New Targets in Advanced Gastric Cancer

Yung-Jue Bang
Seoul National University Hospital
Seoul, KOREA
Systemic treatment of Gastric cancer

Cytotoxic chemotherapy


Targeted therapy

2008 EOX 2010 Trastuzumab 2014 CS Ramucirumab
How about future?

• Better agents/combinations for validated targets
  – HER2
  – VEGF/VEGFR pathway (angiogenesis)
Anti-angiogenesis: predictive biomarkers?

Bevacizumab in Combination With Chemotherapy As First-Line Therapy in Advanced Gastric Cancer: A Biomarker Evaluation From the AVAGAST Randomized Phase III Trial

**Conclusion** Plasma VEGF-A and tumor neuropilin-1 are strong biomarker candidates for predicting clinical outcome in patients with advanced gastric cancer treated with bevacizumab

**Biomarker analyses in REGARD gastric/GEJ carcinoma patients treated with VEGFR2-targeted antibody ramucirumab**

**CONCLUSION** REGARD exploratory analyses did not identify a strong potentially predictive biomarker of ramucirumab efficacy; however, statistical power was limited

New approaches to target HER2

- Different antibody
- Antibody-drug conjugate (ADC)
Pertuzumab & trastuzumab bind to different regions on HER2 and have synergistic activity

- Preferentially inhibits ligand-independent HER2 signalling
- Prevents shedding of HER2 ECD
- Flags cells for destruction by the immune system

- Inhibits HER2 forming dimer pairs
- Suppresses multiple HER signalling pathways, leading to a more comprehensive blockade of HER signalling
- Flags cells for destruction by the immune system

Juntila et al. Cancer Cell 2009
CLEOPATRA study: PFS

Progression-free survival (%)

- Ptz + T + D: median 18.5 months
- Pla + T + D: median 12.4 months

Δ = 6.1 months

HR = 0.62
95% CI 0.51–0.75
p<0.0001

D, docetaxel; PFS, progression-free survival; Pla, placebo; Ptz, pertuzumab; T, trastuzumab

Stratified by prior treatment status and region

Primary objectives:
- Estimate Day 43 trough pertuzumab concentrations to identify the dose that yields a steady state of ≥20 μg/mL in ≥90% of patients
- Safety and tolerability

GC, gastric cancer; GEJ, gastro-oesophageal junction; HER2, human epidermal growth factor receptor 2; PD, progressive disease; PK, pharmacokinetics

Both JOSHUA regimens (840/420 mg and 840/840 mg) result in Day 43 $C_{\text{trough}} \geq 20 \, \mu\text{g/mL}$ in $\geq 90\%$ of patients.

The 840/420 mg regimen results in $C_{\text{trough}}$ at Day 43 in GC $\sim 37\%$ lower than that seen with the 840/420 mg regimen in MBC (CLEOPATRA).

The 840/840 mg regimen results in $C_{\text{trough}}$ at Day 43 in GC comparable to that observed with the 840/420 mg regimen in MBC.

GC, gastric cancer; MBC, metastatic breast cancer
**JACOB study:**
Trastuzumab + Chemo ± Pertuzumab in HER2+ AGC

- Primary endpoint: OS

Patients with HER2 + metastatic gastric /GEJ cancer (planned N = 780)

Stratified by region (Japan vs North America/Western Europe/Australia vs Asia [excluding Japan] vs South America/Eastern Europe), previous gastrectomy, HER2 (IHC 3+ vs IHC 2+ and ISH+)

21-day cycle

- Pertuzumab 840 mg
- Trastuzumab 8 mg/kg x 1 then 6 mg/kg
- Cisplatin 80 mg/m²
- 5-fluorouracil or Capecitabine
  - 800 mg/m²/24 h x 5 d
  - 1000 mg/m² BID x 14 d

- Placebo
  - Trastuzumab 8 mg/kg x 1 then 6 mg/kg
  - Cisplatin 80 mg/m²
  - 5-fluorouracil or Capecitabine
  - 800 mg/m²/24 h X 5 d
  - 1000 mg/m² BID x 14 d

Trastuzumab-DM1: Novel antibody–drug conjugate

- Target expression: HER2
- Monoclonal antibody: Trastuzumab
- Cytotoxic agent: DM1
- Highly potent cytotoxic agent
- Linker: SMCC
- Systemically stable

