New agents on the horizon in gastric cancer

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Germany
Conflicts of Interest

1. Employment or leadership position
   • none

2. Advisory role
   • Amgen, Biontech, Boston Biomedical, Ganymed, Lilly, MSD, Nordic, Roche, Taiho

3. Stock ownership
   • non

4. Patents
   • non

5. Speaker honoraria
   • Amgen, Celgene, Roche, Lilly

6. Financial research support
   • Böhringer-Ingelheim, GSK, Fresenius Biotech,

7. Others
   none

8. Immaterial COIs
   none
Hot Topics

- Immunotherapy
  - Immune Checkpoint Inhibitors
  - Anti-Claudin 18.2: IMAB361

- Stem cell inhibition
  - Anti-Stat3: BBI-608

- Modifiers of Inflammatory Microenvorinment
  - Anti-Matrix-Metallo-Proteinase-9: GS-5745
Figure 2. T-cell Activation in Tumor Milieu.

A Suppression of T-Cell Activation by Tumor

B Activation of T Cell by Antibody Blockade of PD-1 Signaling

Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial


Keynote-012 (n=39)
Decrease in target lesions 53%
Objective response 23%

Pembrolizumab - anti-PD1 mAB

### Tumour proportion score

<table>
<thead>
<tr>
<th>Score</th>
<th>Responses/Total (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7/29 (24%)</td>
</tr>
<tr>
<td>1–49</td>
<td>0/3 (0%)</td>
</tr>
<tr>
<td>50–100</td>
<td>1/3 (33%)</td>
</tr>
<tr>
<td>Total</td>
<td>8/35 (23%)</td>
</tr>
</tbody>
</table>

Data are number of overall responses/number of patients (%). PD-L1 expression was calculated with the clinical trial assay. All tumours were PD-L1 positive in the prototype assay. No complete responses were achieved.

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**Table 4: Responses by PD-L1 expression**

Response Biomarker - Gene Expression?

Immune Checkpoints – Anti-PD1 & Anti-CTLA4

Immune Checkpoints – Anti-PD1 & Anti-CTLA4

Patients with Stage IV G/E/GEJ\textsuperscript{a}
N = 160

- Nivolumab 3 mg/kg IV Q2W
  n = 59
- Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg IV Q3W for four cycles\textsuperscript{b}
  n = 49
- Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg IV Q3W for four cycles\textsuperscript{b}
  n = 52

**Primary Endpoint\textsuperscript{c}**
- Objective response rate (ORR) by RECIST 1.1

**Secondary Endpoints**
- Treatment-related adverse events
- Overall survival (OS)
- Progression-free survival (PFS)
- Duration of response

**Exploratory Endpoints**
- PK/PD/Immunogenicity
- Biomarkers (PD-L1 by Dako, MSI)

**Inclusion Criteria**
- PD-L1 expression status was not mandated for inclusion
- Advanced gastric, GEJ, adenocarcinoma of the esophagus
- RECIST v1.1 measurable disease
- Progression on at least 1 prior chemotherapy
- ECOG PS of 0 or 1
- No autoimmune disease or immune therapy

\textsuperscript{c}Cohorts were enrolled sequentially in the order shown. Patients were treated until disease progression or unacceptable toxicity

\textsuperscript{b}Followed by nivolumab 3 mg/kg IV Q2W

\textsuperscript{a}Follow-up continued until disease progression and/or resolution of AEs, after which they were followed every 3 months for survival. Follow-up time ranged from 5–24 months.

\textsuperscript{E}esophageal; \textsuperscript{G}gastric; \textsuperscript{GEJ}gastroesophageal junction; \textsuperscript{IV}intravenous; \textsuperscript{PD}pharmacodynamic; \textsuperscript{PK}pharmacokinetic; \textsuperscript{PS}performance status; \textsuperscript{Q2W}every 2 weeks; \textsuperscript{Q3W}every 3 weeks; \textsuperscript{RECIST}Response Evaluation Criteria in Solid Tumors

Janjigian Y, et al. ASCO 2016; [4010]
Immune Checkpoints – Anti-PD1 & Anti-CTLA4

Figure 2. Best reduction in target lesion size

A
Nivolumab 3 mg/kg

B
Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg

C
Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg

Best Reduction From Baseline in Target Lesion (%)

