Update on targeted therapies in gastrointestinal malignancies

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Disclosures

• Research collaborations with reimbursed travel/meeting expenses, no direct funds
  • Astra-Zeneca (POLO trial)
  • Caris Life Sciences (Precision Oncology Alliance)
  • Myriad Genetics (collaborative research)

• Research collaborations with no direct funds
  • MERCK (Keynote-177 trial)
  • Foundation Medicine
  • Invitae
  • Ambry
Immunotherapy in GI oncology

- **Vaccine therapy**: None currently standard of care
- **CAR-T therapy**: Limited early data in GI tumors
- **Immune checkpoint blockade (ICB)**
  - Anti-CTLA-4 therapy
  - Anti-PD-1/PD-L1 antibodies
- **Second generation ICB**: Will mention if time

Today's focus
Biomarkers for targeted therapies in GI cancers

- KRAS/NRAS (RAS)
- HER2 expression/amplification
- PD-L1 expression
- CTLA-4 expression
- Microsatellite instability (MSI)
  - Tumor mutational burden (TMB)
  - HRD/PARP inhibition
- BRAF V600E mutations
- NTRK fusions
PARP, BRAF, NTRK inhibitors in GI malignancies

• PARP inhibitors in GI cancers
  • POLO trial
  • TAPUR/MATCH

• BRAF V600E inhibitors in CRC
  • 2018 update to the NCCN guidelines

• NTRK inhibitors in GI cancers
  • Recent trial of Larotrectinib in diverse tumors

WILL NOT COVER
Anti-EGFR and anti-HER2 therapy
Targets and biomarkers
Programmed death receptor 1 (PD-L1)

**Function**
- Expressed on tumors and dendritic cells
- Engages CD8+ T-cell surface PD-1 receptor
- Down-regulates T-cells
  - Increased apoptosis, reduced proliferation, inhibitory cytokines

**Targeting PD-L1/PD-1**
- Monoclonal antibodies
  - Nivo/pembro (PD-1)
  - 4+ others (PD-1 and PD-L1)

**PD-L1 expression**
- Gastric/GEJ (Keynote-059)
  - 57% (1% or higher)
  - Associated with dMMR
- CRC: 25% tumor cells PD-L1+
  - 81% R colon, 19% L colon
- Pancreatic adenocarcinoma
  - 19% PD-L1+ (RNA exp)

Fuchs CS. JAMA Onc 2018; Valentini AM. Oncotarget 2018; Birnbaum DJ Oncotarget 2016
CTLA-4

Expression
Activated and regulatory T-cells

Function
Suppresses activation of CD28 by outcompeting its ligands

Targeting
Monoclonal antibody ipilimumab
Microsatellite instability (MSI)

- Marker of underlying mismatch repair deficiency
- Methods to measure
  - MSI by PCR fragment analysis
  - Immunohistochemistry for MMR protein expression
  - NGS assessment of homopolymer regions in sequenced genes
- 23 May 2017
  - First-ever FDA-approved biomarker for treatment (tumor agnostic)

Colorectal cancer
- ~15-20% have MSI
- 2-3% Lynch syndrome

Gastric cancer
- ~10-22% have MSI

Pancreatic adenocarcinoma
- ~0-13% have MSI


COMMERCIAL SOMATIC PROFILE
- Colon 3-6%
- Gastric 6-9%
- Pancreatic 0.5-2%
MMR prevalence in 12,019 tumors

MSI is seen in nearly every tumor type but prevalence is variable by stage of the tumor.
When measured as a continuous variable, MSI is highly variable by tumor type and whether there is a germline MMR mutation or not. Latham A. JCO 2019
Tumor mutational burden (TMB)

- Mutations per mega-base of DNA
- Associated with neo-antigen load
- Inter- and intra-histology variability
- Influenced by causation—e.g. higher in smoking associated lung cancer and sun-exposure skin cancer

Campbell BB et al. Cell 2017

Seek to harmonize the definition and parameters of TMB
Mutational burden variability

Y-axis is LOG scale

Response to PD-L1 therapy is associated with TMB
TMB 3.6 mt/Mb (0-124)

- TMB is vastly (7-8 fold) more prevalent than MSI

- MSI-H concordance with TMB-H is 83%

Chalmers ZR et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Medicine 2017. 9:34 (Open Access)
Clinical trials of ICB in GI cancers: Colorectal, gastric, pancreas
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency


