<td>2</td>
<td>1st-line</td>
<td>Sorafenib + nivolumab</td>
<td>UCSF</td>
<td>Open</td>
</tr>
<tr>
<td>NCT03298451 (HIMALAYA)</td>
<td>3</td>
<td>1st-line</td>
<td>Durvalumab + tremilimumab vs. durvalumab vs. sorafenib</td>
<td>UCSF</td>
<td>Open</td>
</tr>
<tr>
<td>NCT03755791 (COSMIC-312)</td>
<td>3</td>
<td>1st-line</td>
<td>Atezolizumab + cabozantinib vs. sorafenib</td>
<td>UCSF</td>
<td>Soon to Open</td>
</tr>
<tr>
<td>NCT02562755</td>
<td>3</td>
<td>1st-line</td>
<td>Sorafenib + pexa-vec (oncolytic virus vaccine) vs. sorafenib</td>
<td>Stanford</td>
<td>Open</td>
</tr>
</tbody>
</table>

Case #2

- 66 year-old male with history of pituitary adenoma presented with polyuria, polydipsia, fatigue, and 40 pound weight loss over the past year.
- Multiphasic CT: pancreatic tail mass and bulky liver lesions


**Case #2 (continued)**

- Calcium elevated at 13 mg/dL
- Tissue obtained via EUS with FNA of pancreas mass: adenocarcinoma by outside read.
- Path re-reviewed at Stanford:
  - Chromogranin and synaptophysin positive
  - Consistent with **low grade neuroendocrine tumor**
- Started on lanreotide monthly injections, but interval CT demonstrates ongoing growth of bulky hepatic lesions.

**Case #2 Question #2**

What is your next step in management?

A. Switch to octreotide LAR  
B. Surgical debulking  
C. Everolimus  
D. Sunitinib  
E. Temozolomide + Capecitabine  
F. $^{177}$Lu-DOTATATE

---

**WHO Classification of Neuroendocrine Tumors**

![Table of Neuroendocrine Tumor Classification]

- **Pancreatic NET**
  - <2 mitoses/10 HPF AND <3% Ki-67 index
  - 2–20 mitoses/10 HPF OR 3%–20% Ki-67 index
  - >20 mitoses/10 HPF OR >20% Ki-67 index

---

**NCCN Guidelines Index Table of Contents Discussion**

- If disease progression:
  - Everolimus$^k$ (10 mg/d) (category 1 for progressive disease)
  - Sunitinib$^k$ (37.5 mg/d) (category 1 for progressive disease)
  - PRRT with $^{177}$Lu-dotatate, if somatostatin receptor-positive imaging and progression on octreotide or lanreotide$^k$
  - Cytotoxic chemotherapy: Capecitabine/temozolomide, streptozocin-based or other options$^k$
  - Consider a hepatic-directed therapy for hepatic-predominant disease$^k$
    - Arterial embolization, or
    - Hepatic chemoeembolization, or
    - Hepatic radioembolization (category 2B), or
    - Cyto reduc tive surgery/ablative therapy$^k$ (category 2B)

---
19th Multidisciplinary Management of Cancers: A Case-based Approach

Treatment Armamentarium for pNETs: SSAs and Biologics

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Population</th>
<th>n</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lanreotide (CLARINET)²</td>
<td>Unresectable GEP* NETs, Ki-67 &lt;10%</td>
<td>204</td>
<td>Lanreotide every 28 days vs. placebo</td>
<td>ORR 2% vs. 0% (DCR* 66% vs. 43%) Median PFS NR vs. 18 mo. (HR 0.47)</td>
</tr>
<tr>
<td>Sunitinib⁴</td>
<td>Unresectable advanced pNETs</td>
<td>171</td>
<td>Sunitinib 37.5 mg daily vs. placebo</td>
<td>ORR 9% vs. 0% (DCR 72 vs. 60%) Median PFS 11.4 vs. 5.5 mo. (HR 0.42)</td>
</tr>
<tr>
<td>Everolimus (RADIANT-3)²</td>
<td>Unresectable advanced pNETs</td>
<td>410</td>
<td>Everolimus 10 mg daily vs. placebo</td>
<td>ORR 5% vs. 2% (DCR 78 vs. 53%) Median PFS 11.0 vs. 4.6 mo. (HR 0.35)</td>
</tr>
</tbody>
</table>

*GEP = gastroenteropancreatic; *DCR = Disease control rate (CR + PR + SD).


