Genomic profiling and new immunotherapies: an oncologist’s perspective

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Introduction

• SOC molecular testing in GI cancers
• Promising targeted therapies in GI cancers not yet FDA approved
• Immunotherapies in GI cancer
  • FDA-approved indications
  • Not yet approved (but signals of activity)
  • Clinical trials
• Summary
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- SOC molecular testing in GI cancers
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- Summary
Colon cancer: EGFR, RAS and BRAF

- Anti-EGFR Ab therapy
  - Cetuximab FDA-approval 2004
  - Approved as single-agent or combination with irinotecan
  - EGFR-expressing, refractory to irinotecan
  - Randomized trial cetuximab alone vs cetuximab + irinotecan
    - RR 11% vs 23%
    - DCR 32% vs 55%
    - HR PFS 0.54 (TTP 1.5 mos vs 4.1 mos)
SOC Molecular testing and implications

- Colon cancer: EGFR, RAS and BRAF
  - ~2008: multiple trials retrospectively look at role of kras mutations (exon 2)
    - Kras mutations identified in approximately 40% of patients
    - Kras mut – RR 1% vs kras wt RR up to 40%
    - No difference in outcomes in kras mut treated w/ cetuximab vs supportive care
  - 2012: FDA indication includes frontline with FOLFIRI, kras wt
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  - 2014: “extended RAS testing” – KRAS exons 2, 3, 4 & NRAS all predict lack of benefit to anti-EGFR antibody therapy (additional 10-15% of patients identified)
  - 2015: BRAF V600 mutations (5-10%) also suggest lack of response
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  - 2016: “sidedness” – right-sided colon cancer with apparently no benefit with anti-EGFR antibody therapy (maybe fare worse?)
SOC Molecular testing and implications

“Sidedness”
• Marked survival difference
• Detrimental effect with cetuximab?
• Midgut vs hindgut
• Molecular determinants?
SOC Molecular testing and implications

• Colon cancer: EGFR, RAS and BRAF
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  • 2015: BRAF V600 mutations (5-10%) also suggest lack of response
  • 2016: “sidedness” – right-sided colon cancer with apparently no benefit with anti-EGFR antibody therapy (maybe fare worse?)
• Current status: extended RAS testing and BRAF mutations - ~60% will have biomarker suggesting lack of benefit with anti-EGFR antibody therapy (this is not reflected in PI/FDA-approvals). Additionally with questionable benefit, potential harm in patients with right-sided primary tumors
SOC Molecular testing and implications

• Colon cancer: **BRAF**
  • Poor prognosis (OS ~14 - 18 mos vs > 30 mos if BRAF wt)
  • More common R (15%) vs L (5%)
  • ? better outcomes with FOLFOXIRI
  • No apparent benefit with anti-EGFR antibody therapy
  • Really no response to available BRAF inhibitors

Cremolini Lancet 2015
SOC Molecular testing and implications

- Colon cancer: BRAF
  - JCO 2015 – Vemurafenib in BRAF-mutated colorectal cancer
  - 21 patients
  - PFS 2.1 mos, RR 5% (one patient)

- WHY? – paradoxical MAPK activation
  - RAS activation → CRAF activation, heterodimerization of BRAF-CRAF
  - Re-accumulation of P-ERK → CRAF activation
  - Increase in RTK phosphorylation (EGFR, HER2, MET, etc)

Kopetz
JCO 2015
SOC Molecular testing and implications

- Colon cancer: BRAF
  - Poor prognosis (OS ~14 - 18 mos vs > 30 mos if BRAF wt)
  - ? better outcomes with FOLFOXIRI
  - No apparent benefit with anti-EGFR antibody therapy
  - Really no response to available BRAF inhibitors
  - 2018 NCCN guidelines to include some targeted treatment
    - Dual targeted therapy braf + mek inhibition
    - Triple therapy braf + mek + EGFR inhibition
  - Association with MSI-H – candidates for immunotherapy
SOC Molecular testing and implications

• Colon cancer: summary
  • SOC to check extended RAS, BRAF
  • SOC to check MSI status
  • Everything else probably not SOC (but rare actionable findings – HER2 amplification, POLE mutations, ATM mutations, etc, unclear significance of PTEN loss, PIK3CA mutations)
  • BRAF mutations are a big problem
SOC Molecular testing and implications