**Table 2. Objective Responses According to RECIST Criteria.**

<table>
<thead>
<tr>
<th>Type of Response</th>
<th>Mismatch Repair–Deficient Colorectal Cancer (N=10)</th>
<th>Mismatch Repair–Proficient Colorectal Cancer (N=18)</th>
<th>Mismatch Repair–Deficient Noncolorectal Cancer (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response — no. (%)</td>
<td>0</td>
<td>0</td>
<td>1 (14)*</td>
</tr>
<tr>
<td>Partial response — no. (%)</td>
<td>4 (40)</td>
<td>0</td>
<td>4 (57)†</td>
</tr>
<tr>
<td>Stable disease at week 12 — no. (%)</td>
<td>5 (50)</td>
<td>2 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Progressive disease — no. (%)</td>
<td>1 (10)</td>
<td>11 (61)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Could not be evaluated — no. (%)</td>
<td>0</td>
<td>5 (28)</td>
<td>0</td>
</tr>
<tr>
<td>Objective response rate (95% CI) — %</td>
<td>49 (12–74)</td>
<td>0 (0–10)</td>
<td>71 (29–96)</td>
</tr>
<tr>
<td>Disease control rate (95% CI) — % $</td>
<td>90 (55–100)</td>
<td>11 (1–35)</td>
<td>71 (29–96)</td>
</tr>
<tr>
<td>Median duration of response — wk</td>
<td>Not reached</td>
<td>NA</td>
<td>Not reached</td>
</tr>
<tr>
<td>Median time to response (range) — wk</td>
<td>28 (13–35)</td>
<td>NA</td>
<td>12 (10–13)</td>
</tr>
</tbody>
</table>
ICB for metastatic CRC

• **Keynote 164 trial (Phase II)**
  • Pembrolizumab (anti-PD-1 monoclonal antibody) single-agent
    • Le DT et al JCO 36, no. 15_suppl (May 2018)

• **Checkmate 142 trial (Phase II)**
  • Nivolumab (anti-PD-1 monoclonal antibody) single-agent
    • Overman MJ et al Lancet Oncol 2017
  • Nivolumab + ipilimumab (anti-CTLA4 monoclonal antibody)
    • Overman MJ et al JCO 2018
Cross-trial comparison in front-line metastatic CRC

<table>
<thead>
<tr>
<th>Outcome or toxicity</th>
<th>Pembrolizumab (N=63)</th>
<th>Nivolumab (N=53)</th>
<th>Nivolumab+ Ipilimumab (N=116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>59 yrs (23-83)</td>
<td>53 yrs (44-64)</td>
<td>58 yrs (21-88)</td>
</tr>
<tr>
<td>Female</td>
<td>48%</td>
<td>41%</td>
<td>41%</td>
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<tr>
<td>&gt;1 prior chemo</td>
<td>94%</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>Lynch syndrome</td>
<td>~48%</td>
<td>~</td>
<td>29%</td>
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<tr>
<td>Median F/U</td>
<td>12.6 months</td>
<td>12.0 months</td>
<td>13.4 months</td>
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<tr>
<td>ORR</td>
<td>34%</td>
<td>36%</td>
<td>55%</td>
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<tr>
<td>CR</td>
<td>3%</td>
<td>2%</td>
<td>3%</td>
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<tr>
<td>PR</td>
<td>31% (50%)*</td>
<td>34%</td>
<td>51%</td>
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<tr>
<td>SD</td>
<td></td>
<td>36%</td>
<td>31%</td>
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<tr>
<td>PFS (12 mo)</td>
<td>41%</td>
<td>50%</td>
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<tr>
<td>OS (12 mo)</td>
<td>76%</td>
<td>73%</td>
<td></td>
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<tr>
<td>Median TTResp</td>
<td></td>
<td>70-74%</td>
<td></td>
</tr>
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</table>
Tumor response and PFS

LE DT. NEJM 2015 (PEMBRO)

OVERMAN MJ. JCO 2018 (NIVO+Ipi)