Treatment Armamentarium for pNETs: Chemotherapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Population</th>
<th>n</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptozocin + doxorubicin¹</td>
<td>Unresectable advanced pNETs</td>
<td>125</td>
<td>Streptozocin + doxorubicin vs.</td>
<td>ORR 69 vs. 45% vs. 30%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Streptozocin + 5-FU vs. chlorotozocin</td>
<td></td>
</tr>
<tr>
<td>5-FU + doxorubicin + streptozocin³ [Retrospective]¹</td>
<td>Unresectable advanced pNETs</td>
<td>84</td>
<td>FAS every 28 days</td>
<td>ORR 39% (DCR 89%) Median PFS 18 mo. Median OS 37 mo.</td>
</tr>
<tr>
<td>Streptozocin + 5-FU (ECOG 1281)⁷</td>
<td>Advanced &quot;carcinoid&quot; tumors (5% pNETs)</td>
<td>176</td>
<td>Streptozocin + 5-FU vs. Dxorubicin + 5-FU</td>
<td>ORR 36% vs. 15.9% (DCR 31.4% vs. 31.2%) Median PFS 4.8 vs. 4.7 mo. Median OS 24.3 vs. 15.7 mo. (p=0.03)</td>
</tr>
</tbody>
</table>

*Response criteria included both tumor and biochemical improvement.


Temozolomide + Capecitabine (ECOG 2211; Kunz, ASCO 2018)

Progression Free Survival

<table>
<thead>
<tr>
<th></th>
<th>Median (mo)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Tem</td>
<td>14.4</td>
<td>0.58 (0.36, 0.93)</td>
<td>0.023</td>
</tr>
<tr>
<td>B: Tem+ Cape</td>
<td>22.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Progression Free Survival Probability

NCT01824875
**Overall Survival**

- A: Temozolomide (N=72) -- Median (mo) 38.0, HR 0.41 (0.21, 0.82), p-value 0.012
- B: Temozolomide + Capecitabine (N=72) -- Not reached, p-value 0.41

**Response Rates**

<table>
<thead>
<tr>
<th></th>
<th>Temozolomide (N=72)</th>
<th>Temozolomide + Capecitabine (N=72)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>2.8%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>25.0%</td>
<td>33.3%</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>40.3%</td>
<td>48.6%</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>19.4%</td>
<td>13.9%</td>
<td></td>
</tr>
<tr>
<td>Unevaluables</td>
<td>12.5%</td>
<td>4.2%</td>
<td></td>
</tr>
</tbody>
</table>

**Objective Response Rate (CR+PR)**

- Temozolomide: 27.8%
- Temozolomide + Capecitabine: 33.3%

**Disease Control Rate (CR+PR+SD)**

- Temozolomide: 68.1%
- Temozolomide + Capecitabine: 81.9%

**Response Duration (median)**

- Temozolomide: 9.7 mo
- Temozolomide + Capecitabine: 12.1 mo

**Safety Profile (CTCAE v4.0)**

<table>
<thead>
<tr>
<th>AE Category</th>
<th>AE Term</th>
<th>Temozolomide (N=68)</th>
<th>Temozolomide + Capecitabine (N=71)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worst degree for all treatment-related, Grade 3-4 AEs*</td>
<td>22%</td>
<td>44%</td>
<td>p=0.007</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment related, Grade 3-4 AEs ≥ 5%**

- Hematologic
  - Neutropenia: 46%
  - Lymphopenia: 46%
  - Thrombocytopenia: 13%