Average drug:antibody ratio $\cong 3.5:1$

EMILIA study: PFS


<table>
<thead>
<tr>
<th></th>
<th>Median No. of Months</th>
<th>No. of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapatinib–Capecitabine</td>
<td>6.4</td>
<td>304</td>
</tr>
<tr>
<td>T-DM1</td>
<td>9.6</td>
<td>265</td>
</tr>
</tbody>
</table>

Stratified hazard ratio, 0.65 (95% CI, 0.55–0.77)  
P<0.001

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Lapatinib–capecitabine</th>
<th>T-DM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>496 404 310 176 129 73 53 35 25 14 9 8 5 1 0 0</td>
<td></td>
</tr>
<tr>
<td>No. at Risk</td>
<td>495 419 341 236 183 130 101 72 54 44 30 18 9 3 1 0</td>
<td></td>
</tr>
</tbody>
</table>
GATSBY study: Phase II-III trial

2nd-line HER2+ AGC

Stage 1

- Phase II
  - N≈100

Stage 2

- Dosing decision
- Phase III
  - N=342

- T-DM1 3.6 mg/kg q 3 wk
  - N=40

- T-DM1 2.4 mg/kg q 3 wk
  - N=40

- Chemotherapy
  - N=20

- FPI

Stage 3

- T-DM1 Selected dose
  - N=158

- Phase III LPI

- Final data

Kang YK et al. ASCO GI 2016
# GATSBY study: Results

<table>
<thead>
<tr>
<th></th>
<th>Taxane</th>
<th>T-DM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS, median</td>
<td>8.6 months</td>
<td>7.9 months</td>
</tr>
<tr>
<td>HR (95% CI)*</td>
<td>1.15 (0.87–1.51)</td>
<td>p=0.86</td>
</tr>
<tr>
<td>*HER2 IHC 3+</td>
<td>HR 0.99 (0.70–1.40)</td>
<td></td>
</tr>
<tr>
<td>HER2 IHC2+ /FISH+</td>
<td>HR 1.53 (0.94–2.50)</td>
<td></td>
</tr>
</tbody>
</table>

*HER2 IHC 3+ HR 0.99 (0.70-1.40)
HER2 IHC2+ /FISH+ HR 1.53 (0.94-2.50)

Kang YK et al. ASCO GI 2016
How about future?

• Better agents/combinations for validated targets

• Agents targeting novel molecular targets
Gastric cancer: Molecular subtypes

- **CIN**
  - Intestinal histology
  - TP53 mutation
  - RTK-RAS activation

- **EBV**
  - PIK3CA mutation
  - PD-L1/2 overexpression
  - EBV-CIMP
  - CDKN2A silencing
  - Immune cell signalling

- **GS**
  - Diffuse histology
  - CDH1, RHOA mutations
  - CLDN18–ARHGAP fusion
  - Cell adhesion

- **MSI**
  - Hypermethylation
  - Gastric-CIMP
  - MLH1 silencing
  - Mitotic pathways

TCGA. Nature 2014
Gene amplifications: Mutually exclusive

HGF/c-MET signaling pathway: Therapeutic intervention strategies

- Inappropriate paracrine or autocrine signaling
- Receptor/ligand overexpression or mutation

**Small-molecule MET kinase inhibitors:**
- tivantinib, JNJ38877605, PF-04217903, INC280, EMD1204831

**Small-molecule multikinase inhibitors:**
- cabozantinib, foretinib, crizotinib, golvatinib, MK2461, MPP470, MGCD265

**Antibodies**
- Anti-HGF: rilotumumab, ficlatuzumab
- Anti-c-MET: onartuzumab

**Molecular pathways**
- Survive proliferation + Motility → Invasion metastasis → Tumor progression

Finn RS. clinicaloptions.com/oncology 2014
**Rilotumumab as 1st-line treatment**

- **Phase II**
- **Gastric/GEJ**
  
  \(N = 121\)

- **ECX + Placebo**
- **ECX + Rilotumumab 7.5 mg/kg/3 wks**
- **ECX + Rilotumumab 15 mg/kg/3 wks**