Patients

* = confirmed response □ = % change truncated to 100%

Janjigian Y, et al. ASCO 2016; [4010]
## Table 5. ORR by PD-L1 status

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab 3 mg/kg (n = 59)</th>
<th>Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg (n = 49)</th>
<th>Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1%, n (%)</td>
<td>4/15 (27) [8, 55]</td>
<td>4/9 (44) [14, 79]</td>
<td>3/11 (27) [6, 61]</td>
</tr>
<tr>
<td>&lt; 1%, n (%)</td>
<td>3/25 (12) [3, 31]</td>
<td>6/29 (21) [8, 40]</td>
<td>0/27 (0) [0, 13]</td>
</tr>
<tr>
<td>≥ 5%, n (%)</td>
<td>2/6 (33) [4, 78]</td>
<td>0/1 (0) [0, 98]</td>
<td>1/4 (25) [1, 81]</td>
</tr>
<tr>
<td>&lt; 5%, n (%)</td>
<td>5/34 (15) [5, 31]</td>
<td>10/37 (27) [14, 44]</td>
<td>2/34 (6) [1, 20]</td>
</tr>
</tbody>
</table>

CI = confidence interval

- Up to 44% of patients with PD-L1+ tumors responded to nivolumab 1 mg/kg + ipilimumab 3 mg/kg

Janjigian Y, et al. ASCO 2016; [4010]
### Immune Checkpoints – Anti-PD1 & Anti-CTLA4

Table 2. TRAEs occurring in ≥ 10% of patients

<table>
<thead>
<tr>
<th>Event</th>
<th>Nivolumab 3 mg/kg (n = 59)</th>
<th>Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg (n = 49)</th>
<th>Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade, n (%)</td>
<td>Grade 3–4, n (%)</td>
<td>Any grade, n (%)</td>
</tr>
<tr>
<td>Any event</td>
<td>41 (70)</td>
<td>10 (17)</td>
<td>41 (84)</td>
</tr>
</tbody>
</table>

Janjigian Y, et al. ASCO 2016; [4010]
Immune Checkpoints – Anti-PD1 & Anti-CTLA4

Patient 1st: Nivolumab 3 mg/kg, complete response in patient durable at 14 months

Baseline

4 weeks

8 weeks

MLH1: staining absent in tumor
PMS2: staining absent in tumor

Somatic Mutations Specific to Tumor

1. KRAS (NM_033360) exon2 p.G13D (c.38G>A)
2. TP53 (NM_000540) exon8 p.R273H
3. AKT1 exon8 p.G232R
4. ALK exon3 p.C272W
5. ARID1A exon15 p.R1276
6. ARID1A exon20 p.D1850fs
7. ATR exon39 p.R2190C
8. ATRX exon12 p.R1342W
9. CREBBP exon25 p.P1423fs
10. EPAT3 exon5 p.A427V
11. ERCC4 exon6 p.M361fs
12. GLI1 exon12 p.P679H
13. IRS1 exon1 p.G1127fs
14. JAK1 exon16 p.V746A
15. KDM5C exon20 p.K996T
16. LATS2 exon4 p.M608V
17. MEN1 exon10 p.R521fs
18. MLH1 exon9 splicing variant
19. MLL2 exon31 p.Q2208
20. NFKB1 exon54 p.Y2642C
21. PBRM1 exon18 splicing variant
22. PIK3R1 exon12 p.N488D
23. PMS2 exon11 p.P481H
24. PRDM1 exon6 p.L594H
25. RNF43 exon9 p.G659fs
26. SMARCA4 exon6 p.R70H
27. TBX3 exon7 p.G496fs
28. TET1 exon2 p.K22fs
29. TET2 exon3 p.T229fs
30. ZFHX3 exon2 p.E763fs
31. CTNNB1 rearrangement

Janjigian Y, et al. ASCO 2016; [4010]
Deficient Mismatch Repair

Conclusions – Checkpoint Inhibition

- Promising data on PD-1 / PD-L1 inhibition
- Objective response rates around 20-25%
- Responses of long duration are observed
- Double blockade PD-1/CTLA-4 looks even more active
- Increased side-effects with double blockade
- Selection of pts on basis of biomarkers is yet unclear
- Multiple phase-II and phase-III studies on the way
Claudin 18.2 in Gastric Cancer
Claudin-18 Splice Variant 2 Is a Pan-Cancer Target Suitable for Therapeutic Antibody Development