MMR proficient CRC

Nivo+Ipi—high proportion of responses and robust depth

MMR deficient CRC

PFS free Survival in Cohorts with Colorectal Cancer

PFS

Probability of Progression-free Survival

MMR proficient CRC

MMR deficient CRC

Nivo alone

Nivo+Ipi

PFS (%)
# Response predictors in Checkmate-142

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Objective response</th>
<th>Disease control &gt;12 wks</th>
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<tbody>
<tr>
<td>Tumor PD-L1</td>
<td></td>
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<tr>
<td>&gt;1% (n=21)</td>
<td>29%</td>
<td>52%</td>
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<tr>
<td>&lt;1% (n=47)</td>
<td>28%</td>
<td>75%</td>
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<tr>
<td>Immune cell PD-L1</td>
<td></td>
<td></td>
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<tr>
<td>Rare (n=24)</td>
<td>21%</td>
<td>58%</td>
</tr>
<tr>
<td>Intermediate (n=21)</td>
<td>24%</td>
<td>81%</td>
</tr>
<tr>
<td>High (N=23)</td>
<td>39%</td>
<td>65%</td>
</tr>
<tr>
<td>Other mutations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAF (N=12)</td>
<td>25%</td>
<td>75%</td>
</tr>
<tr>
<td>KRAS (N=26)</td>
<td>27%</td>
<td>62%</td>
</tr>
<tr>
<td>Both WT (N=29)</td>
<td><strong>41%</strong></td>
<td><strong>79%</strong></td>
</tr>
<tr>
<td>Lynch positive (n=27)</td>
<td>33%</td>
<td>70%</td>
</tr>
<tr>
<td>Lynch negative (N=28)</td>
<td>29%</td>
<td>75%</td>
</tr>
</tbody>
</table>

Non-significantly higher response in tumors with high PD-L1 expression on immune cells

Non-significantly higher response in tumors wild-type for BRAF and KRAS
Toxicities of ICB immunotherapy

Most common immunologic side effects of ICB
Most common (5-10%)
Dermatitis/rash, colitis/diarrhea

Less common (1-5%)
Hepatitis, nephritis, pneumonitis

Rare (<1%)
Thyroiditis, DM2, hypopituitarism

Management of immunologic side effects of ICB
Step 1: Hold ICB therapy
Step 2: Lower dose steroids
Step 3: Higher dose steroids
Step 4: Infliximab (in some cases) and/or more steroids
## Cross-trial comparison of AEs

<table>
<thead>
<tr>
<th></th>
<th>Pembro</th>
<th></th>
<th>Nivo</th>
<th></th>
<th>Nivo+Ipi</th>
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<tbody>
<tr>
<td></td>
<td>Any</td>
<td>G3/4</td>
<td>Any</td>
<td>G3/4</td>
<td>Any</td>
<td>G3/4</td>
</tr>
<tr>
<td>ANY AE</td>
<td>98%</td>
<td>41%</td>
<td>70%</td>
<td>21%</td>
<td>73%</td>
<td>32%</td>
</tr>
<tr>
<td>Anemia</td>
<td>20%</td>
<td>17%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>20%</td>
<td>20%</td>
<td>1%</td>
<td>1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24%</td>
<td>5%</td>
<td>20%</td>
<td>1%</td>
<td>20%</td>
<td>2%</td>
</tr>
<tr>
<td>Low albumin</td>
<td>10%</td>
<td>10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgias</td>
<td>15%</td>
<td>0%</td>
<td>6%</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST/ALT elevated</td>
<td>7%</td>
<td>5%</td>
<td>4%</td>
<td>1%</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32%</td>
<td>0%</td>
<td>16%</td>
<td>1%</td>
<td>16%</td>
<td>2%</td>
</tr>
<tr>
<td>Rash</td>
<td>24%</td>
<td>0%</td>
<td>5%</td>
<td>1%</td>
<td>9%</td>
<td>2%</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>10%</td>
<td>0%</td>
<td>10%</td>
<td>0%</td>
<td>13%</td>
<td>1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>12%</td>
<td>0%</td>
<td>10%</td>
<td>0%</td>
<td>12%</td>
<td>1%</td>
</tr>
</tbody>
</table>
Patient reported outcomes (PROs) in combination nivolumab+Ipilimumab

EORTC QLQ-C30

- >60% reported no reductions in health status on study

- Meaningful (>10 points) and statistically significant improvements in symptoms, function, and health status by week 13 or earlier

- Statistically significant improvements in nausea, dyspnea, diarrhea, cognitive function and physical function
Ongoing trials of ICB

Front-line and second-line metastatic CRC
   Anti-PD-1/L1 alone
   Combination with chemotherapy
   With radiation therapy for oligometastatic disease

Adjuvant setting
   In combination with FOLFOX
   Maintenance after completion of adjuvant FOLFOX