• Esophagogastric cancer: Her2
  • Approximately 20% of gastric cancer overexpress Her2
  • Rare overexpression in diffuse-type gastric cancer
• Pathology issues:
  • More heterogeneity than with breast cancer – higher false negative rate
  • Tends to spare digestive luminal membrane
  • CAP/ASCP/ASCO panel guidelines
**SOC Molecular testing and implications**

- **Esophagogastric cancer: Her2**
  - Approximately 20% of gastric cancer overexpress Her2
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- **Pathology issues:**
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  - Tends to spare digestive luminal membrane
  - CAP/ASCP/ASCO panel guidelines
- **Clinical data: TOGA trial**
  - Randomized phase III trial (2010)
  - 5FU + cisplatin +/- trastuzumab
  - RR 47% vs 35%
  - OS 14 vs 11 mos
  - Higher ratio / gene copy number more likely to benefit

---

**Bang, Lancet 2010**
SOC Molecular testing and implications

TOGA

- Her2/CEP17 ratio and gene copy number predictive of benefit
  - Small retrospective analysis suggests ration of 4.7 as optimal cutoff discriminating benefit
    - Ratio > 4.7 = “sensitive” (median OS 21 vs 14 mos)
    - Ratio > 5.1 → OS > 16 mos (median OS 28 vs 14 mos)

Gomez-Martin, JCO 2013
**SOC Molecular testing and implications**

- **Esophagogastric cancer:** **MET**
  - MET expression in 25 – 75%
  - MET amplification ~ 5%
  - Randomized phase 2 trial evaluating ECX +/- rilotumumab (anti-hepatocyte growth factor / ligand-blocking)
    - Median PFS 5.7 vs 4.2 mos
    - Median OS 10.6 vs 8.9 mos

Iveson, Lancet Oncology 2014
SOC Molecular testing and implications

• Randomized phase 3 trials:
  • ECX +/- rilotumumab (RILOMET-1)
    • Median OS 8.8 vs 10.7 mos
  • FOLFOX +/- onartuzumab (METGastric)
    • Median OS 11 vs 11.3 mos
    • PFS 6.8 vs 6.7 mos

• WHY?
  • Early discontinuation (toxicity)
  • Wrong biomarker (expression vs amplification vs mutation, etc)
  • Bad target

Catanecci, Lancet Oncology 2017; Shah JAMA Oncology 2017
SOC Molecular testing and implications

• Gastric cancer: summary
  • SOC to check Her2 amplification
  • Her2 ratio / GCN predictive of benefit
  • MET started out promising, ended up a flop
  • SOC to check MSI status
  • Everything else probably not SOC
Promising molecular testing and implications

• Intrahepatic cholangiocarcinoma
  • Actionable genetic alterations identifiable in ICC
    • FGF alterations
    • IDH1 mutations
    • Other (EPHA2, BAP1, BRCA, KRAS, ERBB family, PTEN, ARID1A, SMAD4, etc)
Targeting FGF alterations in Intrahepatic CC
Targeting FGF alterations in Intrahepatic CC

• Multiple FGFR inhibitors under study
  • ORR 15 - 30% (almost always with FGFR2 fusions)
  • DCR > 50% (range 50-90%)
  • Median PFS 4-6 months, median duration of response 1 year
  • Well-tolerated – fatigue, dry mouth, stomatitis, asthenia, dysgeusia, hyperphosphatemia

• Multiple ongoing trials, phase 2 and phase 3
Targeting IDH1 in Intrahepatic CC

IDH1 Mutations

- IDH1 normal function catalyzes decarboxylation of isocitrate to alpha-KG, ultimately a major source of NADPH production
- Somatic point mutations (R132-) prevent conversion of isocitrate to alpha-KG, AND acquire neomorphic activity enabling IDH-1 to convert alpha-KG to 2HG
- 2HG accumulation induces epigenetic deregulation \(\rightarrow\) DNA and histone hypermethylation \(\rightarrow\) block differentiation, promote proliferation
Targeting IDH1 in Intrahepatic CC

- AG-120 – phase 1 study
  - Dose escalation 3+3 design
  - 73 patients with IDH1 mutated CC
- Toxicity:
  - Very well tolerated. No DLT
- Efficacy:
  - ORR 5%, SD 56%
  - 6 months PFS 38.5%
  - 12-month PFS 21% (8 patients on therapy > 1 year)
- Ongoing international phase 3 trial (ClarIDHy)

