The HER2 Pathway in GI Cancer

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Disclosures

• Participation in advisory board for Amgen, Bayer and Sanofi
RTK/RAS Pathway Alterations in Solid Tumors

STES: stomach and esophageal cancer
CRC: colorectal carcinoma
LIHC: liver hepatocellular carcinoma
CHOL: cholangiocarcinoma
PAAD: pancreatic ductal adenocarcinoma
CIN: chromosomal instability
GS: genomically stable

Sanchez-Vega et al. Cell 2018
The epidermal growth factor receptor (EGFR)/HER family of transmembrane type I receptor associated tyrosine kinases are enzymes that play an important role in fundamental processes like cell proliferation, differentiation, and survival.

The ectodomains of HER1, HER3, and HER4 interact with specific sets of ligands, whereas no natural ligand has been identified thus far for HER2.

However, HER2 can be activated by heterodimerization with other ligand-activated HER co-receptors.
HER family alterations within the RTK-RAS pathway

Sanchez-Vega et al. Cell 2018
HER2 alterations in GI cancers

Sanchez-Vega et al. Cell 2018
HER2 kinase inhibition in HER2-mutant cancers

Combining neratinib with another HER2-targeted therapy is a rational next step, and SUMMIT has been amended to evaluate this approach in multiple HER2-mutant tumour types.
ERBB2 alterations in gastric cancer: distribution according to molecular subtypes

HER2-targeted therapy in gastric cancer

<table>
<thead>
<tr>
<th>Trial/Phase</th>
<th>Setting</th>
<th>Patient selection</th>
<th>Agents</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ToGA Phase 3</td>
<td>1st</td>
<td>IHC 3+ or FISH+</td>
<td>Fluoropyrimidine/cisplatin +/- Trastuzumab</td>
<td>FDA Approval in 2010</td>
</tr>
<tr>
<td>TRIO-013/LOGiC Phase 3</td>
<td>1st</td>
<td>IHC 2+ and FISH+ or IHC 3+ and FISH+</td>
<td>Capecitabine/oxaliplatin +/- lapatinib</td>
<td>No improvement in OS</td>
</tr>
<tr>
<td>JACOB Phase 3</td>
<td>1st</td>
<td>IHC 3+ or IHC 2+ and ISH+</td>
<td>Pertuzumab + trastuzumab and chemotherapy vs trastuzumab and chemotherapy</td>
<td>No improvement in OS</td>
</tr>
<tr>
<td>TyTan Phase 3</td>
<td>2nd</td>
<td>FISH+</td>
<td>Paclitaxel +/- lapatinib</td>
<td>No improvement in OS</td>
</tr>
<tr>
<td>GATSBY Phase 2/3</td>
<td>2nd</td>
<td>IHC 3+ or IHC 2+ and ISH+</td>
<td>T-DM1 vs Taxane</td>
<td>No improvement in OS</td>
</tr>
</tbody>
</table>
Challenges of patients selection in HER2+ gastric cancer

• The degree of IHC expression and of gene dosage are relevant. In patients with an IHC ≤2+, further selection according to the degree of amplification has been suggested

• Intratumoral heterogeneous amplification of ERBB2 and subclonal genetic diversity has been shown to occur in gastric cancers

• HER2 status might change after HER2 inhibition, with loss of HER2 occurring in up to 61% of patients at re-biopsy (++) for HER2 2+) and this might explain failure of HER2-targeting sequential approaches

• 30% of HER2+ tumors lack ERBB2 ampl by NGS or have co-mutations in the RTK-RAS-PIK3CA pathway conferring resistance
HER2 alterations in colorectal cancer

Dienstmann et al. Nature Review Cancer 2017

Distribution of ERBB2 alterations in CRC

- **8887 CRC** (colonic 85.5% and rectal 14.5%) evaluated by comprehensive genomic profiling for genomic alterations in 315 cancer-related genes,

- **569 mCRCs** were positive for ERBB2 (429 cases; 4.8%) and/or ERBB3 (148 cases; 1.7%) and featured ERBB amplification, short variant alterations, or a combination of the 2.

- In the HERACLES-A study, **48/914 (5%)** patients with KRAS ex2 WT harbored ampl/overexpression

Ross JS et al, Cancer 2018
The genetic context of HER2 alterations in CRC

**KRAS co-existence with HER2 mut/amp**

- **KRAS mutations** are underrepresented in ERBB2-amplified tumors (17% in ampl only) compared with wild-type CRC, while there is no difference in ERBB2 mutant.

**MSI co-existence with HER2 mut/amp**

- Microsatellite instability (MSI) is associated with ERBB2 mutations (odds ratio [OR] = 5.98 as compared to WT), while this is not the case for ERBB2 amplification.