**Biomarker population \(n = 90\)**

<table>
<thead>
<tr>
<th>Median OS by c-MET Status, Mos</th>
<th>ECX + Rilotumumab</th>
<th>ECX + Placebo</th>
<th>HR (95% CI)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC c-Met &gt; 50% tumor cells (n = 38/90)</td>
<td>11.1</td>
<td>5.7</td>
<td>0.29</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.11-0.76)</td>
<td></td>
</tr>
<tr>
<td>IHC c-MET (\leq 50%) tumor cells (n = 52/90)</td>
<td>NR</td>
<td>NR</td>
<td>1.84</td>
<td>0.166</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.78-4.34)</td>
<td></td>
</tr>
</tbody>
</table>

- In ECX + placebo arm, high c-Met associated with shorter OS vs low c-Met - HR: 3.22 (95% CI: 1.08-9.63)

Phase III trials targeting HGF/c-Met pathway

RILOMET-1

Patients with MET+, unresectable metastatic or locally advanced gastric or GEJ cancer (Planned N = 450)

Rilotumumab 15 mg/kg q21d + Epirubicin, Cisplatin, Capecitabine (ECX)

Placebo q21d + Epirubicin, Cisplatin, Capecitabine (ECX)

MetGastric

Patients with MET+, HER2-negative, metastatic gastric or GEJ cancer (planned N = 800)

Onartuzumab mFOLFOX6*

Placebo mFOLFOX6*

• Primary endpoint: OS in MET 2+/3+ and ITT populations

Both trials stopped prematurely

ClinicalTrials.gov. NCT01697072 & NCT01662869
Phase II trial of FOLFOX ± Onartuzumab

- No significant PFS improvement in both ITT and MET-positive populations
- No difference in median OS in ITT (10.61 vs 11.27 mos) or MET-positive (8.51 vs 8.48 mos) populations
- Asian pts had longer PFS and OS

**Median PFS**

5.95 vs 6.80
Stratified HR: 1.38
(95% CI: 0.60-3.20; \( P = .4514 \))

Placebo + mFOLFOX6 (n = 19)
Onartuzumab + mFOLFOX6 (n = 16)

FGFR2 amplification in gastric cancer

Prevalence of FGFR2 amplification (FISH 6) was 4.2% in Korean cohort & 7.4% in Caucasian cohort

FGFR2 amplification is associated with poor outcome of patients

FGFR2 amplified gastric cancer models are highly dependent upon FGFR in vivo

- Tumour regressions achieved in both models
- In explant model
  - 1 tumour re-challenged and remained sensitive to AZD4547
  - Complete regression maintained in 4 of 7 tumours at Day 74

Bang YJ et al. ASCO 2015
SHINE study: AZD4547 vs. paclitaxel

Bang YJ et al. ASCO 2015
FPA144: ADCC enhanced FGFR2b monoclonal antibody

Engineered for enhanced antibody-dependent cell-mediated cytotoxicity (ADCC)

Blocks Ligand Binding

FGF 7

FGF 10

FGF 22

FGF 7

FGF 10

FGF 22

FGFR 2b

FPA1 44
## Antitumor activity of FPA144 in FGFR2b+ GC

**Outcome** | **FPA144 Treated (N=9)**
--- | ---
**ORR * (95% CI)** | 33% (*7%, 70%)*
Best Objective Response (%) |  
Complete Response | 0 (0%)
Partial Response | 3* (33%)
Stable Disease | 4 (44%)
Progressive Disease | 2 (23%)
**Disease Control Rate (95% CI)** | 77% (*40%, 97%*)
**12-Week PFS (95% CI)** | 67% (*30%, 93%*)
**Median duration of treatment, days (Range)** | 112 (42-182)

* Pooled across all dosing cohorts (1 at 6 mg/kg, 1 at 10 mg/kg and 1 at 15 mg/kg). All responses were confirmed. Investigator review was used for assessments. Data cutoff was April 1, 2016.

---

Partial Response in a patient treated with 6 mg/kg FPA144

**Screening (Day -14)**

**Cycle 4 Day 1 (Day 83)**

Lee JY et al. ASCO 2016
IMAB362: Anti-CLDN18.2 antibody

- Chimeric IgG1 antibody
- Highly specific for CLDN18.2 (major structural component of tight junctions)

Mode of action:
- ADCC
- Complement-dependent cytotoxicity
- With chemotherapy
  - Enhances T-cell infiltration
  - Induces pro-inflammatory cytokines

