Tumor-agnostic clinical development - ideal and reality

Academia Task for Tumor-Agnostic Clinical Development and the Post-Launch

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Director, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Japan

June 30th, 2018
In May 2017, the U.S. FDA granted accelerated approval for pembrolizumab, an anti-PD-1 monoclonal antibody for treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors. The FDA approval represents the first disease agnostic anti-cancer therapy based on tumor biomarker.

MSD Merck Japan & FALCO has submitted the application for approval for adult patients with unresectable or metastatic, MSI-H solid tumors at March 2018.

Japanese PMDA is also anticipated to grant the same regulatory for pembrolizumab, to which the PMDA has applied ‘Conditional Early Approval System for Pharmaceuticals (one of Priority Review System)’ at June, 2018.
Agenda

• TODAY:
  Accomplishment of SCRUM-Japan for MSI-High tumors before the launch

• TOMORROW:
  Guideline in place

• THE DAY AFTER TOMORROW:
  TMB-high
  RWD
  International Collaboration
The Nationwide Cancer Genome Screening Consortium in Lung and GI Cancers: SCRUM-Japan (n=9,590: Feb/2015 - May/2018)

More than 260 participating institutions

Pan-cancer panel (OCP/OCAv3) analysis

Clinico-Genomic Database

Collaboration with 17 pharma

No. of enrollment

<table>
<thead>
<tr>
<th>Lung Cancer</th>
<th>4,309</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-sq NSCLC</td>
<td>3,673</td>
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<tr>
<td>Sq NSCLC</td>
<td>636</td>
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<tr>
<td>GI Cancer</td>
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<tr>
<td>Esophageal</td>
<td>370</td>
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<tr>
<td>Gastric</td>
<td>1,142</td>
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<tr>
<td>Small intestine</td>
<td>93</td>
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<tr>
<td>CRC</td>
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<tr>
<td>HCC</td>
<td>66</td>
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<tr>
<td>Biliary</td>
<td>417</td>
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<tr>
<td>Pancreas</td>
<td>652</td>
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<tr>
<td>NET</td>
<td>73</td>
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<tr>
<td>GIST</td>
<td>79</td>
</tr>
<tr>
<td>Others</td>
<td>60</td>
</tr>
<tr>
<td>Total</td>
<td>9,590</td>
</tr>
</tbody>
</table>

Molecular-profile based IND regist trials

Umbrella type 26 studies

<table>
<thead>
<tr>
<th>Organ</th>
<th>Target</th>
<th>agent</th>
<th>Phase</th>
<th>sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>NET</td>
<td>cetuximab</td>
<td>I / II</td>
<td>IT (Kanazawa U)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>MET</td>
<td>erlotinb</td>
<td>I / II</td>
<td>IT (Kanazawa U)</td>
</tr>
<tr>
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<td>ROS1</td>
<td>entrectinib</td>
<td>II</td>
<td>Ignyta</td>
</tr>
<tr>
<td>NSCLC</td>
<td>ROS1</td>
<td>Crizotinib</td>
<td>II</td>
<td>Pfizer</td>
</tr>
<tr>
<td>NSCLC</td>
<td>ROS1</td>
<td>D取得</td>
<td>II</td>
<td>Dacrin</td>
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<tr>
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<td>PLC取得</td>
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<td>Pfizer</td>
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<tr>
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<td>MET</td>
<td>capmatinib</td>
<td>II</td>
<td>Nippon</td>
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<tr>
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<td>MET</td>
<td>AZD8041</td>
<td>II</td>
<td>AZD</td>
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<tr>
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<td>MET</td>
<td>Crizotinib</td>
<td>II</td>
<td>IT (Kyoto CC)</td>
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<td>ALK</td>
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<td>Ignyta</td>
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<td>brigatinib</td>
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<td>HER2</td>
<td>T-DM1</td>
<td>II</td>
<td>IT (Okayama U)</td>
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<td>T-Dcat721</td>
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<tr>
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<td>II</td>
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<tr>
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<td>dabrafenib</td>
<td>II</td>
<td>Novartis</td>
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<td>MSD</td>
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<tr>
<td>CRC</td>
<td>HER2</td>
<td>T-Dcat721</td>
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<td>IT (Kanazawa U)</td>
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</table>

