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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.

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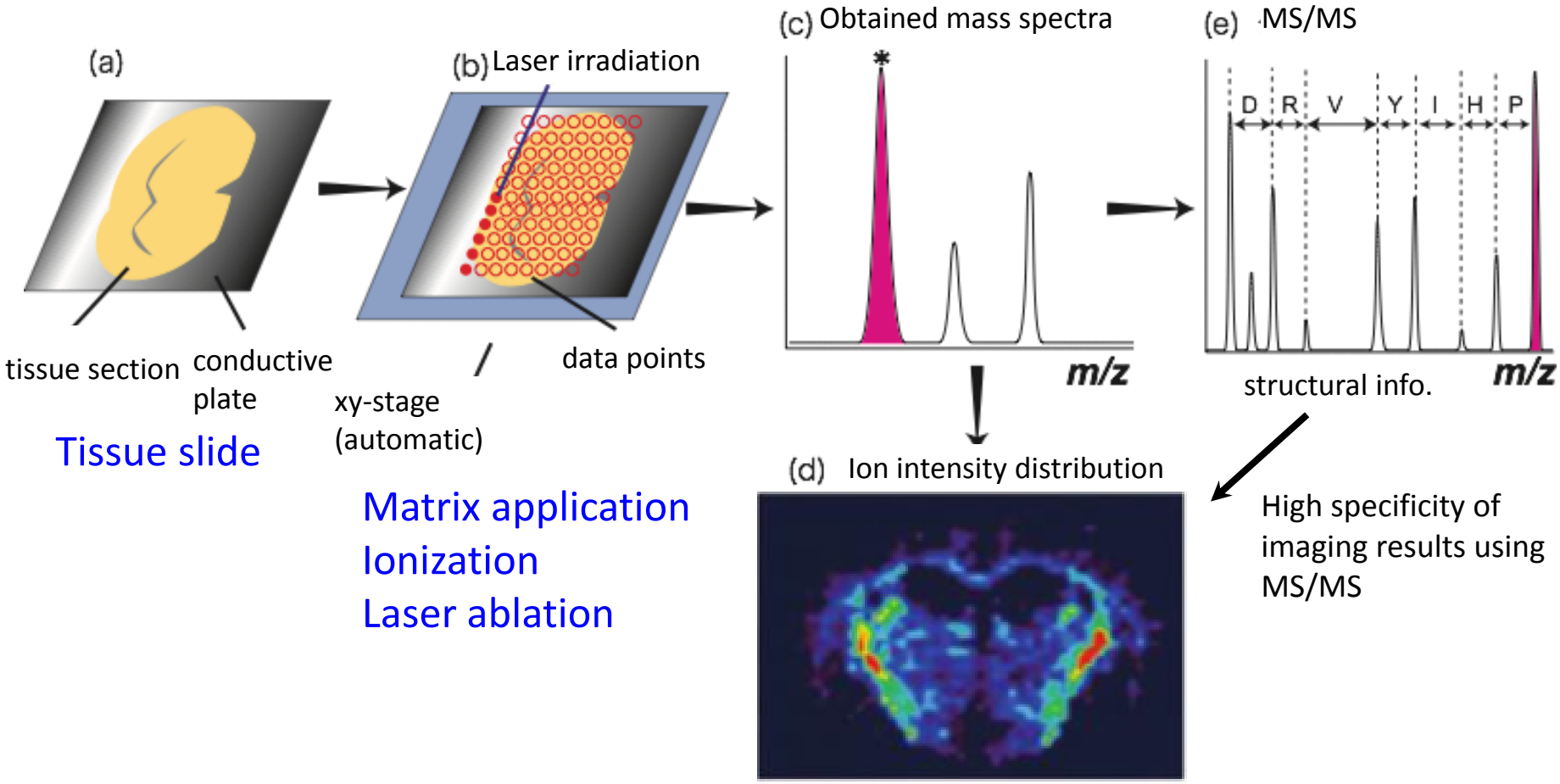
IMS analysis