Most Common Drug-Related AEs, n (%) | Pts With CC (n = 73)
--- | ---
Fatigue | 18 (25)
Nausea | 14 (19)
Diarrhea | 9 (12)
Vomiting | 9 (12)

- 4 pts (5%) had grade ≥ 3 drug-related AEs at 500 mg QD (n = 2) and 1200 mg QD (n = 2)
  - 500 mg QD: fatigue (n = 1), increased blood alkaline phosphatase (n = 1)
  - 1200 mg QD: fatigue (n = 1), decreased blood phosphorous (n = 1)

<table>
<thead>
<tr>
<th>Best Overall Response, n (%)</th>
<th>AG-120 Dosing</th>
<th>All Pts With CC (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 500 mg QD (n = 6)</td>
<td>500 mg QD (n = 62)</td>
</tr>
<tr>
<td>PR</td>
<td>1 (17)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>SD</td>
<td>3 (50)</td>
<td>36 (58)</td>
</tr>
<tr>
<td>PD</td>
<td>1 (17)</td>
<td>21 (34)</td>
</tr>
<tr>
<td>Not assessed</td>
<td>1 (17)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>
Promising molecular testing and implications

- Intrahepatic cholangiocarcinoma
  - Multiple phase 2 trials evaluating role of FGFR inhibitors
  - Phase 3 trial evaluating role of IDH-1 inhibition with AG-120 (ClarIDHy)
  - ? Potentially move it up to first-line setting
    - avoid chemotherapy
    - lag time for NGS results
    - add-on → toxicity
Promising molecular testing and implications

• Cholangiocarcinoma cancer: summary
  • No FDA-approved targeted therapy
  • SOC to check MSI status
  • Given early data suggesting benefits with targeted therapies, would strongly consider genomic profiling (with clinical trial enrollment)
  • Other uncommon mutations potentially targetable
    • DDR (eg BRCA, ATM, POLE, CHEK2, PALB2, etc)
    • mTOR - PTEN, STK11, TSC1, TSC2
    • MAK - BRAF, NF1
Molecular testing and implications

- Hepatocellular carcinoma
  - 2 FDA-approved drugs ("targeted") – sorafenib and regorafenib
    - Modest benefits
    - Moderate toxicity
    - No biomarker
  - BLU-554 – potent, highly selective FGFR4 inhibitor
    - FGF19 signals via FGFR4, aberrant expression appears to drive HCC
    - FGF19 expression ~25-30%
  - Nivolumab – no biomarker
Molecular testing and implications

• Pancreas cancer
  • Rare actionable mutations
    • BRCA2 – platinum sensitivity, PARP inhibitors
    • NTRK fusions
    • ROS1 fusions
  • MSI
Molecular testing and implications

- Pancreas cancer
  - Rare actionable mutations
    - BRCA2 – platinum sensitivity, PARP inhibitors
    - NTRK fusions
    - ROS1 fusions
  - MSI
Genomic profiling – clinical trials and off-label treatment

• Genomic alterations with emerging evidence of benefit:
  • BRCA1, BRCA2
  • other DDR genes (e.g. PALB2, ATM, CHEK2, POLE, BAP1, etc)
  • IDH1 (CC)
  • FGFR2 fusions (CC)
  • Her2 (not gastric)
    • Colon
    • EHCC (mutations)
  • NTRK, ROS1 fusions
Genomic profiling – clinical trials and off-label treatment

• DNA Damage Response genes (BRCA1, BRCA2, PALB2, ATM, CHEK2, POLE, etc)
  • Pancreas, colon, CC, gastric
  • ? Higher response to platinum agents
  • Role of PARP inhibitors
    • Pancreas →
      • Gem + cis + veliparib, PR 66%, DCR 88%
      • Cisplatin, olaparib in mice → cisplatin active, better w/ addition of olaparib
      • ongoing trials w/ veliparib, rucaparib, olaparib
    • Colon → not active in unselected patients, case reports with activity
  • Role of immunotherapy
  • Implications for germline testing, etc.
SOC Molecular testing and implications