Phase I / basket type 16 studies

<table>
<thead>
<tr>
<th>Solid tumor</th>
<th>Target</th>
<th>agent</th>
<th>Phase</th>
<th>sponsor</th>
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<tbody>
<tr>
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<td>MET</td>
<td>Iressa</td>
<td>I</td>
<td>Lilly</td>
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<tr>
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<td>FGFR</td>
<td>D011392</td>
<td>I</td>
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<tr>
<td>Solid tumor</td>
<td>FGFR</td>
<td>TGF212</td>
<td>I</td>
<td>Taiho</td>
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<tr>
<td>Solid tumor</td>
<td>EGFR</td>
<td>erlotinb</td>
<td>I</td>
<td>Sun</td>
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<td>Solid tumor</td>
<td>HER2</td>
<td>GWS572</td>
<td>I</td>
<td>Taiho</td>
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<td>Solid tumor</td>
<td>NTRK1/2</td>
<td>LOXCD-101</td>
<td>I</td>
<td>Loncast</td>
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<td>NTRK1/2</td>
<td>MNIK278</td>
<td>I</td>
<td>Ignyta</td>
</tr>
<tr>
<td>Solid tumor</td>
<td>NTRK1/2</td>
<td>D060611</td>
<td>I</td>
<td>Chiesi</td>
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<tr>
<td>Solid tumor</td>
<td>ROS1</td>
<td>entrectinib</td>
<td>I</td>
<td>Ignyta</td>
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<td>Solid tumor</td>
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<td>Chiesi</td>
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<td>Solid tumor</td>
<td>FGFR</td>
<td>D114888</td>
<td>I</td>
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<td>Chiesi</td>
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<td>Solid tumor</td>
<td>FGFR</td>
<td>TGF212</td>
<td>I</td>
<td>Taiho</td>
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</table>

Central Testing: Multiplex Genome Analysis by NGS with Oncomine™ Comprehensive Assay v3

CRC: Colorectal Cancer
Lung Cancer: NSCLC (Non-small cell lung cancer)
Non-sq NSCLC: Non-small cell lung cancer (excluding squamous cell cancer)
Sq NSCLC: Squamous cell lung cancer
GI Cancer: Gastrointestinal Cancer
Esophageal: Esophageal cancer
Gastric: Gastric cancer
Small intestine: Small intestine cancer
CRC: Colorectal cancer
HCC: Hepatocellular Carcinoma (Hepatitis B virus infection)
Biliary: Biliary tract cancer
Pancreas: Pancreatic cancer
NET: Neuroendocrine tumour
GIST: Gastrointestinal stromal tumour
Others: Other cancers

Total: 9,590 participants
Accomplishment on GI-SCREEN

As of June, 2018

853 Cases

Ongoing

SCRUM-Japan
GI-SCREEN 2013-01-CRC

Version 1.2 - 2.0

1,711 Cases

2016

Ongoing

GI-SCREEN MSI CRC

(2,329 Cases after SCRUM-Japan Project)

3,182 Cases

2017

Ongoing

GI-SCREEN CRC

2,952 Cases

2018

Ongoing

GI-SCREEN Non-CRC

44 Cases

Immune Profiling

Cancer genome alteration, MSI, PD-L1, PD-L2 and clinical data (incl. outcome)

Ongoing

Plasma OncoBEAM RAS CRC Kit

Finish

Tissue RASKET-B Kit

Finish

Tissue MSI Promega Kit

Ongoing

GOZILA

56 Cases

Ukit

59 Cases

GI-screen 2013-01-CRC: Sub-study 1

Finish

Feb 2014
Feb 2015
Apr 2015

Feb 2015
Feb 2014
Apr 2015
**Prevalence of microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) CRC: Cross-trial comparison**

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>N</th>
<th>Prevalence of MSI-H/dMMR</th>
<th>Overlapping BRAF V600E mutation</th>
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<tr>
<td>Pooled dataset ¹</td>
<td>3,063</td>
<td>5.0%</td>
<td>34.6%</td>
</tr>
<tr>
<td>AIO Colorectal Study Group ²</td>
<td>104</td>
<td>4%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Australia and United States ³</td>
<td>NA</td>
<td>Not reported</td>
<td>30%</td>
</tr>
<tr>
<td>Review Article ⁴</td>
<td>NA</td>
<td>3 - 5%</td>
<td>Not reported</td>
</tr>
<tr>
<td>GI-SCREEN-JAPAN ⁵</td>
<td>853</td>
<td>1.9%</td>
<td>40%</td>
</tr>
<tr>
<td>NCCE ⁶</td>
<td>277</td>
<td>1.9%</td>
<td>40%</td>
</tr>
<tr>
<td>GI-SCREEN CRC - MSI * unpublished</td>
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<td></td>
<td></td>
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<tr>
<td>Universal Screening in Stage II and III +</td>
<td></td>
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</table>

Note: GI-SCREEN-JAPAN is the Nationwide Cancer Genome Screening Project for Gastrointestinal Cancer in Japan: NA, not applicable: *Ongoing Prospective Observational Study as of 31st Mar, 2018: +Our institutional Data as of 31st Mar, 2018

Quasi-monomorphic variation range: QMVR

- The mean allele size of mononucleotide markers was generated from the normal DNA.
- QMVR was defined as the mean allele size ±3bp.
- Because of few variant alleles observed in Caucasians as well as in Asians, QMVR might be applicable as references.