Ugur Sahin,1,2 Michael Koslowski,2 Karl Dhaene,3 Dirk Usener,1 Gunda Brandenburg,1 Gerhard Seitz,4 Christoph Huber,2 and Özlem Türeci1

- Member of the Claudin family
- Major structural component of tight junctions
- Broadly expressed in various cancer types
  - ~70-90% biliary duct, pancreatic, gastric, mucinous ovarian cancer
- Not expressed in any healthy tissues, except for stomach mucosa
**IMAB362 in Metastatic Gastric Cancer - FAST**

- **Chimeric IgG1 antibody**
- **Highly specific for CLDN18.2**
- **Modes of action:**
  - Antibody-dependent cellular cytotoxicity (ADCC)
  - Complement-dependent cytotoxicity (CDC)
  - In combination with chemo:
    - enhances T-cell infiltration
    - induces pro-inflammatory cytokines

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**IMAB362-coated Tumour Cell Debris**
- Pro-Inflammatory, Chemoattractant Environment
  - Cross-presentation by APCs**
  - T Cell Infiltration
  - Induction of Adaptive T cell immunity***

*ADCC* stands for Antibody-Dependent Cell-Mediated Cytotoxicity. *CDC* stands for Complement-Dependent Cytotoxicity.

**EOX:**
- Epirubicine, Oxaliplatin, Capecitabine

*Kroemer et al, 2013; Rogers, Veeramani and Weiner, 2014; Biachini and Gianni, 2014*
IMAB362 in Metastatic Gastric Cancer - FAST

Randomized Phase-II Study

CLDN18.2: centrally measured with an analytically validated, CE accredited IVD Kit

Primary endpoint: PFS - to detect a hazard ratio of 0.725 or lower
Log rank test with a 1-sided 10% significance level 70% power

Al-Batran S, et al. ASCO 2016; [4001]
IMAB362 in Metastatic Gastric Cancer - FAST

**Progression-free survival**

mPFS 4.8 vs. 7.9 mo  
HR 0.47  
P=0.0001

**Overall Survival**

mOS 8.4 vs. 13.2 mo  
HR 0.51  
P=0.0001

*based on central imaging assessment in patients with 2+/3+ CLDN18.2 staining in ≥ 40% of tumor cells (Total population)

*in patients with 2+/3+ CLDN18.2 staining in ≥ 40% of tumor cells (Total population)
Conclusions – anti-Claudin 18.2

- **IMAB362**, monoclonal AB directed against **CLDN 18.2** is an emerging drug for 1st-line Tx of metastatic gastric cancer
- **Target assessment** with Claudetect™18.2 looks robust
- PFS and OS improved
- Treatment was **feasible, but vomiting** is a critical issue
- **Validation** of FAST in **phase 3** is planned
Cancer Stem Cells

Hanahan and Weinberg, *Cell* 2011, 144: 646-677
Cancer Stem Cell Therapy

Stat3 is a Key Driver of Cancer Stemness and Immune Evasion Mechanisms

BBI608 is a small molecule that inhibits gene transcription driven by Stat3

Suppression of cancer relapse and metastasis by inhibiting cancer stemness

Youzhi Li, Harry A. Rogoff, Sarah Keates, Yuan Gao, Sylaja Murikipudi, Keith Mikule, David Leggett, Wei Li, Arthur B. Pardee, and Chiang J. Li

Boston Biomedical, Inc., Cambridge, MA 02139

Contributed by Arthur B. Pardee, December 23, 2014 (sent for review December 9, 2014; reviewed by Mikhail V. Blagosklonny and Howard Y. Chang)

Partial or even complete cancer regression can be achieved in some patients with current cancer treatments. However, such truly qualify as bona fide stem cells and how frequent these cells are, it has been demonstrated that these stemness-high malignant

Li Y et al. Proc Natl Acad Sci U S A. 2015 Feb 10;112(6):1839-44
Brighter Trial: Investigation of STAT-3 Inhibitor BBI-608 in 2\(^{nd}\)-line Gastric Cancer

**Randomize**

**1:1**

**Adult Patients with Advanced Gastric and GEJ Adenocarcinoma progressed on first line metastatic therapy**

**BBI608 orally, twice daily**

**plus**

**Paclitaxel 80 mg/m\(^2\) IV, weekly (three out of every four weeks)**

**Placebo orally, twice daily**

**plus**

**Paclitaxel 80 mg/m\(^2\) IV, weekly (three out of every four weeks)**

**Disease Progression based on RECIST or unacceptable toxicity\(^1\)**

**Death**

**Interim Analysis (OS): Test for Superiority at 2/3 of required events (380)**

**Planned sample size: 680 patients**

(340 pts on BBI608 arm and 340 pts on Placebo arm)

**Geographic Locations: N. America, S. America, Europe, Australia, Asia/Japan**

\(^1\)If no other therapies are available at the time of disease progression, and the patient has not experienced any adverse events requiring permanent discontinuation, BBI608/Placebo may be continued.