EOX: Epirubicine, Oxaliplatin, Capecitabine

Al-Batran SE et al. ASCO 2016
FAST study: Design

- Randomized phase II study
- Stratification factor
  - CLDN 18.2 positivity
  - Measurability
- Eligibility: CLDN18.2 2+/3+ in ≥ 40% tumor cells
- Primary endpoint: PFS
FAST study: Results

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

Al-Batran SE et al. ASCO 2016
CLDN18.2 high expressors (≥ 70%)

Progression-free survival

- mPFS 5.6 vs. 7.2 mo
- HR 0.36
- p=<0.0005

Overall survival

- mOS 9 vs. 16.7 mo
- HR 0.45
- p=<0.0005

Al-Batran SE et al. ASCO 2016
Study 19: Olaparib in relapsed serous ovarian cancer

Platinum-sensitive, recurrent high grade serous ovarian cancer; ≥2 prior platinum-based regimens with CR/PR to most recent platinum-based therapy (N = 265)

- Primary endpoint: PFS (RECIST 1.0)
- Secondary endpoints: OS, safety, tolerability
- Exploratory endpoints: time to first subsequent therapy or death (TFST), time to second subsequent therapy or death (TSST)
- Current report: descriptive updated OS analysis at 77% data maturity
  - Study 19 not designed to evaluate OS with statistical significance
  - OS P values deemed nominal for descriptive analysis
  - Type 1 error rate for subgroup analyses with no pre-specified rules

Olaparib
400 mg BID, capsules
(n = 136)

Placebo
BID, capsules
(n = 129)

Treatment until disease progression

Ledermann JA, et al. ASCO 2016
Overall survival in mutated BRCA patients

BRCAm patients*

Number of patients at risk:
- Olaparib: 74, 69, 65, 66, 56, 50, 39, 33, 27, 27, 25, 23, 11, 1, 0
- Placebo: 62, 58, 52, 40, 34, 29, 25, 20, 19, 15, 13, 10, 6, 0, 0

Time from randomization (months)

Overall survival (%)

Deaths, n (%)

<table>
<thead>
<tr>
<th>BRCAm (n=136)</th>
<th>Olaparib (n=74)</th>
<th>Placebo (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>47 (64)</td>
<td>48 (77)</td>
<td></td>
</tr>
</tbody>
</table>

Median OS, months

34.9

30.2

HR=0.62

95% CI 0.41–0.94

Nominal P=0.02480

Maturity: 70%

Criterion for statistical significance not met (P<0.0095)

DCO 30 Sep 2015

Ledermann J et al. ASCO 2016

*Cox proportional hazards analysis
Olaparib showed growth inhibitory effect in gastric cancer cell lines

* 2 out of 11 (18%) GC cell lines are very sensitive to AZD2281 (IC50 < 1 mM) by CFA
* Achievable level in tissue 2-3 mM : 9/11 (82%) IC50 of GC cells are < 3 mM by CFA

Im SA et al. unpublished data
ATM deficiency correlates with Olaparib activity

Reduced ATM expression correlates with cellular sensitivity to olaparib in gastric cancer cell lines

IC50s of olaparib on gastric cancer cell lines associated with ATM expression level. Correlation between cellular sensitivity and ATM deficiency was then analyzed showing that 6 GC cell lines with low or no detectable expression of ATM were sensitive to olaparib. In contrast, the majority of other GC cell lines positive for ATM expression (9 out of 11) were less sensitive or resistant to olaparib.

Im SA et al. unpublished data
Phase II trial of Olaparib + Paclitaxel

Gastric or GEJ ca 2nd-line (N=124)

OS in ATM-ve population

Randomized treatment
- Olaparib/paclitaxel
- Placebo/paclitaxel

Events: Total pts (%)
- Olaparib/paclitaxel: 12:31 (38.7)
- Placebo/paclitaxel: 23:32 (71.9)

Median OS, months
- Olaparib/paclitaxel: NR
- Placebo/paclitaxel: 8.20

Cox PH model*
- HR=0.3595 (95% CI; 0.17, 0.71)
- P=0.003, 2 sided
GOLD: Phase III study

Patients with advanced gastric cancer* who progressed following first-line therapy (n=525)
- China (n=202)
- Japan (n=102)
- Korea (n=201)
- Taiwan (n=20)

Olaparib 100 mg tablet twice daily + weekly paclitaxel 80 mg/m² iv
N=263

Placebo + weekly paclitaxel 80 mg/m² iv
N=262

Co-primary endpoint
- OS all patients (FAS‡)
- OS for patients with an ATM protein-negative tumour§