Okamoto W, …., Yoshino T. ESMO 2017

Tissue MSI Promega Kit
According to the pilot study performed by FALCO Biosystems, the QMVR in 149 healthy Japanese individuals were almost the same as those of the Caucasian group.\(^{(1)}\)

<table>
<thead>
<tr>
<th></th>
<th>NR21</th>
<th>BAT26</th>
<th>BAT25</th>
<th>NR24</th>
<th>MONO27</th>
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<td>Pilot study(^{(1)})</td>
<td>98.4-104.4</td>
<td>111.4-117.4</td>
<td>121.0-127.0</td>
<td>129.5-135.5</td>
<td>149.9-155.9</td>
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<tr>
<td>Patil DT, et al. (^{(2)})</td>
<td>98-104</td>
<td>112-118</td>
<td>121-127</td>
<td>129-135</td>
<td>149-155</td>
</tr>
</tbody>
</table>

Three large Japanese cohorts suggested that the frequencies of variant alleles for 5 mononucleotide markers were rare.\(^{(1)}\)

<table>
<thead>
<tr>
<th></th>
<th>NR21</th>
<th>BAT26</th>
<th>BAT25</th>
<th>NR24</th>
<th>MONO27</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSI analysis of GI-SCREEN 2013-01-CRC</td>
<td>4/602 (0.66%)</td>
<td>0/602 (0%)</td>
<td>3/602 (0.50%)</td>
<td>0/602 (0%)</td>
<td>0/602 (0%)</td>
</tr>
<tr>
<td>Saitama Cancer Center</td>
<td>3/774 (0.39%)</td>
<td>2/3320 (0.06%)</td>
<td>12/3320 (0.36%)</td>
<td>2/774 (0.26%)</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>FALCO Biosystems</td>
<td>2/252 (0.79%)</td>
<td>0/252 (0%)</td>
<td>1/252 (0.40%)</td>
<td>0/252 (0%)</td>
<td>0/252 (0%)</td>
</tr>
</tbody>
</table>

\(^{(1)}\) Bando H, et al. ASCO GI. 2017
The Promega MSI testing was performed using genomic DNA extracted from both tumor and paired normal tissue. The presence of MSI was determined by the appearance of new alleles in the tumor sample that were not present in the normal sample.

The new MSI kits were manufactured under the Quality Management System (QMS) for in vitro diagnostics (IVDs). The presence of MSI was determined by appearance of the tumor allele peak outside the Quasi-Monomorphic Variation Range (QMVR).
### Results: Primary and Secondary endpoints

Okamoto W, …., Yoshino T. ESMO 2017

<table>
<thead>
<tr>
<th>Testing method</th>
<th>Standard method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative (MSS/MSI-L)</td>
</tr>
<tr>
<td>Negative (MSS/MSI-L)</td>
<td>424</td>
</tr>
<tr>
<td>Positive (MSI-H)</td>
<td>0</td>
</tr>
</tbody>
</table>

- **Primary endpoint**
  - Sensitivity: \( \frac{11}{0+11} = 100\% \)
  - Specificity: \( \frac{424}{424+0} = 100\% \)

- **Secondary endpoints**
  - Concordance rate: \( \frac{424+11}{424+0+0+11} = 100\% \)
  - Positive predictive value: \( \frac{11}{0+11} = 100\% \)
  - Negative predictive value: \( \frac{424}{424+0} = 100\% \)
Can we adapt the findings from the CRC study to Non-CRC?

-Our Experience-

We will soon start the confirmatory study to investigate the concordance between MMR-IHC and MSI-PCR in Non-CRC, utilizing the SCRUM-Japan Platform before the launch of pembrolizumab.
Differences in Microsatellite Instability Profiles between Endometrioid and Colorectal Cancers

A Potential Cause for False-Negative Results?

