Imaging Mass Spectrometry of novel drug in human tumor specimens: Distribution of unlabeled drugs to support early phase clinical trial

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Background

- Assessment of drug pharmacokinetics is an important component of early phase drug development.
- Conventional pharmacokinetic analysis has limitations in providing a comprehensive assessment of spatial drug distribution in tissues.
- Imaging Mass Spectrometry (IMS) is an innovative technique in the preclinical study that allows for analysis of the distribution of target molecules in tissues.
- With IMS, we can detect ion of the target molecules in tissues without labeling.
IMS analysis

IMS is initiated by mounting a tissue section on a slide. Applying a matrix solution and laser across the surface of tissue for obtaining mass spectra for drug identification.
Purpose

• The main objective of this study is to verify the efficacy and safety of drugs identification with using IMS.

• We selected olaparib as the drug being identified by IMS.

• The patients who were administered olaparib were participating in a phase 1 trial (NCT01813474).

• Our imaging study was performed as a concomitant of this phase 1 trial.
Method

• In this phase 1 trial, patients with solid tumors received the tablet formulation of olaparib in dose escalation.
• I will show the detailed contents about the phase 1 trial design in the next slide.
• We biopsied in consenting patients during cycle 2 and/or at the time of progression.
• IMS was performed using an Imaging Mass Microscope (Shimadzu, Japan).
• The concentrations of olaparib in tissues were validated by using laser capture microdissection (LCM) and liquid chromatography tandem mass spectrometry (LC-MS/MS).
Trial Design of Olaparib Phase 1 trial

- **Olaparib** (AZD2281, KU-0059436) is a potent inhibitor of poly (ADP-ribose) polymerase enzyme (PARP).
- The primary objective of this Phase 1 study is to investigate the safety and tolerability of olaparib tablet when given orally to Japanese patients with advanced solid malignancies.
- The trial was designed by standard 3+3 cohort to monitor dose-limiting toxicity and to determine maximum tolerated dose.
Olaparib cohort

- Cohort 1; 200mg BID
- Cohort 2; 300mg BID
- Cohort 3; expansion cohort (Cohort 2 is tolerable, 12 patients enrolled to evaluate feasibility of 300mg BID)
Biopsy schedule

The timing of biopsies: during cycle 2 and/or at the time of progression.
## Patients characteristics of IMS study

<table>
<thead>
<tr>
<th>No</th>
<th>Age</th>
<th>Disease</th>
<th>BRCA mutation</th>
<th>Dose</th>
<th>Biopsy site</th>
<th>Best response</th>
<th>Timing of biopsy</th>
<th>Sampling time after dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56</td>
<td>Cervical Cancer</td>
<td>(-)</td>
<td>200mg</td>
<td>Lung TBB</td>
<td>SD</td>
<td>C3D13</td>
<td>9hour 10min</td>
</tr>
<tr>
<td>2</td>
<td>47</td>
<td>Ovarian Cancer</td>
<td>(-)</td>
<td>300mg</td>
<td>Breast CNB</td>
<td>PD</td>
<td>PD(C1)</td>
<td>4hr 15min</td>
</tr>
<tr>
<td>3</td>
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<td>Breast Cancer</td>
<td>(-)</td>
<td>300mg</td>
<td>Lymph node CNB</td>
<td>PD</td>
<td>C2D15</td>
<td>5hr 14min</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>Breast Cancer (+)</td>
<td>(+)</td>
<td>300mg</td>
<td>Breast CNB</td>
<td>PD</td>
<td>PD(C2)</td>
<td>4hr 15min</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>Breast Cancer</td>
<td>(-)</td>
<td>300mg</td>
<td>Breast CNB</td>
<td>PD</td>
<td>C2D15 PD(C3)</td>
<td>30min 30min</td>
</tr>
<tr>
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<td>Peritoneal Cancer</td>
<td>(-)</td>
<td>300mg</td>
<td>Liver CNB</td>
<td>PD</td>
<td>C2D15</td>
<td>6hour 40min</td>
</tr>
</tbody>
</table>

TBB: transbronchial biopsy, CNB: core needle biopsy
Result: Image of Olaparib patient No. 2
(47 y/o ovarian cancer patient, breast core needle biopsy)

Sample size
Width 0.5mm
Length 2 mm
Tissue concentration of olaparib was validated by LC-MS/MS method.

Normalized intensity of olaparib in necrosis area (R1) was higher than that in tumor area (R2+R3).
Result

• Imaging signal levels of olaparib correlated well with the concentration of drug in tumor tissues derived, and that are correlated with conventional techniques used in PK studies.

• Olaparib was distributed in the tumor region and the signal level in areas of necrosis was higher than that observed in living cell areas.
Discussion

• Validation and standardization of IMS would be important to exploit IMS in Proof of Concept study in drug development.

• Further study is needed to explore association between imaging pattern of drug distribution in tumor and clinical response.
Conclusion

• The use of IMS has allowed tracking of distribution of an unlabeled olaparib in target tissues.

• This technique may also allow further understanding of PK/PD relationships for olaparib when dosed in combination with other compounds in future clinical trials.