Should all GI Cancer Patients Undergo NGS Testing? – *Definitely, yes!*

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Disclosures

- **Speaker/Consultant:**
  - AstraZeneca/MedImmune, Caris Life Sciences, Celgene, Merrimack, Perthera, RenovoRx and Sirtex Medical, Merck

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- I will be discussing “off-label” use of approved therapies
  - Almost by definition
Why NGS for Advanced GI Cancers Should be the Standard of Care

- Advanced GI cancers are deadly
  - While outcomes have improved, chemo benefits are limited
  - Standard treatment (chemotherapy) is EXPENSIVE
- Testing DOES reveal legitimately actionable mutations
  - Panel vs. single gene
- Actionable mutations lead to a disproportionate benefit
  - There is survival benefit

All Patients with Advanced GI Cancers Should Undergo NGS Testing
Advanced GI Cancers are Deadly

- GI Cancers cause >3 million deaths each year worldwide
- Benefits from “standard” therapies have only been incremental
  - OS improvements of <2 months have → FDA approval

TAS-102 vs. Placebo, CRC
7.1 vs. 5.3 months

Gem-Nab-Pac vs. Gem, Panc
8.5 vs. 6.7 months

Ram vs. Placebo, Gastric
5.2 vs. 3.8 months

Standard treatment is EXPENSIVE

- NGS Testing + Fusion testing RETAIL costs
  - At most, $7800
  - Recent panel - $1800 including RNA sequencing

GI Cancers **DO** Harbor Actionable Mutations

- **Definition of actionability**
  - Literature supports high degree of benefit in patients with that molecular abnormality (any cancer type)
  - Possible implication of response to therapy, based on mechanism or pathway

- **Actionable mutations identified in every GI malignancy**
  - Pancreatic cancer - ~25%
  - Biliary Cancer - ~20%
  - Upper GI Cancers - ~30% (includes HER2/ERBB2)
  - CRC - ~10% (70% if you count RAS/RAF)

Actionable Mutations in Pancreatic Cancer

- 17 – 48% of pancreatic cancers harbor actionable findings

Highly Actionable

- BRCA1/2
- PALB2
- ATM
- CHEK1/2
- FANCA/C
- NTRK1/3
- ALK
- ROS1
- BRAF
- FGFR1/4
- ERBB2
- TOP2A
- CDK4/6
- STK11
- AKT1/2/3
- TSC12
- RET

Platinum/PARP inhibitor

TRK inhibitor

ALK inhibitor

ROS inhibitor

BRAF inhibitor

FGFR inhibitor

HER2 inhibitor

Anthracycline

CDK inhibitor

mTOR/AKT inhibitor

Actionable Mutations in Biliary Cancer

- Up to 40% of biliary cancers harbor actionable findings
  - HER2
  - FGFR
  - IDH1/2

- Mutation profile depends upon subtype
If an actionable mutation is identified the “appropriate” therapy is typically not FDA approved in that disease.

But, there have been biomarker-based approvals:
- E.g. pembrolizumab in MSI-high disease
  - 3-5% of CRCs
  - 22% of gastric cancers
  - 1% of pancreatic cancers

**Patients with Actionable Mutations Benefit Disproportionately: MSI-High**

Le DT, et al. Science 2017; 357: 409-413
Disproportionate Benefit: TRK inhibitors

A Maximum Change in Tumor Size, According to Tumor Type

- Thyroid tumor
- Soft-tissue sarcoma
- Colon tumor
- Lung tumor
- Appendix tumor
- Melanoma
- GIST
- IFS
- Breast tumor
- Cholangiocarcinoma
- Pancreatic tumor
- Salivary-gland tumor

Drilon A, et al. NEJM 2018; 378(8):731-739
Disproportionate Benefit: TRK inhibitors

- Entrectanib case report
  - 2 NTRK fusion and 1 ROS1 fusion cases
  - Prolonged, and occasionally dramatic benefit
Disproportionate Benefit: BRAF

- **SLI:** Encorafenib, cetuximab, binimetinib in CRC
  - ORR 48%; mPFS 8.0 months

Slide thanks to Axel Grothey and Clinical Care Options
BRAF Mutated Pancreatic Cancer

- From the KYT database - of 766 patients
- 18 BRAF mutations
  - 5 V600E
  - 13 others
  - Almost always exclusive of KRAS mutations
- Sustained PR in a BRAF\textsuperscript{V600E} mutated patient treated with dabrafenib + trametinib

Guan, et al. ASCO-GI, 2017
Disproportionate Benefit: Others

- **HER2 Amplified CRC**
  - 5% of screened patients
  - ORR 30%

- **FGFR Mut Cholangio**
  - 13 – 17% of IHCC
  - ORR 15%

HR-DDR Mutations in Pancreatic Cancer

- 17 – 25% of pancreatic adenocarcinomas harbor mutations in the DDR genes
  - Homologous recombination DNA damage response (HR-DDR) mutations
  - 
  - BRCA1, BRCA2, ATM, PALB2, ATRX, RAD51, and others

- All Patients with Advanced GI Cancers Should Undergo NGS Testing

<table>
<thead>
<tr>
<th>Gene</th>
<th>N (616 Total)</th>
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<tbody>
<tr>
<td>ATM</td>
<td>28 (4.5%)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>18 (2.9%)</td>
</tr>
<tr>
<td>SMARCA4</td>
<td>10 (1.6%)</td>
</tr>
<tr>
<td>BAP1</td>
<td>8 (1.3%)</td>
</tr>
<tr>
<td>BRCA1</td>
<td>8 (1.3%)</td>
</tr>
<tr>
<td>BRIP1</td>
<td>6 (1.0%)</td>
</tr>
<tr>
<td>PALB2</td>
<td>5 (0.8%)</td>
</tr>
<tr>
<td>CHEK2</td>
<td>4 (0.6%)</td>
</tr>
<tr>
<td>FANCA</td>
<td>4 (0.6%)</td>
</tr>
<tr>
<td>FANCC</td>
<td>3 (0.5%)</td>
</tr>
<tr>
<td>RAD50</td>
<td>3 (0.5%)</td>
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<tr>
<td>STAG2</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>BARD1</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>CHEK1</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>FANCG</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>