Yang Wang, Chunjian Shi, Rosana Eisenberg, and Cindy L. Vencvak-Jones

Colorectal (CRCs) and endometrioid (EMCs) cancers in patients with Lynch syndrome exhibit microsatellite instability (MSI) detected by PCR or immunohistochemistry (IHC). While both assays are equally sensitive for CRCs, some suggest that PCR has a higher false-negative rate than IHC in EMCS. We assessed the MSI profiles of 91 EMC and 311 CRC specimens using five mononucleotide repeat markers: BAT25, BAT26, NR21, NR24, and MINT27. EMCS with high MSI (MSI-H) showed a mean left shift of 3 nucleotides (nt), which was significantly different from 6 nt in CRCs. A shift of 1 nt was observed in multiple markers in 76% of MSI-H EMCS, whereas only 12% of MSI-H CRCs displayed a 1-nt shift in one of five markers. IHC against four mismatch repair proteins was performed in 78 EMCS. Loss of staining in one or more proteins was detected in 18 of 19 tumors that were MSI-H by PCR. When EMC tumor cell burden was diluted to <30%, MSI-H was no longer observed in two of three EMCS with a mean nucleotide shift of 1 nt. These results indicate that EMC and CRC MSI profiles are different and that caution should be exercised when interpreting the results, as subtle, 1-nt changes may be missed. These findings provide a potential cause of previously reported discordant MSI and IHC results in EMCS. (J Mol Diagn 2017, 19: 57–64; http://dx.doi.org/10.1016/j.jomd.2016.07.008)
Can we adapt the findings from the CRC study to Non-CRC?

-Our Experience-

We also identified this difference in Ovarian and Breast Cancers.
Accomplishment on GI-SCREEN

As of June, 2018

Cancer genome alteration, MSI, PD-L1, PD-L2 and clinical data (incl. outcome)
Clinical Questions

• Should all cancer patients be tested for MSI / MMR?
• When is the optimal timing for tests?
• Which tests are recommended?
• What is the appropriate biospecimen for tests?
• Which treatment is best for MSI-H / MMR-D patients, particularly for metastatic solid tumors?
• Which line of therapy should immunotherapy be used in MSI-H / MMR-D solid tumors?

etc.
Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO–ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS


1Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; 2CUF Hospitals Cancer Centre, Lisbon, Portugal; 3Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; 4Department of Medical Oncology, University of Ioannina, Ioannina, Greece; 5Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan; 6Department of Medical Oncology, Sun Yat-Sen University (SYSU) Cancer Center, Guangzhou, China; 7Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; 8Department of Radiotherapy & Oncology, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia; 9Division of Medical Oncology, National Cancer Centre, Singapore, Singapore; 10Department of Oncology, National Taiwan University Hospital, and Cancer Research Center, National Taiwan University College of Medicine, Taipei, Taiwan; 11Division of Medical Oncology, Mayo Clinic Cancer Center, Rochester, USA; 12Cancer Institute, Zhejiang University, Hangzhou, China; 13Division of Oncology, Department of Internal Medicine, Yonsei Cancer Center, Seoul, Korea; 14Pantai Cancer Institute, Pantai Hospital Kuala Lumpur, Kuala Lumpur, Malaysia; 15Division of Medical Oncology, National Cancer Centre, Singapore, Singapore; 16National Institute of Cancer Research, National Health Research Institutes, Taiwan, Taiwan; 17Department of Gastrointestinal Medical Oncology, MD Anderson Cancer Centre, Houston, USA; 18Department of Clinical Oncology, School of Medicine, St. Marianna University, Kawasaki; 19Division of Medical Oncology, Cancer Research Institute, Kanazawa University, Kanazawa, Japan; 20Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; 21CBERINC, Department of Medical Oncology, Institute of Health Research, INCLIVA, University of Valencia, Valencia, Spain; 22Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; 23Medical Oncology Department, Vall d’Hebron University Hospital, Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain; 24Department of Medical Oncology and Hematology, Kobe University Hospital, Kobe, Japan; 25Division of Medical Oncology, Seconda Universita di Napoli, Naples, Italy; 26ESMO, Viganello-Lugano, Switzerland

*Correspondence to: Prof. Takayuki Yoshino, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa 277-8577, Japan. Tel: +81-4-7134-6976; Fax: +81-4-7134-6928; E-mail: tyoshino@esest.ncc.go.jp
Summary of Asian Recommendations including consideration of left-versus right-sided primary tumour location