- Gastrointestinal
  - Nausea: 0%
  - Vomiting: 0%
  - Diarrhea: 0%

- Constitutional
  - Fatigue: 1%

*Worst degree is highest grade a patient achieved across all toxicities reported

There were no Grade 5 related AEs

**177Lu-DOTATATE (NETTER-1; Strosberg, NEJM 2017)**

- Phase III RCT of 229 patients with locally advanced unresectable or metastatic midgut NETs
- Inclusion criteria:
  - Well-differentiated (Ki-67 ≤20%)
  - Presence of somatostatin receptors (via Ocreotide Scan)
  - Progression on octreotide LAR within 3 yrs
- Randomized to receive 177Lu-DOTATATE every 8 weeks x 4 doses + octreotide LAR 30mg every 4 weeks vs. octreotide LAR 60mg every 4 weeks.
**Case #2 Conclusion**

- The patient was started on temozolomide + capecitabine, which he tolerated well.
- The first interval CT imaging demonstrated a significant objective response.
- Given history of pituitary adenoma and new hypercalcemia, he was referred to Cancer Genetics for germline testing which revealed RET and PTEN mutations, though an MEN1 phenotype.

**Case #2 Take-Home Points**

- A multidisciplinary approach is key to managing patients with NETs.
- Temozolomide + capecitabine provides higher rates of objective tumor response as compared to SSAs and biologic agents.
- $^{177}$Lu-DOTATATE attained FDA approval in 2018, and represents a new modality of treatment in patients with GEP-NETs.
- The optimal sequencing of these therapies has not been established, and is the subject of ongoing research.
### Ongoing Clinical Trials: Advanced pNETs

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Setting</th>
<th>Intervention</th>
<th>Study Site</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03457948</td>
<td>2</td>
<td>2nd-line, progressive liver metastases</td>
<td>Pembrolizumab + liver-directed therapy.</td>
<td>UCSF</td>
<td>Open</td>
</tr>
<tr>
<td>NCT02893930</td>
<td>2</td>
<td>2nd-line, refractory to mTOR inhibitor</td>
<td>TAK-228 (mTORC1/2 inhibitor)</td>
<td>Stanford</td>
<td>On hold</td>
</tr>
<tr>
<td>NCT02724540 (RETNET)</td>
<td>2</td>
<td>2nd-line +, liver-dominant metastases</td>
<td>Bland embolization vs. TACE vs. drug-eluting bead chemoembolization</td>
<td>UCSF, Stanford</td>
<td>Open</td>
</tr>
<tr>
<td>NCT03419155 (DUET-1)</td>
<td>1</td>
<td>3rd-line, Refractory to SSA + 1 add'l line of therapy.</td>
<td>XmAB18087 (CD3 – SSTR BiTE)</td>
<td>Stanford</td>
<td>Open</td>
</tr>
</tbody>
</table>

### Case #3

- 63 year-old male with history of HTN presented with dark urine and clay-colored stools.
- At baseline, healthy and active, and takes no medications.
- CT AP: Bulbous appearance to the head of the pancreas without a discrete hypoenhancing lesion.

### Case #3 (continued)

- ERCP with EUS/FNA of head of pancreas revealed adenocarcinoma.
- CT Chest: No evidence of thoracic metastatic disease.
- The patient was deemed to have potentially resectable disease, and underwent a Whipple procedure. Surgical pathology shows:
  - Moderately-differentiated PDAC, 2.5 x 2.4 x 2 cm
  - Negative margins
  - 0/21 examined lymph nodes involved
  - Staging: pT2 pN0 cM0

### Case #3 Question #1

What is your next step in management?

A. Adjuvant gemcitabine
B. Adjuvant gemcitabine + capecitabine
C. Adjuvant modified FOLFIRINOX
D. Adjuvant chemoradiation
E. I would have given neoadjuvant therapy
### Case #3 Question #2

Would Your Answer Change if the Patient was 80 versus 50 years old?