• Summary:
  • Colorectal: extended ras, braf, MSI
  • Gastroesophageal: Her2
  • Pancreas: not much
  • Cholangiocarcinoma: promising early data
  • Hepatocellular carcinoma: not much (FGFR4/FGF19)
• Orphans:
  • Neuroendocrine tumor / neuroendocrine carcinoma
  • Small bowel tumors (extrapolate from colon / ampullary / pancreas cancer)
  • Appendix cancer (extrapolate from colon cancer)
  • Anal cancer
• ? MSI in everyone
Genomic profiling – clinical trials and off-label treatment

• What do we do?
• NGS –
  • Foundation Medicine
  • Others: Caris, Tempus, Guardant, ARUP, etc
• MSI
• Practical issues:
  • Reimbursement / payment
  • Tumor samples
  • Repeat biopsies
  • Liquid biopsies
Ongoing issues w/ genomic profiling

- Oncogene addiction
- Driver mutations, passenger mutations, co-mutations, resistance mutations
  - adding multiple medications —> overlapping toxicity, *contracts / budgets*
- Sub-clonal populations, tumor heterogeneity
- Germline vs somatic mutations
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- Promising targeted therapies in GI cancers not yet FDA approved
- **Immunotherapies in GI cancer**
  - FDA-approved indications
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  - Clinical trials
- Summary
Immunotherapy development

2017:
- CAR T-cell therapy
- anti-PD1 Ab therapies:
  - HCC
  - gastric carcinoma
  - MSI-H cancers
Cancer immunotherapy
Immunotherapy: MSI-H (“tissue agnostic”)

• phase 2 trial: refractory cancers
  • MSI-H colorectal (n=11)
  • MSS colorectal (n=21)
  • MSI-H non-colorectal (n=9)
• MSI-H CRC
  • ORR 40%
  • 20-wk PFS 78%
• MSI-H non-CRC
  • ORR 71%
  • 20-wk PFS 67%

Le NEJM 2015
Immunotherapy: MSI-H (“tissue agnostic”)

- 5 uncontrolled single arm trials
- 149 patients
- RR 40%
- response duration - 78% responses > 6 months
Immunotherapy: MSI-H ("tissue agnostic")
Immunotherapy: MSI-H ("tissue agnostic")

Who to test?
- all colon cancers?
- all GI cancers?
- other cancers?
Immunotherapy: MSI-H (“tissue agnostic”)

Who to test?
- all colon cancers? - **yes**
- all GI cancers? - **yes ?**
- other cancers? - **???

![Graphs showing various metrics related to immunotherapy outcomes](image)
Immunotherapy: gastroesophageal cancer

- Keynote 059 — phase 2 trial gastric/GEJ (refractory)
  - 259 patients — 57% PDL1+ (>\(=1\%\), 223C)
  - ORR PDL1+ 16% vs PDL1- 6%
  - Median duration of response: 14 mos
  - 1st line ORR 26%

Wainberg ESMO 2017
FDA grants accelerated approval to pembrolizumab for advanced gastric cancer

On September 22, 2017, the Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co., Inc.) for patients with recurrent locally advanced or metastatic, gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 as determined by an FDA-approved test. Patients must have had disease progression on or after two or more prior systemic therapies, including fluoropyrimidine- and platinum-containing chemotherapy and, if appropriate, HER2/neu-targeted therapy.
Immunotherapy: gastroesophageal cancer

ATTRACTION-2: Japan, salvage setting with nivolumab

Kang Lancet 2017
Immunotherapy: hepatocellular carcinoma

- CHECKMATE-040
- phase 1/2
- child-pugh A, sorafenib failure
- 262 patients
  - 159 sorafenib failure
  - 80 sorafenib naive
- ORR 20% in expansion, DCR 56%
- OS 16 mos, 29 mos if sorafenib naive

6-month PFS 37%
9-month PFS 28%
Immunotherapies: signals of activity

• Biliary tract cancers
  • KEYNOTE 026 — 17% response rate
  • KEYNOTE 158 — 100 cases cholangiocarcinoma, results pending this year
• Neuroendocrine carcinoma (high grade)
  • Merkel cell carcinoma, SCLC, case reports with high grade NET/NEC
• What about colon?
  • Generally disappointing
  • Multiple ongoing trials evaluating immunotherapy combinations
  • anti-PDL1 Ab + MEK inhibitor with responses
Immunotherapies: clinical trials