Yoshino T, et al. *Annals of Oncology* 2018

<table>
<thead>
<tr>
<th>Molecular pathology and biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation 6 with revision: Tumour mismatch repair (MMR) testing</strong></td>
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<tr>
<td>6a. <strong>Immunohistochemistry (IHC) tests for MMR proteins or PCR tests for microsatellite instability (MSI)</strong> in the metastatic disease setting can assist clinicians in genetic counselling [Ⅱ, B].</td>
</tr>
<tr>
<td>6b. <strong>Tumour MMR</strong> testing has strong predictive value for the use of immune check-point inhibitors in the treatment of patients with mCRC [Ⅱ, B].</td>
</tr>
</tbody>
</table>

The frequency of DNA MMR deficiency in stage IV CRC is about 4–8% in Western countries [9], and about 1.9–3.7% in Japan [61, 62]. Since Asian experts view IHC and PCR as complementary techniques for evaluating tumour MMR deficiency, all the Asian experts agreed [A=100%] with the recommendations for tumour MMR testing accompanied by the modifications to recommendations 6a and b indicated in bold text above. They also all agreed that tumour MMR testing has strong predictive value for the use of immune check-point inhibitors in the treatment of mCRC patients [63, 64].

**Next Step: GL for MSI-High Solid Tumor**

What we learned from the US FDA Approval

Goal is to identify patients most likely to benefit from treatment

Challenges in drug development for a tumor-agnostic indication

• Study design for providing evidence of clinical efficacy (vs traditional randomized controlled studies)
• Identification of study population
**Liquid Biopsy**

**Liquid biopsies**

- **CTCs (circulating tumor cells)**
  - Cancer cells released from primary tumor mass into the blood stream

- **ctNA (circulating tumor nucleic acids)**
  - ctDNA (circulating tumor DNA), miRNAs, mRNA, and lncRNA

- **Exosomes**
  - Small membrane derived vesicles contain various molecules such as signal proteins, micro RNA, mRNA, lipids, and exoDNA

**Samples:** blood, serum/plasma, urine, CSF, saliva

Advantages of ctDNA Analysis

- Minimal Invasiveness
- Rapid turnaround time
- Low cost of sampling procedure
- Capturing intratumoral heterogeneity
The Guardant360® Assay Receives Expedited Access Pathway Designation for Breakthrough Devices from FDA

NEWS PROVIDED BY
Guardant Health
Feb 15, 2018, 12:18 ET

REDWOOD CITY, Calif., Feb 15, 2018 /PRNewswire/ -- The Guardant360® assay, the leading comprehensive liquid biopsy, received an Expedited Access Pathway (EAP) designation from the United States Food and Drug Administration, Guardant Health announced. If approved, the Guardant360 assay could be the first FDA-approved comprehensive liquid biopsy.

“This marks a critical milestone for our work with the FDA, and an important moment in the development of comprehensive liquid biopsies,” said Guardant Health Co-Founder and President AmirAlik Talasaz. “This designation allows us to work hand in hand with the FDA as we prepare our submission to the FDA later this year. Accomplishing this goal will be critical as we deepen our capabilities for our partners in the biopharma industry.”

Guardant360 is a comprehensive liquid biopsy that helps oncologists select the optimal treatment for advanced cancer patients without the need for an invasive tissue biopsy. Guardant360 has been extensively validated and is supported by more than 20 clinical outcome studies. It is available in more than 30 countries.

The Expedited Access Pathway is intended to speed review of breakthrough technologies and medical devices that serve unmet medical needs. Through the program, the FDA will work with Guardant Health to finalize its data development plan, providing access to senior FDA officials and facilitating a collaborative, cross-disciplinary review. The FDA is expected to replace the EAP soon with its new Breakthrough Devices Program. Premarket Approval Applications from EAP-designated devices typically receive priority review at the FDA, and all submissions designated as Breakthrough Devices are set to receive priority review.

“Our FDA submission for Guardant360 is Guardant Health's top priority for 2018,” said Guardant Health Co-Founder and CEO Helmy Eltoukhy. “The ability to tap into the FDA’s expertise and support will be invaluable as we work toward our goal of seeking the first FDA approval for a comprehensive liquid biopsy.”
Simultaneous Press Release from Japan and USA