Paclitaxel treatment was on days 1, 8 and 15 of a 28-day cycle until progression,† unmanageable toxicity or consent withdrawal

- Secondary endpoints included: PFS; ORR; HRQoL||; safety and tolerability

- Study designed to detect HR=0.7 with a median OS improvement of 8.0→11.4 months in the overall population, and HR=0.35 with a median OS improvement of 8.0→22.9 months in the ATM protein-negative population
  - Statistical significance was 0.025 (the Hochberg approach)

*Including the gastro-oesophageal junction (GEJ); †Evaluated by RECIST 1.1; §adjusted for ATM status, country and gastrectomy status at baseline; ||Assessed by the EORTC QLQ-C30 global HRQoL scale

Bang YJ et al. ESMO 2016
Defining the ATM protein negative (ATM–ve)

• All patients were required to provide a tumour sample (from either a resection or biopsy) for ATM protein testing

• The ATM (Y170) immuno-histochemistry assay was used to define the ATM–ve population (Ventana, Tucson, Arizona, USA)

• Frequency of ATM–ve tumours in GOLD was 18%

<table>
<thead>
<tr>
<th>Criteria for ATM clinical diagnostic assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description</strong></td>
</tr>
<tr>
<td>Staining of any intensity in &lt;25% of tumour cell nuclei</td>
</tr>
<tr>
<td>Presence of ≥25% tumour cell nuclear staining of any intensity</td>
</tr>
</tbody>
</table>

Bang YJ et al. ESMO 2016
Overall survival in the FAS

Due to Hochberg’s multiple testing procedure, statistical significance was $P<0.025$ for each population.

Bang YJ et al. ESMO 2016
Overall survival in the ATM-ve patients

ATM-ve (n=94; 68.1% OS maturity)

<table>
<thead>
<tr>
<th>Olaparib/paclitaxel</th>
<th>Placebo/paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events: total patients (%)</td>
<td>29:48 (60.4)</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>12.0</td>
</tr>
<tr>
<td>HR=0.73</td>
<td>97.5% CI (0.40, 1.34); P=0.2458*</td>
</tr>
</tbody>
</table>

*Due to Hochberg’s multiple testing procedure, statistical significance was P<0.025 for each population
Secondary endpoints

Due to Hochberg’s multiple testing procedure, statistical significance was $P<0.025$

*Response rate in patients with measurable disease only
†Patients whose baseline score was $\geq 10$

PFS, progression-free survival
OR, odds ratio
ORR, objective response rate
HRQoL, health-related quality of life

Olaparib/paclitaxel (n=263 FAS; n=48 ATM–ve)
Placebo/paclitaxel (n=262 FAS; n=46 ATM–ve)

Bang YJ et al. ESMO 2016
# Ongoing phase III studies of targeted agents in AGC

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Trial</th>
<th>Regimen</th>
<th>n</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2</td>
<td>Pertuzumab</td>
<td>JACOB</td>
<td>XP + trastuzumab ± pertuzumab</td>
<td>780</td>
<td>Ongoing</td>
</tr>
<tr>
<td>VEGFR</td>
<td>Ramucirumab</td>
<td>RAINFALL</td>
<td>XP ± ramucirumab</td>
<td>616</td>
<td>Ongoing</td>
</tr>
<tr>
<td><strong>Second-line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mTOR</td>
<td>Everolimus</td>
<td>AIO-STO-0111</td>
<td>Paclitaxel ± everolimus</td>
<td>480</td>
<td>Ongoing</td>
</tr>
<tr>
<td>EGFR</td>
<td>Nimotuzumab</td>
<td>NCT01813253</td>
<td>Irinotecan ± nimotizimab</td>
<td>400</td>
<td>Ongoing</td>
</tr>
<tr>
<td>STAT3</td>
<td>BBI608</td>
<td>BRIGHTER</td>
<td>Paclitaxel ± BBI608</td>
<td>680</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

[www.clinicaltrials.gov](http://www.clinicaltrials.gov)
How about future?