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Ross JS et al, *Cancer* 2018

Loree et al, *JNCI* 2018

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<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nurses’ Health Study/ Health Professionals Follow-Up Study</th>
<th>MD Anderson cohort</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>ERBB2 WT</td>
<td>ERBB2 MT</td>
</tr>
<tr>
<td><strong>MSI status, No. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>423 (84.6)</td>
<td>15 (51.7)</td>
</tr>
<tr>
<td>Unstable</td>
<td>77 (15.4)</td>
<td>14 (48.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>83</td>
<td>7</td>
</tr>
<tr>
<td><strong>Molecular phenotype, No. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP53 mutant</td>
<td>293 (50.3)</td>
<td>11 (30.6)</td>
</tr>
<tr>
<td>APC mutant</td>
<td>333 (57.1)</td>
<td>13 (50.0)</td>
</tr>
<tr>
<td>KRAS mutant</td>
<td>166 (28.7)</td>
<td>9 (28.6)</td>
</tr>
<tr>
<td>NRAS mutant</td>
<td>24 (4.1)</td>
<td>3 (8.9)</td>
</tr>
<tr>
<td>BRAF mutant</td>
<td>116 (19.9)</td>
<td>10 (27.8)</td>
</tr>
<tr>
<td>PIK3CA mutant</td>
<td>117 (20.1)</td>
<td>13 (36.1)</td>
</tr>
</tbody>
</table>

Loree et al, *JNCI* 2018
Clinicopathological characteristics of HER2-positive mCRC

- **N=100 HER2-positive mCRCs**
- **HERACLES diagnostic criteria applied**: (IHC 3+ or 2+ in ≥50% of cells, confirmed by FISH)
- **116 consecutive HER2-negative patients selected as controls**
- **HER2-positive patients who received treatment with anti-EGFR agents showed poorer outcome** (objective response rate, 31.2% vs. 46.9%, p = .031; progression-free survival, 5.7 months vs. 7 months, p = .087).
HER2 amplification is a driver of resistance to cetuximab in mCRC patient-derived xenografts

Bertotti A et al, *Cancer Discovery* 2011
Anti-HER2 preclinical trials in HER2+ mCRC PDXs

HER2+ mCRC-PDXs are sensitive to dual HER2-blockade with lapatinib + trastuzumab but not with either drug alone.

These findings prompted the HERACLES trials series. 

Bertotti A et al, Cancer Discovery 2011
A consensus driven diagnostic algorithm for ‘HER2 positivity’ in mCRC was previously built on 348 tumor colon samples. The algorithm involves IHC and FISH staining, and is based on the following main features in CRC:

- IHC U-shaped as in gastric
- Good correlation IHC-ISH
- Cellularity of amplification quite homogeneous
- Low intra-sample heterogeneity

**Main features in CRC:**

**BREAST**
- IHC 3+
- IHC 2+ and ISH amplification
- In ≥ 10% tumor cells

**GASTRIC**
- IHC 3+
- IHC 2+ and ISH amplification
- In ≥ 10% tumor cells

**COLORECTAL**
- IHC 3+
- IHC 2+ and ISH amplification
- In ≥ 50% tumor cells

HER2-targeted therapy in mCRC: HERACLES-A

Complete response 1 (4%, 0 to 11)
Partial response 7 (26%, 9 to 43)
Objective response 8 (30%, 14 to 50)
Disease control† 16 (59%, 39 to 78)
Duration of response (weeks) 38 (24 to 94+)

PFS according to HER2 GCN
≥9.45
<9.45

HER2-targeted therapy in mCRC: MyPathway

- 57 HER2-amplified mCRCs treated with trastuzumab + pertuzumab
  ORR = 32%

Patient selection:
- FISH or CISH + (HER2/Ch17 > 2 or HER2 GCN > 6)
- NGS: HER2 amplification based on copy number gain
- IHC 3+

Meric-Bernstam F et al, Lancet Oncol 2019
HER2-targeted therapy in mCRC: NCCN Guidelines

CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE*  

SUBSEQUENT THERAPY  

FOLFOX® or irinotecan®  

or  

FOLFIRI® or (bevacizumab® [preferred] or ziv-afibercept® or ramucirumab®)  

or  

Irinotecan® or (bevacizumab® [preferred] or ziv-afibercept® or ramucirumab®)  

or  

FOLFIRI® + (cetuximab® or panitumumab®) (KRAS/NRAS/BRAF WT only)  

or  

Irinotecan® + (cetuximab® or panitumumab®) (KRAS/NRAS/BRAF WT only)  

or  

Irinotecan® + (cetuximab® or panitumumab®)  

or  

Dabrafenib® + trametinib® (BRAF V600E mutation positive)  

or  

Encorafenib® + binimetinib® (cetuximab® or panitumumab®) (BRAF V600E mutation positive)  

or  

([Nivolumab ± ipilimumab] or pembrolizumab®) (dMMR/MSI-H only)  

or  

(Trastuzumab + [pertuzumab or lapatinib]) (HER2-amplified and RAS wild-type) (category 2B)  