**National Cancer Center Japan**

To the press

**SCRUM-Japan GI-SCREEN** Aims for Realizing of Cancer Precision

**Medicine Utilizing Liquid Biopsy by Analyzing Comprehensive Cancer Genome Alterations in Blood**

March 13, 2018

National Cancer Center, Japan

In February 2018, National Cancer Center (President, Dr. Hitoshi Nakagama, Tokyo, Japan) and National Cancer Center Hospital East (Director, Dr. Atsushi Ohtsu, Kashiwa, Japan) launched a new project “Research on Liquid Biopsy in Patients with Advanced Gastrointestinal Cancers”. This study is conducted using a highly sensitive genetic analysis technology “Guardant360® assay” as part of a Nationwide cancer genome screening project for various gastrointestinal cancer, “SCRUM-Japan GI-SCREEN”. The Guardant360® assay, developed by Guardant Health in the U.S. is a new diagnostic technique capable of analyzing fragments of tumor DNA circulating in the blood by next-generation sequencer technology, and providing cancer genetic information accurately and quickly. As conventional tumor tissue biopsies are highly invasive, biopsies of multiple regions and repeated biopsies can cause significant risk to the patients and delays in reaching a treatment decision. However, liquid biopsy is minimally invasive and enables the analysis of fragments of tumor DNA circulating in the blood. For these reasons, it can overcome the problems faced by tumor tissue biopsy.

**Guardant Health and National Cancer Center**

**East Japan Announce Liquid Biopsy Arm of GI Cancer Trial**

REDWOOD CITY, Calif., March 12, 2018 /PRNewswire/ -- The Guardant360® assay, the leading comprehensive liquid biopsy, will be used to launch a new arm of a nationwide trial run by SCRUM-Japan GI-SCREEN, organized by the National Cancer Center Hospital East (NCCEI, Kashiwa, Japan). The study will match patients with advanced gastrointestinal IGI cancer, including gastric and colorectal cancer (CRC), to novel therapies in clinical trials that target specific gene alterations.

COZILA Guardant originates in Zaiatsu Liquid biopsy Arm trial will initially use Guardant360 to test 200 advanced CRC patients in Japan whose cancer has progressed after standard treatment with anti-EGFR therapy. Those who test positive for amplification in the ERBB2 gene will be enrolled in a clinical trial exploring the effectiveness of changing to an anti-ERBB2 combination targeted therapy with trastuzumab + pertuzumab (Clinical trial information: UMIN000030500). The study will expand to include 2,000 patients with a variety of GI cancers and treatment arms.

“We are more than happy to collaborate with Guardant Health to investigate new therapeutic options for patients with GI cancers. Other treatment arms will open in the upcoming year,” said GI-SCREEN Principal Investigator Dr. Takayuki Yoshino.

The study is part of a larger effort in Japan, called SCRUM-Japan GI-SCREEN, to assess the genomic profile of patients with advanced cancer in their GI tracts and match them to associated targeted therapies.

“We are excited to be working with NCCE Japan to help study new therapeutic options for patients in Japan with GI cancers,” said Guardant Health CEO Helmy Eltoukhy. “Tumors that metastasize from the GI tract can be especially difficult to access, making tissue specimen collection challenging. Through a simple blood draw, we can help match these patients to the experimental treatments being studied by NCCE Japan.”
GI-SCREEN GOZILA Project

Umbrella & Basket Clinical Trials (IIS Only to be listed) based on NGS-Based Liquid Screening

GOZILA Project
Guardant Originates in Zipangu Liquid biopsy Arrival

*Each arm to have a junior/senior investigator leadership team
*Flexible design: arms open and close with best available science

**GOZILA Project**

**Guardant**

**Originates in**

**Zipangu**

**Liquid biopsy**

**Arrival**

**Nationwide Genome Screening Project**

**SCRUM-Japan GI-SCREEN**

24 sites

CRC cohort, N = 1,000
• Before anti-EGFR, N = 500
• Refractory to anti-EGFR, N = 500

Non-CRC cohort, N = 1,000
• Gastric cancer, N = 300
• Esophageal cancer, N = 150
• Hepatocellular carcinoma, N = 100
• Biliary tract cancer, N = 150
• Pancreatic cancer, N = 100
• Neuroendocrine tumor/carcinoma, N = 50
• GIST, N = 100
• Others, N = 50

Non-GI Cancer cohort, N = 100

**Pan Cancer**

**ctDNA analysis**

**HER2 Positive**

Trastuzumab + Pertuzumab (TRIUMPH)

**BRAF V600E MT**

Eribulin (BRAVERY)

**BRAF Non-V600E MT**

Binimetinib + Encorafenib + Cetuximab (BIG BANG)

**MET Amplification**

Drug A + Drug B

FPI, 1Q 2019

**Any**

X alteration

Nivolumab (TMB-H basket)