Prevention setting
   High risk patients with Lynch syndrome after hemi-colectomy
ICB across other GI cancers

Trials in pancreatic and gastro-esophageal cancers

• Brahmer JR et al (Phase I): NEJM 2012

• Le DT et al (Phase II): Science 2017

• Keynote-059
  • Fuchs CS et al (Phase II): JAMA Onc 2018

• Keynote-181
  • Kojima T et al (Phase III): GI ASCO 2019
Phase I BMS-936559 anti-PD-L1 in diverse solid tumors

Early trial of ICB in diverse tumors including pancreas

• Advanced NSCLC, melanoma, RCC, ovarian cancer, CRC, pancreatic cancer, gastric cancer, breast cancer

• 0/14 responses in pancreatic adenocarcinoma
• Not selected for MSI-H status

Brahmer JR NEJM 2012
ICB in other MSI-H cancers

MSI-H gastro-esophageal and pancreatic cancers showed responses

With permission from Science
ICB in gastro-esophageal and pancreatic adenocarcinomas

Pancreatic cancers
Anti-PD-1/L1 therapy only approved for MSI-H tumors

Gastroesophageal cancers
Anti-PD-1/L1 therapies approved in advanced, PD-L1+ cancers

Phase II KEYNOTE-059
Gastric and GEJ
ORR 15.5% in PD-L1+
Response duration 16.3 months

Phase III KEYNOTE-181
SCC and AC of esophagus
~1/3 w/HIGH PD-L1 (CPS≥10)
Anti-PD-L1 extended mOS in CPS≥10 group (9.3 vs 6.7 mo)(P=0.007)

Steven D. Leach, MD
Director, Norris Cotton Cancer Center at Dartmouth

Fuchs CS et al Jama ONC 2018; Kojima T et al Gl ASCO 2019 Abstract 2
Other interesting research

- Safety of anti-PD-1/L1 therapies with concurrent rheumatologic illnesses
  - Leonardi GC. JCO 2018

- Moderators of efficacy of therapy
  - Hereditary risk (Lynch vs somatic MSI)
  - Sex (Wallis CJD JAMA Oncology 2019)
  - Nutritional status (Rishi Jain, Assistant Professor @ FCCC)
Malnutrition, toxicity and response in Phase I/II trials

Presented at 2018 Cancer Cachexia Conference
High PG-SGA and clinical trial outcomes

**Duration on Clinical Trial**
- High PG-SGA
  - Yes: 48 days
  - No: 105 days

**Overall Survival (OS)**
- High PG-SGA
  - Yes: 51%
  - No: 85%

Patients with adequate nutrition were on study longer (105 vs 48 days)
Patients with adequate nutrition lived longer
Dual RAS targeting

**RESULTS**

- mPFS increased 4.4 from 2.0 months
- Response rate 16% vs 4%; Disease control rate 67% vs 22%
- AEs: 28% neutropenia, 13% anemia

**SWOG 1406**: Randomized trial of irinotecan and cetuximab with or without vemurafenib in *BRAF*-mutant metastatic colorectal cancer

GI ASCO 2018 (Kopetz S et al. Abstract 520)
Dual RAS+ MEK targeting

NCCN UPDATE: TRIPLET FOR BRAF V600E+ mCRC

BRAF INHIBITION: ENCORAFAFENIB
MEK INHIBITION: BININETIMIB
EGFR INHIBITION: CETUXIMAB/PANITUMUMAB

ABSTRACT 688: Updated results of the BEACON CRC safety lead-in: Encorafenib (ENCO) + binimetinib (BINI) + cetuximab (CETUX) for BRAFV600E-mutant metastatic colorectal cancer (mCRC).

RESULTS: 30 patients; mPFS 8 months, RR 48%; 3 CRs
Homologous recombination deficiency (HRD)

Has been primarily investigated as a target for platinum therapy and PARP inhibitors

- PARP approvals in ovarian and breast cancer
- Pancreas → Kaufman et al JCO 2014
  - Phase II BRCA1/2+ PC (RR 22%, PFS 4.6 mo, OS 9.8 mo)
  - Under investigation in the Phase III POLO trial

Evidence suggests tumors with mutations in HRD associated genes (BRCA1/2, ATM, PALB2, etc) are also targetable by anti-PD-1/PD-L1 therapy
gHRD and sHRD mutations in pancreatic adenocarcinoma (PAC)

