Kicking the Tires: Biomarker Testing in Stomach Cancer

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Disclosures

• Consulting/Advisory: Eli Lilly, Merck, Bristol Myers Squibb, Foundation Medicine Inc., Natera, Pieris

• Stock/Equity: Turning Point Therapeutics

• Other: Patriots fan (YES, even this year)

• Medical Advisory Board: Debbie’s Dream Foundation, Hope for Stomach Cancer
Overview

• Background on molecular testing: How, why, questions to ask your doctor

• Current biomarker testing: what you need to know about your tumor and why

• Emerging targets: EBV, CLDN18.2, FGFR2b, Refining HER2

• The future: Sequence, Treat, Repeat
Cancer is the end result of cumulative influence from environmental risk factors, innate host features, and acquired errors in the genome.
From the Clinic to the Bench to the Clinic

Why don’t both tumors follow the rules?

**RESPONDER**

- NO CCNE1 amplification, EGFR amplified population

**NON-RESPONDER**

- CCNE1 amplified population, some cells lost Her2, EGFR co-amplification etc
Types of Molecular Profiling Used in Stomach Cancer

• Tissue based – “DNA sequencing”, “Genomic Profiling”, etc.
  • Larger panel of genes examined (150-500)
  • Requires biopsy or surgical sample
  • Only examines the changes occurring in the biopsy area
  • 2-4 week turnaround for results
  • Still “gold standard” for biomarker testing

• Blood based – “Liquid biopsy”, “circulating tumor DNA (ctDNA)”
  • Smaller panel of genes (50-80), but getting better
  • 1-2 tubes of blood
  • Reflects tumor makeup more broadly
  • 7-14 day turnaround

• Germline – “Genetic testing”
  • Blood or normal tissue (saliva, cheek swab)
  • Examines normal cell DNA for changes all cells have
  • Used to test for changes you were inherited and influence cancer risk
  • Often used as comparator for tumor testing
Definitions and Concepts

Cell-free DNA in blood is a normal process

Includes germline pathogenic alterations

Release influenced by comorbidities, BMI, age, sex, autoimmune diseases, infections

ctDNA refers to the fraction of cfDNA that is derived from tumor cells (not normal)

Shedding related to tumor location, burden, stage, tumor type

Multiple applications in oncology

Cell-free DNA (cfDNA)

Circulating tumor DNA (ctDNA)
Current Standard Molecular Testing: The Bare Minimum

- **HER2 (ERBB2):** All stage IV patients at diagnosis. Testing is positive in 12-20% of patients. Associated with benefit from trastuzumab (Herceptin)

- **PD-L1:** All stage IV patients at diagnosis. Positive to varying degrees in 50-70% of patients. Associated with benefit from immune checkpoint inhibitors like pembrolizumab and nivolumab (Keytruda and Opdivo)

- **MMR or MSI testing:** All stage IV patients at diagnosis, favor for all stage II-III at diagnosis. Positive in 3-5% of stage IV and 10-20% stage II-III. Associated with even greater benefit from immune checkpoint inhibitors like pembrolizumab (Keytruda). Also predicts lack of benefit from chemo in stage II-III.
Questions for Your Care Team

1. What are the biomarker results for my tumor?

2. Should we consider more extended tumor testing?

3. Should we consider genetic testing?

4. Is there a role for liquid biopsy?
HER2 Testing and Trastuzumab Benefit

- Too much HER2 can be tested by looking at the protein and/or the number of gene copies
- Drug approval is linked to biomarker testing
- Addition of biologic drug trastuzumab improved survival
- Response rates improved from 35 to 47% with addition of trastuzumab
- Adding <3 months of life not good enough

[Graph showing survival probability with and without trastuzumab]