See Subsequent therapy  

Regorafenib®  

or  

Trifluoridine + tipiracil®  

or  

Best supportive care

Previous oxaliplatin-based therapy without irinotecan

1 Larotrectinib is a treatment option for patients with metastatic colorectal cancer that is NTRK gene fusion positive.
Liquid biopsy for monitoring treatment with HER2-targeted therapy in mCRC

- Alterations in **RAS/RAF** at baseline:
  ✓ 6/7 (86%) refractory patients
  ✓ 3/22 (14%) cases with clinical benefit
- At secondary resistance: emerging **KRAS** mutant clones and **BRAF** amplification were identified at progression in two SD patients and one PR case,
  Other alterations detected at progression:
  ✓ **ERBB2** p.L755S and p.V777L,
  ✓ **EGFR**,
  ✓ **PIK3CA**
  ✓ **PTEN**
Patient signed IC for DONUM, a warm autopsy protocol (NCT03385980) that enables rapid processing of postmortem tissue samples.
Molecular heterogeneity of individual metastatic deposits explains differential response

Siravegna et al., Cancer Cell 2018

Complex integration of longitudinal tracking of individual metastasis in ctDNA
HER2-targeted therapy in BTC

MyPathway

MDACC cohort (Javle et al, 2015)

A patient with FGF3-TACC3 fusion previously treated with the FGFR-directed agents pazopanib and dovitinib developed HER2 amplification as a secondary event. He was treated with trastuzumab with SD and CA19-9 response.
HER-2 targeted therapeutic strategies: future avenues

Modified from Meric-Bernstam F et al, Clin Cancer Res 2019
Trastuzumab deruxtecan (DS-8201a)

**DS-8201a Structure and Mechanism of Action (MoA)**
- Propriety drug-linker and payload
- Cysteine residue
- Drug-Linker
- Conjugation chemistry
- The linker is connected to the cysteine residue of the antibody

**Payload (Dxd)**
- Exatecan derivative

**Efficacy Outcomes with DS-8201a in HER2-expressing Solid Tumors in the Ongoing Phase 1 Trial (April, 2018 cutoff)**

<table>
<thead>
<tr>
<th></th>
<th>Confirmed ORR*</th>
<th>Confirmed DCR* (95% CI)*</th>
<th>PFS Median (95% CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2+ breast cancer</td>
<td>54.5% (54/99)</td>
<td>93.9% (93/99)</td>
<td>NR</td>
</tr>
<tr>
<td>HER2+ gastric cancer</td>
<td>43.2% (19/44)</td>
<td>79.5% (35/44)</td>
<td>5.6 (3.0, 8.3)</td>
</tr>
<tr>
<td>Other HER2- expressing/mutated</td>
<td>38.7% (12/31)</td>
<td>83.9% (26/31)</td>
<td>12.1 (2.7, 14.1)</td>
</tr>
</tbody>
</table>

*Subjects who had ≥2 postbaseline scans, had progressive disease, or discontinued treatment for progressive disease or any other reason prior to second postbaseline scan.

**Study Design**
- **Cohort A**
  - HER2-positive mCRC
  - (IHC 3+ or IHC 2+/ISH+)
  - DS-8201a 6.4 mg/kg q3wk n=50
- **Cohort B**
  - HER2-expressing mCRC
  - (IHC 2+/ISH-)
  - DS-8201a 6.4 mg/kg q3wk n=20
- **Cohort C**
  - HER2-expressing mCRC
  - (IHC 1+)
  - DS-8201a 6.4 mg/kg q3wk n=20

**Primary Endpoint**
- ORR (proportion who achieved a best overall response of CR or PR) assessed by the independent radiologic facility review based on RECIST version 1.1 in Cohort A

**Secondary Efficacy Endpoints**
- OS
- PFS
- DCR
- DoR
- ORR based on RECIST version 1.1 in Cohorts B and C
- ORR assessed by the investigator based on RECIST version 1.1

**Study Details**
- *T Yoshino et al. ESMO-GI 2018 #P-295.*
Conclusions

- HER2 is a well known oncogenic target in GI cancers and the therapeutic actionability of gene amplification has been demonstrated for standard of care in gastric cancer and recently emerged as an option for colorectal cancer.
  ✓ In colorectal cancer, dual blockade with trastuzumab + either lapatinib or pertuzumab gives rise to significant RR and PFS. In biliary tract tumors, promising results have been obtained.
  ✓ The extent of benefit of HER2 inhibition can be different according to the degree of HER2 amplification. Molecular heterogeneity of individual metastatic deposits explains differential response and resistance. Lack of HER2 expression can occur.
  ✓ Plasma determination of ERBB2 copy number is a promising companion tool
- HER2 mutations are actionable therapeutic targets also in GI tumors, although clinical actionability may vary across histologies according to the type of mutations and the context of the tissue of origin. Dual HER2 blockade might provide better results.