High risk familial pancreatic cancer
Mayo FPC and familial pancreatic cancer
Prevalence 4.2-9.2% HRD mutations
8 ATM, 2 BRCA1, 11 BRCA2, 1 PALB2

PANCGENE study (n=727)
Prevalence 5.0% (31 BRCA1/2, 4 PALB2)

DFCI unselected PAC (n=289) (CGA 2017)
Prevalence 11.5% HRD genes (n=289)

Commercial panel testing PAC (AACR 2017)
Prevalence ~11.0% HRD genes

Clinical trial PAC (POLO Trial)
Prevalence ~6-7% BRCA1/2

4-12% PACs have germline HRD mutations
~35% pancreatic tumors show evidence of somatic HRD mutations

PARP inhibitors

Persistent SSBs
- Trapped PARP-DNA complex
- BRCA1/2 mediated
  - Homologous recombination
  - Fanconi Anemia
  - Other pathways

Adapted from Y. Pommier

PARP inhibitors in pancreatic adenocarcinoma

**Completed studies**
- PI/II: CisIriMC+olaparib
  - 4 year responder
- PI: CisGem+olaparib
- PI: Talazoparib in HRD deficient tumors
- PII: Rucaparib
  - 1 CR/2 PR/4 SD

**Ongoing studies**
- PI/II: Chemo+ veliparib
  - NCT01585805
  - NCT01489865
- PIII: POLO trial
- Phase II: Olaparib+ICB (Reiss Binder)

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**Randomized Phase III POLO trial**
- International multi-site, double blind, placebo
- Randomized 3:2 olaparib/placebo
- Trial is currently ~ 100% accrued

**Target population**
- Front-line metastatic, BRCA1/BRCA2+ germline
- Responsive to platinum x 6 wks
- Maintenance PARP

**Outcomes**
- 1\(^0\): PFS
- 2\(^0\): OS, ORR, DCR
Phase III Trial Maintenance (POLO)
Platinum Therapy → Olaparib/Placebo

Ongoing

Met PC, gBRCA1/2+
ECOG 0-1
Responsive to platinum for >6 weeks

Randomize

Olaparib
300 mg PO BID

Placebo

Randomization 3: 2
Primary Endpoint: PFS (central review mRECIST 1.1)

NCT02184195 (Astra Zenica, Myriad) Golan, T., Kindler, H
Tropomyosin Receptor Kinase (TRK) Signaling Pathway

Develop activating fusions with various genes (0.21% cancers)

Fusions are targetable with receptor tyrosine kinase inhibition
~1-5% GI cancers

TRK specific inhibitor approved in November 2018 (Larotrectinib)

86% of patients responding
Median time to response 1.8 months
At 1 year, 71% of patients with ongoing response
55% at 1 year progression free

Prevalence in GI tumors
CRC 0.5%
Appendix 2-4%
Cholangio/GB 1-2%
Pancreatic 1-2%

Targeted therapies approved in GI malignancies

### Approved therapy targets in the US

<table>
<thead>
<tr>
<th></th>
<th>RAS</th>
<th>MSI</th>
<th>HER2</th>
<th>BRAF</th>
<th>NTRK</th>
<th>PD-L1</th>
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<tbody>
<tr>
<td>Colorectal</td>
<td></td>
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<tr>
<td>GE tumors</td>
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<tr>
<td>Pancreatic</td>
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<tr>
<td>Small bowel</td>
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<tr>
<td>Biliary</td>
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<td>Anus</td>
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### Emerging targets

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<tr>
<th></th>
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<th>PARP</th>
<th>FGFR</th>
<th>IDH1</th>
<th>TMB</th>
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<td>Anus</td>
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TAPUR and MATCH → BRAF, HER2, ROS1, ALK, GNAQ/GNA11, PTEN......
## Ongoing basket trials

### SELECT TARGETS AND TREATMENTS

<table>
<thead>
<tr>
<th>TAPUR</th>
<th>MATCH</th>
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<tbody>
<tr>
<td>BRCA ½, ATM</td>
<td>FGFR Mut/Fusions</td>
</tr>
<tr>
<td>BRAF V600E/D/K/R</td>
<td>GNAQ/GNA11</td>
</tr>
<tr>
<td>HER2</td>
<td>PIK3CA</td>
</tr>
<tr>
<td>ALK/ROS1/MET</td>
<td>PTEN</td>
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THANK YOU