A. Yes  
B. No

---

#### 19th Multidisciplinary Management of Cancers: A Case-based Approach

**NCCN Guidelines for Adjuvant Therapy of Resected Pancreatic Adenocarcinoma**

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th>Other Recommended Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine + capecitabine (category 1)</td>
<td>Gemcitabine (category 1)</td>
</tr>
<tr>
<td>Modified FOLFIRINOX (category 1, ECOG 0-1)</td>
<td>Bolus 5-FU/leucovorin (category 1)</td>
</tr>
<tr>
<td>Continuous infusion 5-FU</td>
<td>Capcitabine (category 2B)</td>
</tr>
</tbody>
</table>
| Induction chemotherapy (gemcitabine, 5-FU/LV, or CI 5-FU) followed by chemoradiation. | Induction chemotherapy (gemcitabine, 5-FU/LV, or CI 5-FU), followed by chemoradiation, followed by subsequent chemotherapy:  
  - Gemcitabine → chemoradiation → gemcitabine  
  - Bolus 5-FU/LV → chemoradiation → bolus 5-FU/LV  
  - CI 5-FU → chemoradiation → CI 5-FU |

---

#### 19th Multidisciplinary Management of Cancers: A Case-based Approach

**Adjuvant Therapy for Resected Pancreatic Adenocarcinoma**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>n</th>
<th>Intervention</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG1</td>
<td>1985</td>
<td>43</td>
<td>5-FU + split-course XRT (40 Gy) + add’t 5-FU up to 2 years vs. observation</td>
<td>20 vs. 11 mo. (p=0.04)</td>
</tr>
<tr>
<td>EORTC2</td>
<td>1999</td>
<td>114</td>
<td>5-FU + split-course XRT (40 Gy) vs. observation</td>
<td>17.1 vs. 12.6 mo. (p=0.10)</td>
</tr>
</tbody>
</table>
| ESPAC-13 | 2004 | 289 | 2x2: 5-FU alone vs. 5-FU + split-course XRT (40-60 Gy) vs. combination vs. observation. | CMT vs. no CMT: 15.9 vs. 17.9 mo. (p=0.05)  
ChemO vs. no ChemO: 20.1 vs. 15.5 (p<0.01) |
| CONKO-0014 | 2007 | 368 | Gemcitabine vs. observation | 22.8 vs. 20.2 mo. (p=0.01) |
| RTOG 97-045 | 2008 | 451 | 5-FU → 5-FU + XRT (50.4 Gy) → 5-FU vs. gemcitabine → 5-FU + XRT (50.4 Gy) → gemcitabine | 16.9 vs. 20.5 mo. (p=0.09) |
| ESPAC-36 | 2010 | 1088 | Gemcitabine vs. 5-FU | 23.6 vs. 23.0 mo. (p=0.39) |


---

**Gemcitabine + Capecitabine (ESPAC-4; Neoptolemos, Lancet 2017)**

- **Phase III, open-label RCT of 732 patients.**
- **Inclusion Criteria:**
  - Adults with localized PDAC undergoing R0 or R1 surgical resection.
  - No prior neoadjuvant or adjuvant therapy.
  - ECOG 0-2.
- **Intervention:** Within 12 weeks of surgery, randomized to receive gemcitabine + capecitabine vs. gemcitabine alone for 6 months.
- **Primary endpoint:** Overall survival
Gemcitabine + Capecitabine (ESPAC-4; Neoptolemos, Lancet 2017)

- 5-year OS: 28.8 vs. 16.3% (p=0.03)
- Gem mOS: 25.5 mo
- Gem+Cape mOS: 28.0 mo
- HR 0.82 (95% CI, 0.68-0.98; p = 0.032)

mFOLFIRINOX (PRODIGE-24; Conroy, NEJM 2018)

- Phase III, open-label RCT of 493 patients.
- Inclusion Criteria:
  - Adults with localized PDAC undergoing R0 or R1 surgical resection.
  - No prior neoadjuvant or adjuvant therapy.
  - ECOG 0-1.
  - Pre-treatment CA 19-9 < 180 U/mL.
- Intervention: Within 12 weeks of surgery, randomized to modified FOLFIRINOX vs. gemcitabine for 6 months.
- Primary endpoint: Disease-free survival