- Better agents/combinations for validated targets
- Agents targeting novel molecular targets
- Blockade of immune checkpoints
Systemic treatment of Gastric cancer

Cytotoxic chemotherapy
- FAM
- FAMTX
- FP/CF
- DCF
- XP

Targeted therapy
- Trastuzumab

Immunotherapy
- Ramucirumab

Timeline:
- 1980
- 1991
- 1993
- 1997
- 2000
- 2008
- 2010
- 2014
- 2016
The cancer-immunity cycle consists of stepwise events leading to effective killing of cancer cells.

Various factors released in the microenvironment can stimulate or inhibit cycle activity; thus their pathways may be targetable.
CTLA-4 and PD-1/L1 Checkpoint blockade

**Priming phase**
(lymph node)

- Dendritic cell
- T cell
- MHC
- TCR
- CD28
- B7
- CTLA-4

**Effector phase**
(peripheral tissue)

- T cell
- Cancer cell
- MHC
- TCR
- PD-1
- PD-L1

T-cell migration

CA184-162: Sequential Ipilimumab

**Gastric/GEJcancer**

- At least SD after completion of 1L* chemo with platinum/fluoropyrimidine

**Ipilimumab 10mg/kg**

- BSC (Option to continue fluoropyrimidine)

**R**

- N=114

**Primary endpoint:** irPFS

**Secondary endpoint:** mWHO PFS, OS

**Exploratory endpoint:** Safety, Biomarkers

- **Key assumptions:**
  - \( P = 0.2 \) two-sided, Power = 80%
  - HR (irPFS) = 0.64 (2.25 months; 4 → 6.25)

---

* 4-6 cycles 1L or equivalent

CA184-162: Results

irPFS

OS

Moehler M, Bang YJ et al. ASCO 2016
**KEYNOTE-012: Gastric cohort**

- Recurrent or metastatic adenocarcinoma of the stomach or GEJ
- ECOG PS 0-1
- PD-L1+ tumor
- No systemic steroid therapy
- No autoimmune disease (active or history of)
- No brain metastases

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

---

* Positivity defined as PD-L1 staining in stroma or ≥1% of tumor cells.

*Bang YJ, et al. ASCO 2015*
# Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total N = 39</th>
<th>Non-Asian n = 20</th>
<th>Asian n = 19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>63.0 (33-78)</td>
<td>63.0 (33-71)</td>
<td>64.0 (34-78)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28 (71.8)</td>
<td>12 (60.0)</td>
<td>16 (84.2)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (28.2)</td>
<td>8 (40.0)</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>17 (43.6)</td>
<td>9 (45.0)</td>
<td>8 (42.1)</td>
</tr>
<tr>
<td>1</td>
<td>22 (56.4)</td>
<td>11 (55.0)</td>
<td>11 (57.9)</td>
</tr>
<tr>
<td>Prior gastrectomy, n (%)</td>
<td>20 (51.3)</td>
<td>9 (45.0)</td>
<td>11 (57.9)</td>
</tr>
<tr>
<td>No. of prior therapies for advanced disease, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>9 (23.1)</td>
<td>6 (30.0)</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>≥2</td>
<td>26 (66.7)</td>
<td>11 (55.0)</td>
<td>15 (78.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (10.3)</td>
<td>3 (15.0)</td>
<td>1 (5.3)</td>
</tr>
</tbody>
</table>

Bang YJ, et al. ASCO 2015
## Best overall response

<table>
<thead>
<tr>
<th></th>
<th>Total N = 36&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Asia n = 17&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Rest of World n = 19&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, &lt;sup&gt;b&lt;/sup&gt; % (95% CI)</td>
<td>22.2 (10.1-39.2)</td>
<td>23.5 (6.8-49.9)</td>
<td>21.1 (6.1-45.6)</td>
</tr>
</tbody>
</table>

### Best overall response, n (%)

<table>
<thead>
<tr>
<th></th>
<th>Total N = 36&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Asia n = 17&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Rest of World n = 19&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>8 (22.2)</td>
<td>4 (23.5)</td>
<td>4 (21.1)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>5 (13.9)</td>
<td>3 (17.6)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>19 (52.8)</td>
<td>7 (41.2)</td>
<td>12 (63.2)</td>
</tr>
<tr>
<td>No assessment</td>
<td>1 (2.8)</td>
<td>0</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Not determined</td>
<td>3 (8.3)</td>
<td>3 (17.6)</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Patients with measurable disease per RECIST v1.1 by central review at baseline.<br>
<sup>b</sup>All responses were confirmed.<br>
<sup>c</sup>Patient with centrally evaluable disease at baseline who discontinued therapy due to clinical progression before the first scan.<br>
<sup>d</sup>Patients with centrally evaluable disease at baseline for whom best overall response could not be determined.<br>

