New agents on the horizon in gastric cancer

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Outline

• Molecular characterization of gastric cancer
• Beyond HER-2 inhibition
• FGFR pathway
• PI3K/mTOR pathway
• Immune activating agents
• Cancer Stem Cells
Acquired capacities of cancer: phenotype

Hanahan & Weinberg, Cell 2011
Gastric Cancer is a heterogeneous disease

- **Location**
  - GEJ vs Cardia vs Antrum

- **Ethnicity**
  - East vs West

- **Etiology/epidemiology**
  - Sporadic (90%)
  - Familial aggregation (10%)
  - Hereditary (1%)

- **Histology**
  - Intestinal vs Poorly Cohesive

Molecular characterization of GC

A

B

C


=72/193 (37.3%)
Molecular characterization of GC

TCGA. Nature 2014
Molecular characterization of GC

PD-L1 / CD274

PD-L2 / PDCD1LG2

mRNA expression (RNA Seq RPKM)/(log2)

CIN  EBV  GS  MSI

Molecular Subtype

mRNA expression (RNA Seq RPKM)/(log2)

CIN  EBV  GS  MSI

Molecular Subtype

TCGA. Nature 2014
Beyond HER2 inhibition
HER3 and gastric cancer

- HER3 has been associated with tumor resistance to therapeutic agents targeting EGFR or HER2 in NSCLC and breast cancer

- HER3 has been identified as a potential therapeutic target in breast cancer and NSCLC, and currently its potential role as a potential mechanism of resistance of EGFR/HER2 inhibitors is being evaluated

1Baselga & Swain, Nature Rev Cancer 2009
2Kruser et al, ExpCell Res 2010
MoAbs targeting HER-3

- U3-1287 - AMG888 (phase I NCT00730470)
- MM-121 (phase I NCT00734305)
- LJM716 (phase I NCT01598077)
- MEHD7945A, dual EGFR & HER3 MoAb (phase I NCT01207323)
- MCLA128, dual HER2 & HER3 MoAb (phase I study with expansion cohorts)
FGFR pathway
## Targeting FGFR Clinical studies

<table>
<thead>
<tr>
<th>Treatment arms</th>
<th>Setting</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01457846</td>
<td>AZD4547 vs paclitaxel</td>
<td>2nd-line</td>
</tr>
<tr>
<td>NCT01719549</td>
<td>Dovitinib (TKI258)</td>
<td>2nd, 3rd-line</td>
</tr>
<tr>
<td>NCT01921673</td>
<td>Dovitinib + docetaxel</td>
<td>2nd-line</td>
</tr>
</tbody>
</table>

Targeting FGFR Pathway in GC
AZD4547: SHINE RP2 study

- **Primary endpoint**: PFS

- **FGFR2** amplified or polysomy, patients selected by FISH

- **PFS (Primary end-point)**: No differences
PI3K/mTOR pathway
Targeting PI3K/mTOR

• PI3K/mTOR pathway: Important regulator of cell growth, survival, proliferation, angiogenesis, and metabolism

• 50% to 60% of gastric cancers demonstrate dysregulation of the pathway

• mTOR inhibitors demonstrated preclinical and early clinical efficacy in gastric cancer

Xu DZ, et al. BMC Cancer 2010
Targeting PI3K/mTOR Pathway in GC
Everolimus: GRANITE-1 phase III study

GC
After failure to first-line or second-line chemotherapy (n=633)

R
2:1

Everolimus 10 mg/day + BSC (n = 439)
Placebo + BSC (n = 217)

No patient selection based on PI3K/mTOR status

Primary endpoint: OS

A

Probability of Overall Survival (%)

Kaplan-Meier medians
Everolimus: 5.4 months
Placebo: 4.3 months
Hazard ratio: 0.90 (95% CI, 0.75 to 1.08)
Log-rank P = .124

B

Probability of Progression-Free Survival (%)

Kaplan-Meier medians
Everolimus: 1.7 months
Placebo: 1.4 months
Hazard ratio: 0.66 (95% CI, 0.56 to 0.78)
Log-rank P < .001

**Primary Objective:** Progression-free survival (PFS) in all patients (ITT) and PFS in patients with PTEN low tumors

**Secondary Objectives (ITT and PTEN low):** Overall survival (OS); Objective response rate (ORR); Duration of OR

**Secondary Objectives (ITT):** Safety and Pharmacokinetics (PK)
Immune activating agents
Cancer-immunity cycle

- **Primed and activation**
  - Anti-PD1
  - Anti-PDL1
  - Anti-CTLA-4
  - Anti-CD137 (agonist)
  - Anti-OX40 (agonist)
  - Anti-CD27 (agonist)
  - IL-2
  - IL-12

- **Cancer antigen presentation**
  - Vaccines
  - IFN-α
  - GM-CSF
  - Anti-CD40 (agonist)
  - TLR agonist

- **Release of cancer cell antigens**
  - Chemotherapy
  - Radiation therapy
  - Targeted therapy