Bang, Lancet Oncol 2014
MMR/MSI in Stage IV and Immunotherapy Benefit

**MSI-Low Stomach Cancer**

**MSI-High Stomach Cancer**

Megabase of DNA

= Mutation

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<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>MSI - High Response</th>
<th>MSI-Low Response</th>
<th>DOR</th>
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<tbody>
<tr>
<td>KN-059</td>
<td>Pembro</td>
<td>57%</td>
<td>9%</td>
<td>NR vs 8.4</td>
</tr>
<tr>
<td>Nature Med</td>
<td>Pembro</td>
<td>86%</td>
<td>~17%</td>
<td>-</td>
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<tr>
<td>KN-061</td>
<td>Pembro</td>
<td>47%</td>
<td>&lt;20%</td>
<td>NR vs -</td>
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</table>

- Biomarker testing linked to drug access
- Biomarker able to identify subgroup (3-5%) of stage IV gastric cancer patients more likely to benefit from immune therapy
- Standard testing from protein or PCR sequencing
- Can also be tested from blood or by broader genomic profiling
Immunotherapy Effective Across Treatment Lines in MSI-H

- MSI-H or dMMR is strongly associated with improved outcomes with immune checkpoint inhibitor therapy
- Activity is independent of the line of therapy
- Stomach cancer patients NEED to know this about their cancer
MSI Testing Needs to Be Considered Earlier

- Patients with locoregional disease who are MSI-High have longer disease-free duration than patients who are MSS/MSI-low

- Patients with MSI-H tumors may not get any benefit, and could be harmed, with our standard chemotherapy-based approaches

- Anywhere from 8-20% of non-metastatic gastric cancers are reported to be MSI-H
A Word on PD-L1

- Tumor cells have evolved ways to avoid being killed by our immune system
- One common way is using a stop signal called PD-L1

- Tested from a biopsy sample
- A protein test that is widely available
- Between 50-75% of stomach cancers test positive
- Degree of positive may be related to chance of benefit
- Positive test linked to drug access in stomach, GEJ and esophageal cancer in the US
- Result may change over time, sometimes need to consider repeat biopsy
Heterogeneity and Biomarker Testing

Nature 2014;512:143-144
Biomarker Changes May Impact Treatment Outcomes

- HER2 testing results vary in time and space
- HER2 positive tumors can evolve over time
- We should consider repeat biopsy and testing in patients who progress, especially on targeted therapies

Makiyama et al., phase II T-ACT trial, ASCO 2018

Janjigian YY et al., Cancer Discovery 2017
PART III: EMERGING TARGETS

- EGFR inhibitors
- Cyclin-dependent kinase inhibitors
- Immune activating anti-CTLA4 mAb
- Telomerase Inhibitors
- Selective anti-inflammatory drugs
- PARP inhibitors
- Proapoptotic BH3 mimetics
- Inhibitors of VEGF signaling
- Inhibitors of HGF/c-Met
- Aerobic glycolysis inhibitors
- Sustaining proliferative signaling
- Evading growth suppressors
- Avoiding immune destruction
- Enabling replicative immortality
- Tumor-promoting inflammation
- Resisting cell death
- Deregulating cellular energetics
- Genome instability & mutation
- Inducing angiogenesis
- Activating invasion & metastasis
Emerging Targets and Biomarkers

- EBV
- FGFR2
- CLDN18.2
- Revisiting HER2
EBV: Connecting a Virus to Some Stomach Cancers

• One of the most common human viruses, majority are infected at some point
• Up to 8-11% of stomach cancers are associated with EBV
• Relatively straightforward testing available in many pathology labs
• Associated with increased response to immune therapies

All the EBV+ Responded
FGFR2: A Target with a Mixed Record

- FGFR2b is overexpressed in up to 30% of non-HER2+ gastroesophageal cancers

- Bemarituzumab is a non-chemo antibody that blocks FGFR2b on cancer cells

- Recent positive phase II data in combination with 1L FOLFOX chemo

- Not yet captured with standard testing, but FGFR2 amplification is

Catenacci et al., JCO 2020
CLDN18.2: Targeting the Ties that Bind

- Claudin 18.2 (CLDN18.2) protein involved in holding cells closely together
- Overexpressed (>= 75%) in roughly 1/3 patients
- Need to be tested through clinical trial, not standard testing
- Targeted by non-chemo antibody, Zolbetuximab
- Being studied in phase III with chemotherapy (SPOTLIGHT trial)
Revisiting HER2: Never Settle