Analysis cut-off date: March 23, 2015.
Pembrolizumab in PD-L1-positive Gastric cancer

- Median time to response: 8 weeks (range, 7-16)
- 4 of 8 responses ongoing at the time of data cutoff
- Median response duration: 40 weeks (range, 20+ to 48+)
- Median PFS: 1.9 months (95% CI, 1.8-3.5)
- 6-month PFS rate: 26%
- Median OS: 11.4 months (95% CI, 5.7-NR)
- 6-month OS rate: 66%

Avelumab in AGC: Study design

Patients with confirmed locally advanced or metastatic GC/GEJC, unselected for PD-L1 expression

Treatment with avelumab 10 mg/kg IV Q2W

Select assessments: safety, BOR, PFS

2nd-line group (2L): disease had progressed following 1st-line therapy

Switch-maintenance group (SwM): disease had not progressed on 1st-line therapy

Chung HC et al. ECCO 2015
### Clinical activity of Avelumab

<table>
<thead>
<tr>
<th>Clinical activity endpoint</th>
<th>2L population (n=20)</th>
<th>SwM population (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR, n (%)</td>
<td>0</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>3 (15.0)</td>
<td>3 (5.5)</td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>7 (35.0)</td>
<td>26 (47.3)</td>
</tr>
<tr>
<td>PD, n (%)</td>
<td>7 (35.0)</td>
<td>16 (29.1)</td>
</tr>
<tr>
<td>Non-evaluable, n (%)*</td>
<td>3 (15.0)</td>
<td>9 (16.4)</td>
</tr>
<tr>
<td><strong>ORR, % (95% CI)</strong></td>
<td>15.0 (3.2, 37.9)</td>
<td>7.3 (2.0, 17.6)</td>
</tr>
<tr>
<td><strong>DCR, %</strong></td>
<td>50.0</td>
<td>54.5</td>
</tr>
<tr>
<td><strong>PFS, median, weeks (95% CI)</strong></td>
<td>11.6 (6.0, 21.9)</td>
<td>14.1 (9.9, 18.0)</td>
</tr>
<tr>
<td><strong>PFS rate at 24 weeks, % (95% CI)</strong></td>
<td>19.3 (3.7, 44.1)</td>
<td>34.0 (19.8, 48.6)</td>
</tr>
</tbody>
</table>

CR, complete response; DCR, disease control rate (defined as responses + SD); ORR, objective response rate; PFS, progression-free survival; PD, progressive disease; PR, partial response

* Evaluable data were those with both baseline tumor assessments and ≥1 treatment-related assessment as of the date of data cut-off.
Future perspective

• Who get benefits?

• How about combinations?
  – With other immune check-point blocking agents
  – With chemotherapeutic agents
  – With targeted agents
Association between efficacy and PD-L1 expression in Gastric cancer

- Preliminary evidence of a relationship between PD-L1 expression and efficacy in this preselected population

- Data suggest a relatively low cutoff is sufficient to detect most responders

<table>
<thead>
<tr>
<th></th>
<th>Central review (N=35)</th>
<th>Investigator review (N=38)</th>
<th>Overall survival (N=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>0.082</td>
<td>0.120</td>
<td>0.010</td>
</tr>
<tr>
<td>PFS</td>
<td>0.269</td>
<td>0.237</td>
<td></td>
</tr>
</tbody>
</table>

Assessing PD-L1 expression as a continuous variable

Bang YJ, et al. ASCO 2015
Identified immune-related gene expression signatures

- 4 immune-related gene expression signatures were established in melanoma patients treated with pembrolizumab in KEYNOTE-001\textsuperscript{1,2}
- Signatures were independently tested in gastric cancer patients from KEYNOTE-012\textsuperscript{2}
  - ORR in the 33 evaluable patients was 30%

**Association of immune-related gene expression signatures and ORR & PFS**

<table>
<thead>
<tr>
<th>Signature</th>
<th>Nominal 1-Sided P Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ORR&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>IFN-γ (6 gene)</td>
<td>0.077</td>
</tr>
<tr>
<td>TCR signaling (13 gene)</td>
<td>0.034</td>
</tr>
<tr>
<td>Expanded immune (18 gene)</td>
<td>0.062</td>
</tr>
<tr>
<td>De novo (33 gene)</td>
<td>0.068</td>
</tr>
</tbody>
</table>

- Potential diagnostic performance of IFN-γ signature
  - Negative predictive value = 92%
  - Positive predictive value = 45%
  - Prevalence = 61%

<sup>a</sup>From logistic (ORR) or Cox (PFS) regression, with signature scores as a continuous variable.