- ** Trafficking of T cells to tumours**

- **Infiltration of T cells into tumours**
  - Anti-VEGF

- **Recognition of cancer cells by T cells**
  - CARs

- **Killing of cancer cells**
  - Anti-PDL1
  - Anti-PD1
  - IDO inhibitors

- **Tumour**
- **Blood vessel**
- **Lymph node**
• PD-1 is a negative co-stimulatory receptor expressed primarily on activated T cells

• Binding of PD-1 to its ligands PD-L1 and PD-L2 inhibits effector T-cell function

• Expression of PD-L1 on tumor cells and macrophages can suppress immune surveillance and permit neoplastic growth

• Anti-PD-1/PD-L1 antibodies have demonstrated clinical activity in multiple tumor types
**KEYNOTE-012: Gastric Cancer Cohort**

**Patients**
- Recurrent or metastatic adenocarcinoma of the stomach or GEJ
- ECOG PS 0-1
- PD-L1–positive tumor
- No active brain metastases

**Screening:** 65 of 162 (40%) patients assessed for PD-L1 expression had PD-L1-positive tumors

**Patients:** 19 patients from Asia and 20 patients from the rest of the world

**Treatment:** 10 mg/kg IV Q2W

**Response assessment:** Performed every 8 weeks per RECIST v1.1 by central radiology review

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**Assessed in archival tumor samples using a prototype IHC assay (22C3 antibody). Positivity defined as PD-L1 staining in stroma or e1% of tumor cells.**
KEYNOTE-012: Gastric Cancer Cohort

Maximum Change

53.1% of patients experienced a decrease from baseline

OS

Overall Survival, %

Time, months

n at risk

Asia 17 15 12 11 10 8 1 0 0
ROW 19 16 13 11 8 7 6 5 0

- Total population
  - 6-month OS rate: 66%
  - Median OS: 11.4 months (95% CI, 5.7-NR)

Only patients with measurable disease per RECIST v1.1 by central review at baseline and at least 1 post-baseline tumor assessment were included (n = 32). Analysis cut-off date: March 23, 2015.
# Immune Checkpoint Inhibitors in GC

<table>
<thead>
<tr>
<th>Target</th>
<th>Drug</th>
<th>Clinical Trial</th>
<th>N</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-1</td>
<td>Pembrolizumab MK3475 \textit{KEYNOTE-012} \textsuperscript{1}</td>
<td>Ph I</td>
<td>39</td>
<td>ORR 33.3% (inv), 22.2% (central review) DCR 36% Durable response (40w)</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td>Ongoing Trials: KEYNOTE-062 (Pembro vs paclitaxel 2nd L), KEYNOTE-061 (Pembro vs CIS/FU +/- Pembro 1st L), KEYNOTE-059 (Pembro 3rd L), Ph I/II Nivolumab +/- ipilimumab, Ph I Pembro + ramucirumab, Ph I Nivolumab (EBV+).</td>
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<tr>
<td>PD-L1</td>
<td>MEDI47361 \textsuperscript{2}</td>
<td>Ph I</td>
<td>26</td>
<td>ORR 7% 12w DCR 25%</td>
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<tr>
<td></td>
<td>MPDL3280A1 \textsuperscript{3}</td>
<td>Ph I</td>
<td>1</td>
<td>PR (9.8 months on study)</td>
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<tr>
<td></td>
<td>Avelumab \textsuperscript{4}</td>
<td>Ph I, Japanese pts</td>
<td>20</td>
<td>ORR 15% DCR 65%, 12w PFS rate 43.3%</td>
</tr>
<tr>
<td></td>
<td>Ongoing Trials: Ph Ib/II MEDI47361 + tremelimumab (2\textsuperscript{nd} L), Avelumab (3\textsuperscript{rd} L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTLA-4</td>
<td>Tremelimumab \textsuperscript{5}</td>
<td>Ph I</td>
<td>18</td>
<td>DCR 22% 1 pt &gt; 30 months</td>
</tr>
<tr>
<td></td>
<td>Maintenance Ipilimumab</td>
<td>Ph II, completed</td>
<td>114</td>
<td>\textit{Not yet presented}</td>
</tr>
</tbody>
</table>

Cancer stem-cells
Cancer Stem Cells

Cancer Stem Cells (CSC)
- Highly tumorigenic
- Fundamentally responsible for continued malignant growth
- Initiators (seeds) of metastasis
- Resistant to chemo and current targeted therapies

Hanahan & Weinberg, Cell 2011
Targeting Cancer Stem Cells in GC
BBI-608 (Stat 3 inh): BRIGHTER Phase III study

GC
After failure to first-line chemotherapy
(n=680)

R 1:1

BBI608 480 mg/bid +
Paclitaxel 80 mg/m² iv d1,8,15
(n = 340)

Placebo bid +
Paclitaxel 80 mg/m² iv d1,8,15
(n = 340)

NCT02178956

→ Primary endpoint: OS
Acknowledgements

- Maria Alsina, MD

Thank you