- anti-PD1 Ab + “drug X”
  - second immunomodulatory agent
    - second checkpoint inhibitor (e.g., CTLA4, LAG, etc)
    - costimulatory agonist (OX40, GITR, etc)
    - anti-VEGF
  - oncolytic virus
    - other (e.g., IDO, mTOR, p53 stabilizer, chemokine, cytokine)
- chemotherapy (with antigen release)
- abscopal effect —> add RT, SIRT
Immunotherapy: summary

- MSI-H cancers ("tissue agnostic")
  - 40% ORR
  - 50% durable control (>2 years?)
- PDL1+ gastroesophageal carcinomas
  - RR 10-15%
  - Duration of response > 1 year
- Hepatocellular carcinoma
  - RR 20%
  - impressive OS (> 2 years in TKI naive patients)
- ? Promising: cholangiocarcinoma, ? high grade NET/NEC
- Problems: MSS CRC, pancreas cancer
  - **Need better biomarker / predictors**
    - TMB, immune infiltrate, PDL1 status, gamma-IFN signature
New cancer drugs approved by the FDA in 2017

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Company</th>
<th>Description</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aliqopa (copanlisib)</td>
<td>Bayer</td>
<td>For the treatment of follicular lymphoma</td>
<td>Approved September 2017</td>
</tr>
<tr>
<td>Alunbrig (brigatinib)</td>
<td>Ariad Pharmaceuticals</td>
<td>For the treatment of advanced ALK-positive metastatic non-small cell lung cancer</td>
<td>Approved April 2017</td>
</tr>
<tr>
<td>Bavencio (avelumab)</td>
<td>EMD Serono/Pfizer</td>
<td>For the treatment of Merkel cell carcinoma</td>
<td>Approved March 2017</td>
</tr>
<tr>
<td>Besponsa (inotuzumab ozogamicin)</td>
<td>Pfizer</td>
<td>For the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia</td>
<td>Approved August 2017</td>
</tr>
<tr>
<td>Calquence (acalabrutinib)</td>
<td>Acerta Pharmaceuticals</td>
<td>For the treatment of mantle cell lymphoma</td>
<td>Approved November 2017</td>
</tr>
<tr>
<td>IDHIFA (enasidenib)</td>
<td>Celgene</td>
<td>For the treatment of relapsed or refractory acute myeloid leukemia with IDH2 mutation</td>
<td>Approved August 2017</td>
</tr>
<tr>
<td>Imfinzi (durvalumab)</td>
<td>AstraZeneca</td>
<td>For the treatment of advanced or metastatic urothelial carcinoma</td>
<td>Approved May 2017</td>
</tr>
<tr>
<td>Kisqali (ribociclib)</td>
<td>Novartis</td>
<td>For the treatment of breast cancer</td>
<td>Approved March 2017</td>
</tr>
<tr>
<td>Kymriah (tsigenlecleucel)</td>
<td>Novartis</td>
<td>For the treatment of refractory B-cell precursor acute lymphoblastic leukemia</td>
<td>Approved August 2017</td>
</tr>
<tr>
<td>Nerlynx (neratinib)</td>
<td>Puma Biotech</td>
<td>For the treatment of HER2 breast cancer</td>
<td>Approved July 2017</td>
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<tr>
<td>Rydapt (midostaurin)</td>
<td>Novartis</td>
<td>For the treatment of FLT3 positive acute myeloid leukemia and mastocytosis</td>
<td>Approved April 2017</td>
</tr>
<tr>
<td>Verzenio (abemaciclib)</td>
<td>Eli Lilly</td>
<td>For the treatment of HR+, HER2+ breast cancer</td>
<td>Approved September 2017</td>
</tr>
<tr>
<td>Vyxeos (daunorubicin and cytarabine)</td>
<td>Jazz Pharma</td>
<td>For the treatment of newly-diagnosed therapy-related AML or AML with myelodysplasia-related changes</td>
<td>Approved August 2017</td>
</tr>
<tr>
<td>Xermelo (telotristat ethyl)</td>
<td>Lexicon Pharmaceuticals</td>
<td>For the treatment of carcinoid syndrome diarrhea</td>
<td>Approved February 2017</td>
</tr>
<tr>
<td>Yescarta (axicabtagene ciloleucel)</td>
<td>Kite Pharmaceuticals</td>
<td>For the treatment of relapsed or refractory large B-cell lymphomes</td>
<td>Approved October 2017</td>
</tr>
<tr>
<td>Zejula (niraparib)</td>
<td>Tesaro</td>
<td>For the treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer</td>
<td>Approved March 2017</td>
</tr>
</tbody>
</table>
FDA approvals in oncology: 2017

- FDA granted regular approval to tixiserion/irinotecan (JAVO): Janssen Pharmaceuticals Inc. for the treatment of adult patients with locally advanced or metastatic colorectal cancer who progress during or after initial treatment with fluoropyrimidines (5-FU) or who have received prior irinotecan-based chemotherapy. More information, August 18, 2017.