<sup>b</sup>Assessed per RECIST v1.1 by investigator review.

Bang YJ, et al. WCGIC 2015
Future perspective

• Who get benefits?

• How about combinations?
  – With other immune check-point blocking agents
  – With chemotherapeutic agents
  – With targeted agents
**CheckMate-032: Nivolumab ± Ipilimumab**

<table>
<thead>
<tr>
<th></th>
<th>Nivo alone</th>
<th>Nivo 1+Ipi 3</th>
<th>Nivo 3+Ipi 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>59</td>
<td>49</td>
<td>59</td>
</tr>
<tr>
<td>ORR</td>
<td>12%</td>
<td>26%</td>
<td>14%</td>
</tr>
<tr>
<td>OS, median</td>
<td>6.8 mo</td>
<td>6.9 mo</td>
<td>5.0 mo</td>
</tr>
<tr>
<td>12-mo OS</td>
<td>38%</td>
<td>34%</td>
<td>36%</td>
</tr>
</tbody>
</table>

Janjigian YY et al. ASCO 2016
KEYNOTE-059: Pembrolizumab + CF

- Combination of pembrolizumab & CF has a manageable safety profile
- No treatment-related discontinuations attributed to pembrolizumab
- No treatment-related deaths

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Dose Frequency</th>
<th>Route of Administration</th>
<th>Regimen/Treatment Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>200 mg</td>
<td>Q3W</td>
<td>IV infusion</td>
<td>Day 1 of each 3-week cycle</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>80 mg/m²</td>
<td>Q3W</td>
<td>IV infusion</td>
<td>Day 1 of each 3-week cycle for 6 cycles</td>
</tr>
<tr>
<td>5-FU†</td>
<td>800 mg/m²</td>
<td>Q3W</td>
<td>Continuous IV infusion†</td>
<td>Days 1-5 of each 3-week cycle</td>
</tr>
<tr>
<td>Capecitabine (Japan only)†</td>
<td>1000 mg/m², 2 times per day</td>
<td>Q3W</td>
<td>Oral</td>
<td>Days 1-14 of each 3-week cycle</td>
</tr>
</tbody>
</table>

5-FU = 5-fluorouracil; IV = intravenous; Q3W = every 3 weeks.
†For cohort 2, sites in Japan administered 5-FU or capecitabine in combination with cisplatin.
‡5-FU was continuously infused for the duration of 120 hours.

Fuchs CS et al. ASCO 2016
MEK inhibitor + PD-L1 antibody

- MEK inhibition can result in intratumoral T-cell accumulation and MHC I upregulation, and synergizes with anti-PD-L1 agent to promote durable tumor regression.

**Graphs:**
- CD8⁺ T cell per tumor cell
- Class I MHC
- Tumor volume (mm³)

_Ebert et al. Immunity 2016_
• 4 patients had partial responses (17%; KRAS mutant CRC 20%)
• MSI status of responders: 3 were mismatch-repair proficient; 1 not evaluable
• Tumor volume reduction was not associated with PD-L1 status: TC3 (n=1; PD), TC0 (n=18), NA (n=4)
• Median duration of response: not reached (range: 5.4 to 11.1+ mos)
• Stable disease can be durable (≥ 6 mo)
• 6-months OS: 72% (KRAS mutant CRC, 77%)

Bendell J et al. ASCO 2016
**VEGF mediation of immune suppression**

- Promotes inhibitory immune cells
  - Tregs
  - MDSCs
  - TAMs
- Compromises APC and T effector cell function
- Impairs lymphocyte development and trafficking

---

*Ott PA, et al. Front Oncol 2015;5:202*
Conclusion

• We have witnessed the evolution of systemic treatment
  – Cytotoxic chemotherapy
  – Targeted agent
  – Immunotherapy

• We should make more efforts to explore
  – Combination of these agents to enhance efficacy
  – Potential biomarkers to realize ‘Precision medicine’