**Any Y alteration**

**X-targeted Tx**

FPI, 1Q, 2019

**Y-targeted Tx**

FPI, 4Q, 2019

**ctDNA analysis**

**CRC Only**

**Non-CRC cohort**

**Non-GI Cancer cohort**

**Pan Cancer**

Nakamura Y, Yoshino T. *Oncologist*. 2018
Global Collaboration for ctDNA Analysis to elucidate the Clinical Utility

**Opportunities for collaboration**
- Pooling and comparing cfDNA profiling results
- Pooling efficacy results (of similar trials)
- Develop novel concepts utilizing blood-based biomarkers
- International multi-site trials for extremely rare targets (FGFR, RET, NTRK1/2/3)
- Pool data for establishing cutoffs (copy number corrected, etc)

**Next steps**
- Follow up at GI ASCO, potentially ESMO – update progress on treatment arms, collaborative data sharing
- Proposal: COLOMATE-GOZILA investigator summit at Mayo CME conference (San Diego, CA) in March 2019
  - Will include pharma collaborators
TMBs Across Various Advanced GI Malignancies in GI-SCREEN & Collaboration with Certain Companies

- The OCP panel can assess TMB with a high correlation with WES.
- TMB varied widely across various advanced GI malignancies.
- TMB analysis may be used as an agnostic histologic indicator to identify patients with GI malignancies who can benefit from immunotherapy

Nakamura Y, Yoshino T. ASCO 2018
TMB-H Basket | Nivolumab for TMB-H GI Cancers

From September, 2018

- Advanced GI cancers refractory or intolerant to standard chemotherapy
  - Colorectal cancer
  - Gastric cancer
  - Esophageal cancer
  - Others (Biliary tract cancer, Pancreatic cancer, Hepatocellular carcinoma, Small intestine cancer, Appendiceal cancer, Anal canal cancer, Neuroendocrine tumor/carcinoma, GIST)
- Tumor mutation burden-high identified by Guardant360

Nivolumab
3 mg/kg DIV, Q2W until PD

Sample size: 70 (40 at 1st stage, 30 at 2nd stage)
Study design: Bayesian two-stage adaptive design
Primary endpoint: Objective response rate (ORR) by RECIST v1.1
Secondary endpoints: Progression-free survival (PFS) by RECIST v1.1 and irRECIST, Duration of response (DoR) by RECIST v1.1 and irRECIST, Disease control rate (DCR) by RECIST v1.1 and irRECIST, Overall survival (OS), Incidences of adverse events

UMIN000033182
Prospective registry study for control data at CTD evaluation:
SCRUM-Japan Registry (since 07/2017)

◆ Data collection for efficacy

Subjects for SCRUM registry

Subjects for SCRUM registry

Lung cancer

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<th>LC-SCRUM</th>
<th>target</th>
<th>Freq. (%)*</th>
<th>Estimated sample size</th>
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<tr>
<td>Non-sq NSCLC</td>
<td>RET fusion</td>
<td>3.0</td>
<td>60</td>
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<td></td>
<td>MET ex14skip</td>
<td>4.8</td>
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<tr>
<td></td>
<td>MET amp</td>
<td>1.0</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>ERBB2 mut</td>
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<td>124</td>
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<tr>
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<td>ERBB2 amp</td>
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<tr>
<td>Sq NSCLC</td>
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<tr>
<td></td>
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<tr>
<td></td>
<td>FGFR3 fusion</td>
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<tr>
<td></td>
<td>PIK3CA amp</td>
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<tr>
<td>total</td>
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*: frequency in the SCRUM-Japan previous cohort

GI cancers

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<th>Freq. (%)*</th>
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<td>MET amp</td>
<td>0.4</td>
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<td></td>
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<td>0</td>
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<td>ERBB2 amp</td>
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<td>Biliary tract cancer</td>
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<td>ERBB2 amp</td>
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<td>IDH1 mut</td>
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<td></td>
<td>PALB2 mut</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>total</td>
<td></td>
<td></td>
<td><strong>195</strong></td>
</tr>
</tbody>
</table>
TRIUMPH Study Design

Eligibility criteria A
- Metastatic CRC
- Age ≥ 20 years
- ECOG PS 0-1
- RAS wild-type in tissue
- HER2 positive confirmed by tissue analysis and/or HER2 amplified and RAS wild-type confirmed by ctDNA analysis
- Refractory or intolerable to standard therapy, including anti-EGFR mAb

Eligibility criteria B
- No prior treatment with HER-targeted therapy
- Measurable lesion based on RECIST
- Adequate organ function
- Normal left ventricular ejection fraction, etc.