Median DFS: 21.6 vs. 12.8 mo (HR 0.58, p<0.001)
Median OS: 54.4 vs. 35.0 mo (HR 0.64, p<0.001)
3-year OS: 63.4 vs. 48.6%
19th Multidisciplinary Management of Cancers: A Case-based Approach

<table>
<thead>
<tr>
<th>AEs Grade ≥3 More Common in Treatment Arm vs. Control Arm</th>
<th>ESPAC-4 (Gem + Cape), ECOG 0-2</th>
<th>PRODIGE-24 (mFOLFIRINOX), ECOG 0-1</th>
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</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>☑</td>
<td>☑</td>
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<tr>
<td>Thrombocytopenia</td>
<td>☑</td>
<td>☑</td>
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<tr>
<td>Diarrhea</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>Infection</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>Fatigue</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>☑</td>
<td>☑</td>
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<tr>
<td>Abdominal pain</td>
<td>☑</td>
<td>☑</td>
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<tr>
<td>Mucositis</td>
<td>☑</td>
<td>☑</td>
</tr>
</tbody>
</table>

Case #3 Conclusion

- Due to his excellent performance status, the patient was started on modified FOLFIRINOX.
- He is currently on-treatment and doing well aside from mild to moderate fatigue.

Ongoing Clinical Trials: (Neo)Adjuvant Therapy in PDAC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Setting</th>
<th>Intervention</th>
<th>Site</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02562716</td>
<td>2</td>
<td>Peri-operative, resectable PDAC</td>
<td>FOLFIRINOX vs. gemcitabine + nab-paclitaxel</td>
<td>Open</td>
<td></td>
</tr>
<tr>
<td>NCT02839343</td>
<td>2</td>
<td>Pre-operative, borderline resectable PDAC</td>
<td>FOLFIRINOX + SBRT vs. FOLFIRINOX alone</td>
<td>UC Davis</td>
<td>Open</td>
</tr>
<tr>
<td>NCT01964430</td>
<td>3</td>
<td>Adjunct; resected PDAC</td>
<td>Gemcitabine + nab-paclitaxel vs. gemcitabine</td>
<td>Closed</td>
<td></td>
</tr>
</tbody>
</table>

APACT Trial: Updates

- Phase III RCT of 866 patients with resected pancreatic adenocarcinoma.
  - Inclusion criteria:
    - T1-3 + N0-1 PDAC undergoing R0-R1 resection
    - ECOG 0-1
    - CA 19-9 < 100 U/mL
  - Treatment: Gemcitabine + nab-paclitaxel vs. gemcitabine x 6 months

Press release

March 12, 2019: SUMMIT, N.J.--(BUSINESS WIRE) -- The Celgene-sponsored, pivotal, Phase 3 apact study did not achieve the primary endpoint of improvement in disease-free survival, as confirmed by independent radiological review, compared to gemcitabine alone. Overall survival, a secondary endpoint of the study, was improved, reaching nominal statistical significance.
Case #3 Take-Home Points

- Adjuvant chemotherapy for resectable PDAC improves outcomes, while the routine role of chemoradiotherapy remains controversial.
- mFOLFIRINOX demonstrates an impressive treatment benefit compared to gemcitabine alone, but comes at the cost of increased toxicity; patient selection is key.
- For those who cannot tolerate mFOLFIRINOX, gemcitabine + capecitabine remains a preferred option.
- The role of neoadjuvant therapy is emerging as a treatment paradigm, with many ongoing trials.

Case #4

75 year-old woman presented in with melena, found to have severe anemia.
- CT AP: Wall-thickening at the distal transverse colon.
- Biopsies showed moderately-differentiated colonic adenocarcinoma.
- Transverse colectomy revealed pT3N1 (stage IIIB) disease.
- Molecular profiling showed KRAS-wt and MSI-H/dMMR.

Case #4 (continued)

- Prior to adjuvant therapy, interval CT showed a new liver lesion, biopsied and confirmed to be adenocarcinoma.
- FOLFIRI + cetuximab started as first-line therapy for metastatic disease.
- After 4 mo of treatment: CT showed progression of hepatic disease, development of intra-abdominal lymphadenopathy, subcutaneous metastatic implants, and new pulmonary lesions.