- Know Your Tumor® (KYT) Dataset
  - 16.5% HR-DDR

- Caris Database Review
  - 16.9% HR-DDR

PARP Inhibitors in Pancreatic Cancer

- Anecdotal evidence in pancreatic cancer- Consistent evidence of efficacy in *BRCA1/2* mutant tumors
  - Lowery, et al - 15 patients with known *BRCA1/2* mutations
    - 4 patients with PARPi-based therapy
    - 3 PRs and one SD for 6 months
  - Kaufman, et al - Olaparib in 23 patients with germline *BRCA1/2* mutations
    - 23 pancreatic cancer patients
    - 22% ORR, 1 CR & 4 PRs
  - Shroff, et al - Rucaparib in 19 *BRCA1/2* mutated patients
    - 16% ORR, 1 CR and 2 PRs
    - Benefit in somatic mutated patients

PARP + Platinum in Pancreatic Cancer

- Phase 1B: Cisplatin, Gemcitabine, Veliparib
  - O’Reilly, et al, 2018 – 1 CR and 6 PRs
    - Phase Ib dose-finding ORR = 78%, mOS (gBRCA+) = 23 months
    - Randomized Phase II trial in pancreatic cancer ongoing

A Panel is More Cost and Time Effective

- Pennell, et al – recent analysis in NSCLC
- Compared NGS vs. sequential single gene testing vs. “exclusionary” testing + single gene sequential testing vs. hotspot panel testing
- Evaluated time-to-test results and costs
  - Time to test results were fastest with the NGS and hotspot panels
  - NGS panel testing was the most cost efficient
  - 200+ genes for the cost of 2-3 single gene tests

<table>
<thead>
<tr>
<th>Testing Strategy</th>
<th>Medicare-Insured Patients (n = 2,066)</th>
<th>Commercially Insured Patients (n = 156)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Cost</td>
<td>Cost Difference (\text{v} ) NGS</td>
</tr>
<tr>
<td>NGS</td>
<td>2,190,499</td>
<td>—</td>
</tr>
<tr>
<td>Sequential</td>
<td>3,721,368</td>
<td>1,530,869</td>
</tr>
<tr>
<td>Exclusionary</td>
<td>3,584,177</td>
<td>1,393,678</td>
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<tr>
<td>Hotspot panel</td>
<td>4,331,295</td>
<td>2,140,795</td>
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</tbody>
</table>

**TABLE 3. Total Cost and Cost Difference Versus NGS**

Pennell NA, et al. JCO Precision Oncology 2019
## “Standard” Panel for CRC

### “Standard of Care” Testing for CRC

<table>
<thead>
<tr>
<th>Gene</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>$400</td>
</tr>
<tr>
<td>NRAS</td>
<td>$400</td>
</tr>
<tr>
<td>BRAF</td>
<td>$400</td>
</tr>
<tr>
<td>MLH1</td>
<td></td>
</tr>
<tr>
<td>MSH2</td>
<td></td>
</tr>
<tr>
<td>MSH6</td>
<td></td>
</tr>
<tr>
<td>PMS2</td>
<td></td>
</tr>
<tr>
<td>HER2</td>
<td>$400</td>
</tr>
<tr>
<td>NTRK1/3</td>
<td>$400</td>
</tr>
<tr>
<td>FGFR</td>
<td>$400</td>
</tr>
<tr>
<td>ALK/ROS</td>
<td>$400</td>
</tr>
</tbody>
</table>

- and/or MSI testing: $400

- One time NGS panel: $3200

- One time NGS panel: $2860
Gold Standard: Overall Survival Benefit

- 1028 pancreatic cancer patients
- All underwent molecular profiling (w/NGS)
- 677 patients with outcome information
  - 189 with Actionable Findings
    - 46 received molecularly matched therapy
    - 143 received “unmatched” therapy
  - 488 with no actionable findings
- Overall survival
  - Matched 1y > unmatched
  - Matched 1.3y > no actionable marker

Patients Treated in the Advanced Setting

- Received a Molecularly-Matched Therapy (n=46)
- Only Unmatched Therapies (n=143)
- Treated, No Marker (n=488)

Overall Survival (OS)

- Matched 1y > unmatched
- Matched 1.3y > no actionable marker

Molecularly-Matched vs Only Unmatched History (Highly Actionable)

p-value = 0.000388, HR = 0.42 [0.26-0.68]

Molecularly-Matched vs Patients without Highly Actionable Findings

p-value = 0.00000229, HR = 0.34 [0.22-0.53]

Pishvaian, et al, ASCO, 2019; Manuscript submitted
Summary: We Should be Testing

- Actionable mutations are not “rare”
  - EU definition of rare: <1/2000 people = .05%
- Testing is MUCH less expensive than standard (and targeted) therapies
- Testing DOES reveal legitimately actionable mutations
- Actionable mutations lead to a disproportionate benefit
  - With survival benefit
“Germline testing is recommended for any patient with confirmed pancreatic cancer, using comprehensive gene panels for hereditary cancer syndromes”\(^1\)

“Tumor/somatic gene profiling is recommended for patients with locally advanced/metastatic disease [80\% of patients] who are candidates for anti-cancer therapy to identify uncommon but actionable mutations”\(^1\)
Thank you and Questions?