Meet eligibility criteria A

Meet eligibility criteria B

Design: Unblinded, single-arm, multi-center phase II study
Primary endpoint*: Objective response rate (ORR) by investigator’s assessment
Secondary endpoints*: PFS, DoR, TTF, DCR, OS, Incidence of adverse events, Efficacy of the previous anti-EGFR treatment
Sample size: 18 patients (25 patients, if enrolled at good rate)

* Endpoints will be evaluated in each analysis set with HER2 positive in tissue or ctDNA

Trastuzumab 8 mg/kg followed by 6 mg/kg + Pertuzumab 840 mg followed by 420 mg Q3W until PD

Natural history follow-up

Nakamura Y, Yoshino T. *Oncologist*. 2018
Ongoing investigator-initiated IND registration study for orphan-fractionated cancer associated with registry data collection: TRIUMPH study / SCRUM-Japan Registry

**HER2 amplified CRC**

**SCRUM-Japan GI-SCREEN**
- 20 participating centers
- TRIUMPH study
- 7 participating centers
- HER2 amplified CRC screened in SCRUM-Japan
  - (HER2 ≥ 4 copies)
- 13 non-participating centers
  - HER2 amplified CRC screened in SCRUM-Japan
  - (HER2 ≥ 4 copies)

**Central labo**
- HER2 IHC
- HER2 ISH

- HER2 positive
- eligible
- out of study for any reason
- ineligible

**study treatment**
- Trastuzumab+Pertuzumab

**SCRUM-Japan Registry**
- Natural history data (internal control)
- Natural history data (external control)

International Harmonization of Diagnostic Criteria for HER2-Amplified Metastatic Colorectal Cancer, collaborated with SWOG-USA, HERACLES-Italy, and Korea
Prospective collaboration for HER-2 +ve for mCRC

**TRIUMPH Study**

- HER2-positive mCRC
- Age ≥ 20 years
- ECOG PS 0-1
- RAS wild-type
- Refractory or intolerable to standard therapy, including anti-EGFR mab

**KOREAN Study**

- HER2-positive mCRC
- Age ≥ 20 years
- ECOG PS 0-1
- RAS wild-type
- Refractory or intolerable to standard therapy, including anti-EGFR mab

**Trastuzumab**
8 mg/kg followed by 6 mg/kg

**Pertuzumab**
840 mg followed by 420 mg Q3W until PD

**Prospective combination for regulatory approval**

Trastuzumab + Pertuzumab + Atezolizumab

Natural history follow-up

**Meet eligibility**

**Not meet eligibility**

Natural history follow-up
Global Collaboration for HER2 Positive mCRC

International Harmonization of Diagnostic Criteria for HER2-amplified colorectal cancer

Meta-analysis projection of HER2-amplified metastatic colorectal cancer

Fujii S, Yoshino T, et al, ASCO 2018

Ongoing project

Ongoing project

Combined natural history
Utilization of Real World Data | Comparison of Endpoints in Each Sub-study with Data in SCRUM Japan Registry

HER2 amplification cohort
- Trastuzumab + Pertuzumab (TRIUMPH)
- HER2 positive mCRC

BRAF V600E MT cohort
- Eribulin (BRAVERY)
- BRAF V600E MT mCRC

BRAF non-V600E MT cohort
- Encorafenib + Binimetinib + Cetuximab (BIG BANG)
- BRAF non-V600E mCRC

MET amplification cohort
- Drug A + Drug B (MET-BEIGE)
- MET-amplified mCRC

Gene X alteration cohort
- X-targeted Tx
- Gene X altered GI cancer

SCRUM Japan Registry

Nationwide Genome Screening Project
- SCRUM-Japan GI-SCREEN

Collection of RWD
- Consultation
- Apply for approval review
- Regulatory Agency
Conclusion

• TODAY:

Elucidate the prevalence & characteristics of MSI-High Pan-Cancer before the launch

• TOMORROW:

New Guideline Projection with US Investigators (Dr. Axel Grothey as one of co-chairs)

• THE DAY AFTER TOMORROW:

Further identification of study population for a tumor-agnostic indication
Utilization of RWD for approval

International Collaboration to get approval from regulators, incl. FDA, EMA and PMDA

Our mission is to provide an engaging smile on patients’ face, prioritized for cancer patients.
Achievement of SCRUM-Japan: The Nationwide Cancer Genome Screening Project


Contact email address; scrum-seika2018@east.ncc.go.jp
Thank you for your kind attention!!

Let’s go where no one has gone before!

tyoshino@east.ncc.go.jp