**DS-8201**

*Proprietary Drug-Linker*

**Conjugation chemistry**
The linker is connected to cysteine residue of the antibody

**Proprietary Payload (DXd)**

**DX-8951 derivative**

**Margetuximab**

*Non-Fc Optimized Killing*

*Fc Optimized Killing*

**Markedly Increased Killing of Tumors**

Source: Macrogenics

**Margetuximab + Pembrolizumab after trastuzumab**

**Efficacy Results in Gastric Cancer Population by Biomarker Expression**

<table>
<thead>
<tr>
<th>Biomarker Expression</th>
<th>n</th>
<th>ORR (%)</th>
<th>DCR (%)</th>
<th>mRFS</th>
<th>mOS</th>
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<tr>
<td>Total</td>
<td>61</td>
<td>29.5%</td>
<td>65.6%</td>
<td>5.07</td>
<td>14.62</td>
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<tr>
<td>HIC3+</td>
<td>55</td>
<td>32.7%</td>
<td>69.1%</td>
<td>4.70</td>
<td>12.48</td>
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<tr>
<td>ERBB2**</td>
<td>35</td>
<td>40.0%</td>
<td>77.1%</td>
<td>4.77</td>
<td>14.62</td>
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<tr>
<td>PDL1+</td>
<td>26</td>
<td>46.2%</td>
<td>80.8%</td>
<td>4.14</td>
<td>6.74</td>
</tr>
<tr>
<td>HIC3+/PDL1++</td>
<td>22</td>
<td>52.2%</td>
<td>82.6%</td>
<td>4.14</td>
<td>6.74</td>
</tr>
</tbody>
</table>

**Prior attempts to continue HER2 targeting have failed**

**Both DS-8201a (Enhertu) is now approved in Japan, review in US**

**Margetuximab being studied with immunotherapy and chemotherapy**

**Highlights importance of biomarker selection, and repeat testing after trastuzumab**

**Patients on trastuzumab should explore options and care teams plan for future lines**

Source: Daichi-Saiko

Lancet Oncol 2019;20:827-836

ASCO GI 2019, Abstr #65
The Future – Serial Testing to Capture Tumor Changes and Adapt Treatment

**Biologically Uninformed – Still Standard/Common**

- Diagnosis Stage IV, Her2-, MSS, PD-L1-No
- Further testing

**Chemo #1 (1L)**

- Chemo stopped working, how to decide?

**Chemo #2 (2L)**

- Chemo stopped working, how to decide?

**Overall Survival**

**Biologically Informed – Here and hopefully more to come**

- Diagnosis Stage IV, Extended Molecular Testing, ctDNA, immune profiling?

**Chemo/Targeted/Immuno #1 (1L)**

- Treatment stopped working. Look at DNA again (blood, tissue) to help guide therapy

**Chemo/Target/Immuno #2 (2L)**

- Treatment stopped working. Look at DNA again (blood, tissue) to help guide therapy

**Chemo/Target/Immuno #3 (3L)**

- Treatment stopped working. Look at DNA again (blood, tissue) to help guide therapy

**Overall Survival**
1. You need to know your tumor

2. You need to know your tumor

3. Biomarkers testing can be done from biopsy, blood, or both, discuss with your care team

4. Standard biomarker testing in advanced disease is HER2, MSI/MMR, and PD-L1 at the minimum

5. All advanced patients should discuss more extended testing (my opinion)

6. Repeat biomarker testing should be a discussion at key treatment decision time points. People and tumors can change

7. Clinical trials and collaborative research are the mechanisms to improve survival
Where to Learn More

• Your care team, each other. Ask the questions

• Debbie’s Dream Foundation – and other events like this

• NCCN – excellent patient guide, available in Spanish, Korean, Russian, Japanese, Italian, Mandarin

• Count Me In Project – excellent opportunity to participate in research, free at https://escproject.org/home

• Andrea Eidelman (DDF CEO) – here is her cell, 954-STO-MACH
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