Tissue slide

Matrix application
Ionization
Laser ablation

High specificity of imaging results using MS/MS

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

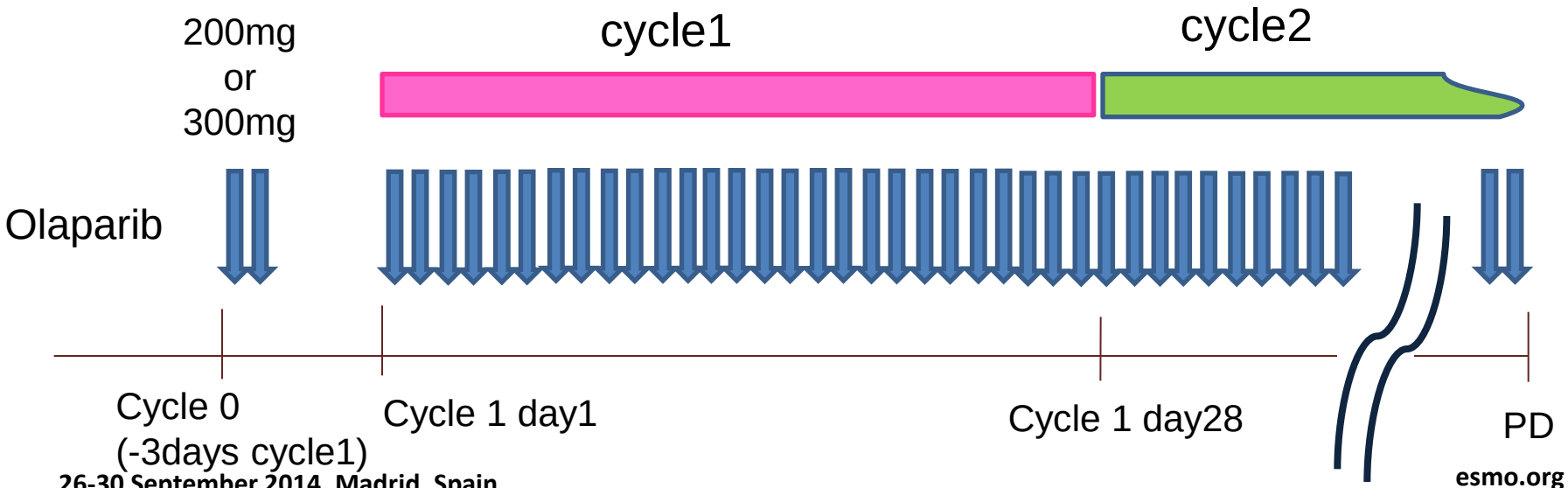
- In this phase 1 trial, patients with solid tumors received the tablet formulation of olaparib in dose escalation.
- I will show the detailed contents about the phase 1 trial design in the next slide.
- We biopsied in consenting patients during cycle 2 and/or at the time of progression.
- IMS was performed 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 Phase1 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.

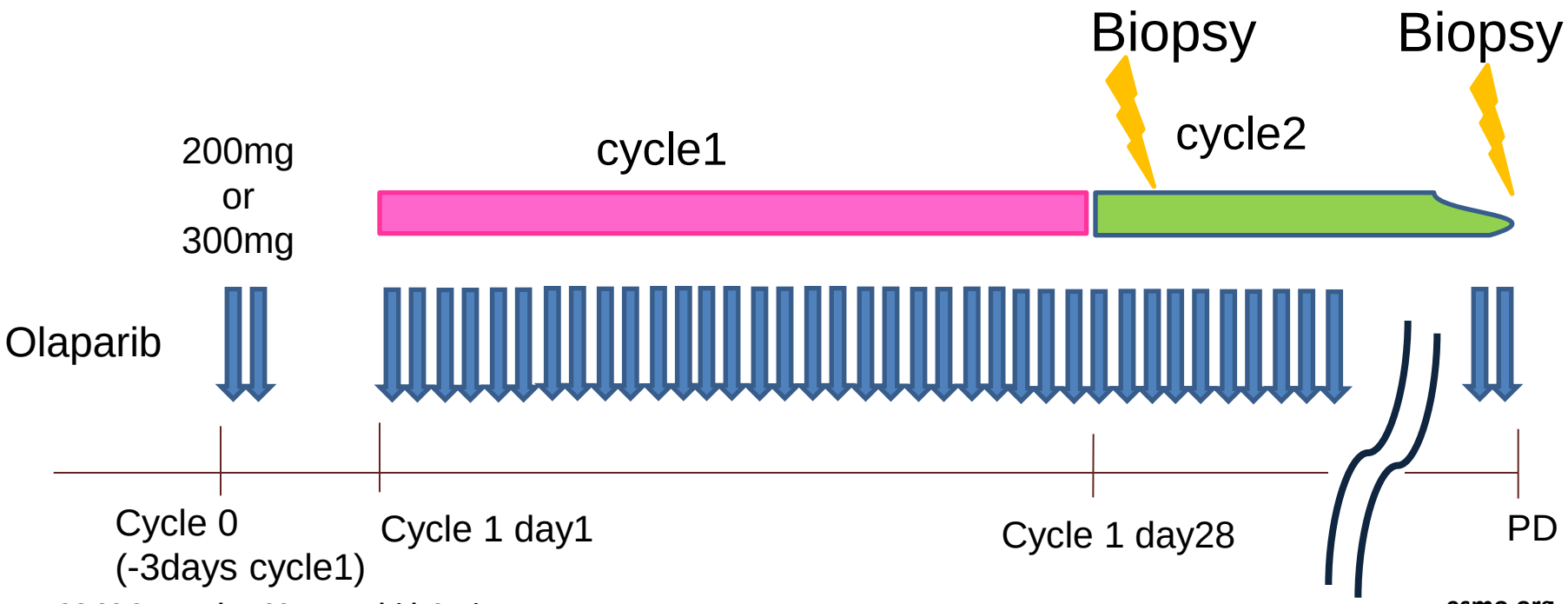
Olaparib cohort

- 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.