- FDA granted regular approval to Respivir (INN): AstraZeneca Pharmaceuticals LP for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in a first complete or partial response to prior platinum-based chemotherapy. More information, August 18, 2017.

- FDA approved instabucuramin (BESPOKIN, Myha Pharmaceuticals Inc.), a subsyndrome of Plerix for the treatment of adult patients with thrombocytopenia or refractory B-cell precursor acute lymphoblastic leukemia (ALL). More information, August 17, 2017.

- FDA granted regular approval to a low-dose concentrated solution of danusibucin and cytarabine (FINM) by Jazz Pharmaceuticals Plc. for the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). More information, August 12, 2017.

- FDA approved brentuximab vedotin (CITRUM), auburn University Health Sciences for the treatment of adult patients with Hodgkin's lymphoma or non-Hodgkin's lymphoma with a history of relapse or progression during or following prior platinum-based chemotherapy in which there have been disease progression during or following prior platinum-based chemotherapy in which there have been disease progression during or following prior platinum-based chemotherapy. More information, May 10, 2017.

- FDA granted regular approval to cabatuxumab (Keytruda, Merck & Co.) for the treatment of adult patients with metastatic colorectal cancer who progress during or after initial treatment with fluoropyrimidines (5-FU) or who have received prior irinotecan-based chemotherapy. More information, November 5, 2017.


- FDA granted regular approval to astatdor (INN): Celgene Corporation for the treatment of adult patients with acute myeloid leukemia (AML) or MDS, with myelodysplasia-related changes AML, MDS, two types of AML, having a poor prognosis. More information, April 11, 2017.

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<th>Pancreas Cancer:</th>
<th>Cholangiocarcinoma:</th>
<th>Hepatocellular:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• FOLFOX +/- PD1 (MSI-H)</td>
<td>• Preoperative chemo</td>
<td>• FGFR inhibitor</td>
<td>• SBRT (unresectable)</td>
</tr>
<tr>
<td>• FOLFOX + PD1 + IDO</td>
<td>• Gem/ABI +/- olaratumab</td>
<td>• IDH1 inhibitor</td>
<td>• anti-FGFR4/FGF19</td>
</tr>
<tr>
<td>• FOLFIRI + VEGF/DLL4</td>
<td>• Gem/ABI + PD1 + IDO</td>
<td>• anti-CD166 ADC (“probody”)</td>
<td>• anti-PD1 + bevacizumab</td>
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<tr>
<td>• FOLFIRI + MEK (kras mutated)</td>
<td>• Gem/ABI + BBI668</td>
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<tr>
<td>• BRAF inhibitor (“paradox breaker”)</td>
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<tr>
<td>• Immunotherapy combinations</td>
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<tr>
<th>Gastroesophageal:</th>
<th>Neuroendocrine:</th>
<th>GIST:</th>
<th>All-comers:</th>
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<tr>
<td>• Chemo +/- PD1</td>
<td>• anti-DLL3 ADC (“Rova-T”)</td>
<td>• novel KIT inhibitors</td>
<td>• immunotherapies:</td>
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<td>• MEK ADC</td>
<td>• anti-PD1 (high grade)</td>
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<td>• Immunotherapy combinations</td>
<td>• anti-PD1 + anti-LAG (well-differentiated)</td>
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<td>anti-TGFb +/- anti-PD1</td>
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- **BRAF inhibitor (“paradox breaker”)**
- **Immunotherapy combinations**
- **FGFR inhibitor**
- **IDH1 inhibitor**
- **anti-CD166 ADC (“probody”)**
Genomic profiling and immunotherapies: summary

<table>
<thead>
<tr>
<th>Standard:</th>
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<th>Experimental:</th>
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<tr>
<td>Colon: kras, nras, braf, MSI</td>
<td>Colon: HER2</td>
<td>Colon: immunotherapy combinations</td>
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