Data from Boston Biomedical
Modification of Tumor Micromilieu

Matrix Metalloproteinase-9 Inhibition

Shah M, et al. ASCO 2016; [4033]

CXCL, chemokine (C-X-C motif) ligand; IL, interleukin; MSC, mesenchymal stem cell; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.
Matrix Metalloproteinase-9 Inhibition

Antitumorigenic Effects of MMP9 Inhibition

**Orthotopic Tumor Growth**

- Vehicle
- IgG
- Tumor Anti-MMP9
- Stroma Anti-MMP9
- 5-FU

**Tumor-Associated Fibrillar Collagen**

Isotype

Anti-MMP9

*Efficacy of murine anti-MMP9 antibodies (targeting tumor- or stroma-derived MMP9) in established orthotopic colorectal cancer model; 1MMP9 inhibition associated with changes in fibrillar collagen measured by 2nd harmonic imaging microscopy; red: pan-cytokeratin; blue: nuclei; white: 2nd harmonic. IgG, immunoglobulin-G; SEM, standard error of mean; 5-FU, fluorouracil.

Shah M, et al. ASCO 2016; [4033]
Matrix Metalloproteinase-9 Inhibition

Phase IB: MMP-9 inhibitor GS-5745
800mg i.v. q2wk in combination with FOLFOX

Objective Response Rate

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Treatment Naïve n=29</th>
<th>Treatment Experienced n=11</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>3 (10)*</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>13 (45)</td>
<td>4 (36)</td>
</tr>
<tr>
<td>SD</td>
<td>3 (10)</td>
<td>3 (27)</td>
</tr>
<tr>
<td>Non-CR/non-PD</td>
<td>5 (17)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>PD</td>
<td>3 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Discontinued study before 1st tumor assessment</td>
<td>2 (7)</td>
<td>3 (27)</td>
</tr>
<tr>
<td>Best response rate, % (90% CI)</td>
<td>55 (38, 71)</td>
<td>36 (14, 65)</td>
</tr>
</tbody>
</table>

*1 patient with target lesion and 2 with no target lesion achieved complete response (CR). CI, confidence interval; PR, partial response; SD, stable disease.

Treatment-naive patients: 55% response rate

Shah M, et al. ASCO 2016; [4033]
Matrix Metalloproteinase-9 Inhibition

Swimmer’s Plot: GS-5745 Exposure and Tumor Response

Median duration of response 10.6 months

Shah M, et al. ASCO 2016; [4033]
Matrix Metalloproteinase-9 Inhibition

Kaplan-Meier Estimates of PFS

Median PFS 12.0 months
In treatment naive

Previously Treated
Treatment Naive

Censored
+ Discontinued
+ Ongoing

Median PFS
Treatment naive: 12.0 mo (90% CI 5.5–18.0)
Treatment experienced: 4.8 mo (90% CI 1.7–13.9)

No. at Risk
Treatment Naive 29 22 19 15 12 12 9 5 3 2 0
Treatment Experienced 11 8 7 3 2 1 1 0 0 0 0

PFS, progression-free survival.

Shah M, et al. ASCO 2016; [4033]
Summary

**Immunotherapy**
Anti PD-1, alone or in combination with anti-CTLA-4 shows promising activity in Phase IB-II.

**Anti-CLDN 18.2 directed antibody (IMAB362)** indicates good activity in combination with EOX in Phase II.

**Stem Cell Directed Therapy**
Anti-STAT-3 molecule (BBI608) shows promising activity in combination with chemotherapy in Phase IB.

**Tumor Microenvironment Modifier**
MMP-9 directed treatment (GS-5745) shows promising activity in combination with FOLFOX in Phase IB.

**All approaches are now studied in phase III**
Thank you for your kind attention!

Leipzig University Cancer Center - 2018