Case #4 Question #1

For patients with metastatic colorectal cancer, the FDA has approved the use of checkpoint inhibitors in all of the following scenarios, except:

A. Patients with dMMR/MSI-H tumors progressing through prior fluoropyrimidine, oxaliplatin, and irinotecan.
B. Patients with tumors expressing PD-L1 ≥1% progressing through prior fluoropyrimidine, oxaliplatin, and irinotecan.
C. Patients with dMMR/MSI-H tumors for which there are “no satisfactory alternative treatment options”.
D. All of the above scenarios have been granted FDA approval.
In reports of the effects of PD-1 blockade in human tumors, only 1 of 33 patients with colorectal cancer had a response to this treatment, in contrast to substantial fractions of patients with melanomas, renal-cell cancers, and lung tumors who have a response. What was different about this single patient?

Answer: dMMR/MSI-H

---

**Table:**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>n</th>
<th>ORR/DCR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pMMR CRC</td>
<td>18</td>
<td>0/11</td>
</tr>
<tr>
<td>dMMR CRC</td>
<td>10</td>
<td>40/90</td>
</tr>
<tr>
<td>dMMR non-CRCs</td>
<td>7</td>
<td>71/71</td>
</tr>
</tbody>
</table>

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**Figure:**

**Pembrolizumab in mCRC (KEYNOTE-164; Le, ASCO 2018)**

- Phase II study enrolling 63 patients.
- Inclusion criteria:
  - Adults with dMMR/MSI-H locally advanced unresectable or metastatic CRC
  - Progressed through ≥1 prior line of therapy
  - ECOG 0-1
  - Life expectancy ≥ 3 months
- Intervention: Pembrolizumab 200mg every 3 weeks, for up to two years.
- Primary endpoint: ORR

**ORR:** 32%

**DCR:** 57%

**Median Duration of Response:** NR
**Pembrolizumab in mCRC (KEYNOTE-164; Le, ASCO 2018)**

- **Median PFS:** 4.1 mo; **12-month PFS:** 41%
- **Median OS:** NR; **12-month OS:** 76%

**CheckMate 142: Nivolumab Monotherapy Cohort**

- **n = 74**
- **ORR:** 31%
- **DCR:** 69%
- **Median Duration of Response:** NR

**Nivolumab +/- Ipilimumab (CheckMate 142; Overman, Lancet Oncology 2017, JCO 2018)**

- Phase II study with two cohorts.
- Inclusion criteria:
  - Adults with dMMR/MSI-H recurrent or metastatic CRC
  - Progressed through, or refused prior therapy with fluoropyrimidine + oxaliplatin or irinotecan
  - ECOG 0-1
- Intervention:
  - Nivolumab 3 mg/kg every 2 weeks.
  - Nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks x 4 doses, then nivolumab 3 mg/kg every 2 weeks alone.
- **Primary endpoint:** ORR

- **CheckMate 142: Nivolumab Monotherapy Cohort**
  - **Median PFS:** 14.3 mo.
  - **Median OS:** NR
CheckMate 142: Nivolumab + Ipilimumab Cohort

- \( n = 119 \)
- ORR: 55%
- DCR: 80%
- Median Duration of Response: NR

Median PFS: NR
Median OS: NR

Ongoing Clinical Trials: dMMR mCRC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Setting</th>
<th>Intervention</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02060188</td>
<td>2</td>
<td>2nd-line + Nivolumab + Ipilimumab/Various agents</td>
<td>Accrued</td>
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<tr>
<td>(CheckMate-142)</td>
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<td></td>
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</tr>
<tr>
<td>NCT02563002</td>
<td>3</td>
<td>1st-line</td>
<td>Pembrolizumab vs. standard of care chemotherapy</td>
<td>Accrued</td>
</tr>
<tr>
<td>(KEYNOTE-177)</td>
<td></td>
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</tbody>
</table>

Case #4 Conclusion
- Due to her tumor’s dMMR status, she was enrolled in a clinical trial and began treatment with pembrolizumab and completed 2 years of treatment.
- Recent CT scan showed persistent resolution of all sites of disease except for a singular, stable subcutaneous metastatic implant.
- Patient continues to do well.
**Case #4 Take-Home Points**
- dMMR/MSI-H tumors are exquisitely sensitive to treatment with checkpoint inhibitors.
- The FDA has approved the use of pembrolizumab and nivolumab +/- ipilimumab for dMMR/MSI-H mCRC that has progressed through treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.
- The FDA has also approved pembrolizumab for the treatment of dMMR/MSI-H tumors “for which no satisfactory alternative treatment” exists.
- Trials of immunotherapy in novel settings (MMR-unselected, frontline) are ongoing.

**Case #5**
58 year-old male presented with progressive nausea, vomiting, and abdominal distension.
- CT AP revealed an ill-defined area of colonic thickening at the hepatic flexure, with extensive omental caking and peritoneal implants concerning for carcinomatosis. Biopsy confirmed adenocarcinoma.
- Further staging studies showed no evidence of liver, lung, or other distant metastases.
- The patient was counseled on the option to pursue cytoreductive surgery + heated intraperitoneal chemotherapy (HIPEC).

**Background: Peritoneal Carcinomatosis**
- Occurs in 30-40% of colorectal cancer cases.
- In 2-4% of cases, peritoneal carcinomatosis may occur in isolation.
- PC carries a comparatively worse prognosis as compared to patients with other sites of metastatic disease:

**Background: HIPEC in Colorectal Cancer**

- **Verwaal et al, JCO 2003 and Annals Surg Onc 2008:**
  - Randomized 105 patients with recurrent or metastatic CRC and isolated peritoneal carcinomatosis to receive either:
    - Systemic chemotherapy alone (5-FU or irinotecan) with allowance only for surgery in cases of malignant obstruction.
    - Upfront cytoreduction + HIPEC, followed 6 weeks later by systemic chemotherapy.

  Median PFS: 12.6 vs. 7.7 mo.
  Median OS: 22.2 vs. 12.6 mo.


  Median OS: 30.1 mo.
  5-year DFS: 10%
  5-year OS: 27%

**PRODIGE 7/ACCORD 15 (Quenet et al, ASCO 2018)**

- Phase III, randomized controlled trial of 265 patients.
- Inclusion Criteria:
  - Adults age 18-70 with CRC and isolated peritoneal carcinomatosis.
  - Had undergone R0-R2 surgical resection (≤1mm residual tumor).
  - Peritoneal Cancer Index < 25.

**Primary Endpoint: Overall survival**
Rationale:
Rates of metachronous peritoneal metastases following resection of T4 or perforated colonic primary tumors has been reported from 15-50%.
Smaller retrospective and pilot studies demonstrate that the use of adjuvant HIPEC in this population reduces the relative risk of recurrence by 60-80%.

Phase III randomized controlled trial of 204 patients.

Inclusion Criteria:
Adults with T4N0-2M0 or perforated colon cancer
Case #5 Take Home Points

- Two recent large randomized trials failed to demonstrate a benefit for HIPEC in patients at-risk for the development of, or with established peritoneal carcinomatosis from colorectal cancer.

- The decision to pursue HIPEC remains an individualized one, and multidisciplinary discussion is important.

Case #6

73 year-old woman was found to have an ascending colon mass on routine screening colonoscopy. She underwent a right hemicolectomy which revealed a stage IIA adenocarcinoma (T3N0M0, +LVI, pMMR, well-differentiated).

Case #6 Question #1

Would you offer adjuvant chemotherapy to this patient?

A. Yes
B. No

Retrospective review of 1147 patients with stage II colon cancer and Oncotype DX recurrence scores.

Rationale:

- The use of adjuvant chemotherapy in stage II colon cancer patients depends on presence of certain risk factors.
- Sidedness is a known prognostic factor in patients with metastatic CRC.
- The Oncotype DX assay has shown ability to predict patients at increased risk for recurrence following resection.

Question: Is a higher Oncotype recurrence score correlated with sidedness in pMMR stage II colon cancer??

Thank You!