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Patients characteristics of IMS study

No	Age	Disease	BRCA mutation	Dose	Biopsy site	Best response	Timing of biopsy	Sampling time after dosing
1	56	Cervical Cancer	(-)	200mg BID	Lung TBB	SD	C3D13	9hour 10min
2	47	Ovarian Cancer	(-)	300mg BID	Breast CNB	PD	PD(C1)	4hr 15min
3	35	Breast Cancer	(-)	300mg BID	Lymph node CNB	PD	C2D15	5hr 14min
4	59	Breast Cancer	(+)	300mg BID	Breast CNB	PD	PD(C2)	4hr 15min
5	48	Breast Cancer	(-)	300mg BID	Breast CNB	PD	C2D15 PD(C3)	30min 30min
6	56	Peritoneal Cancer	(-)	300mg BID	Liver CNB	PD	C2D15	6hour 40min

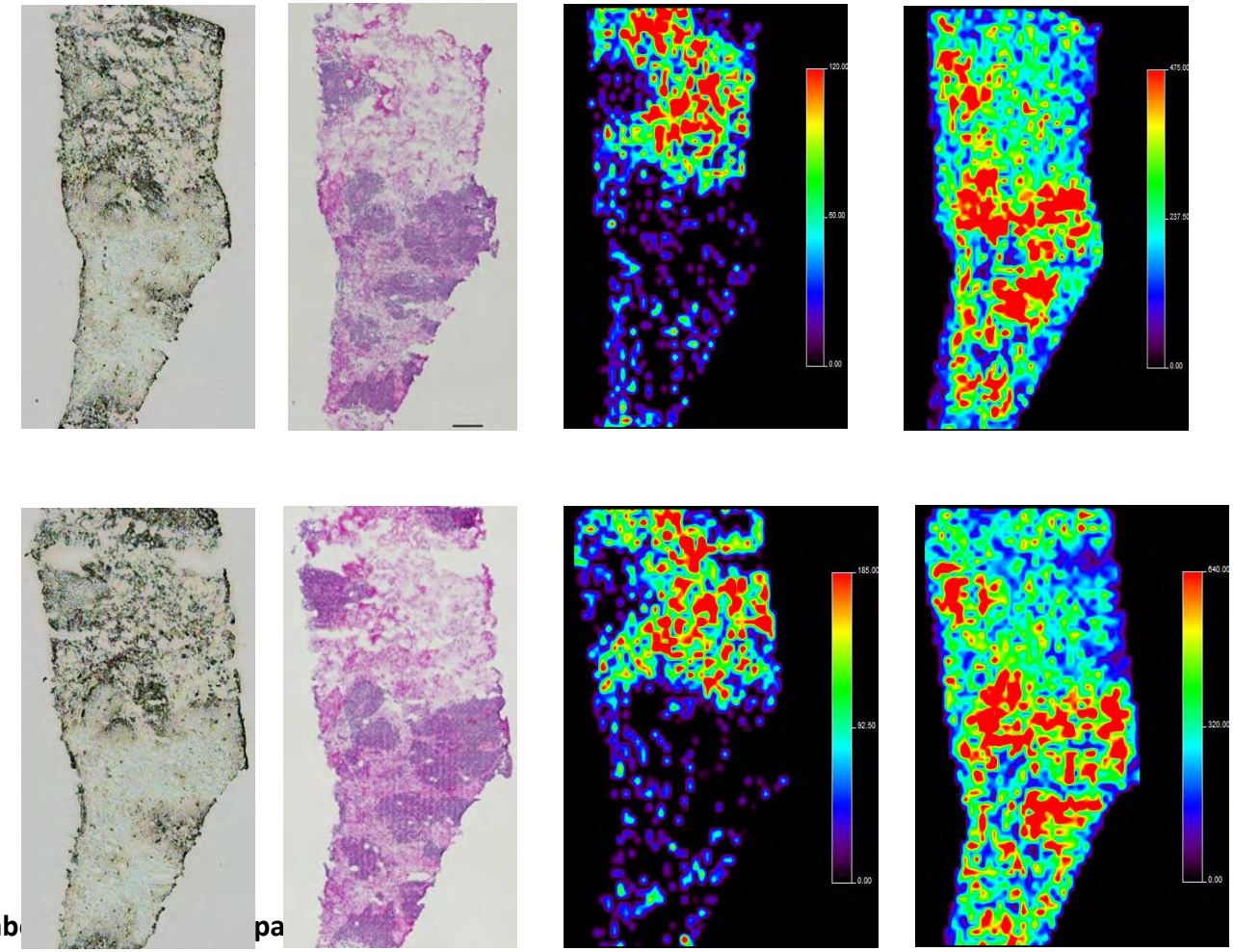
TBB: transbronchial biopsy, CNB: core needle biopsy

Result : Image of Olaparib patient No. 2

(47 y/o ovarian cancer patient, breast core needle biopsy)

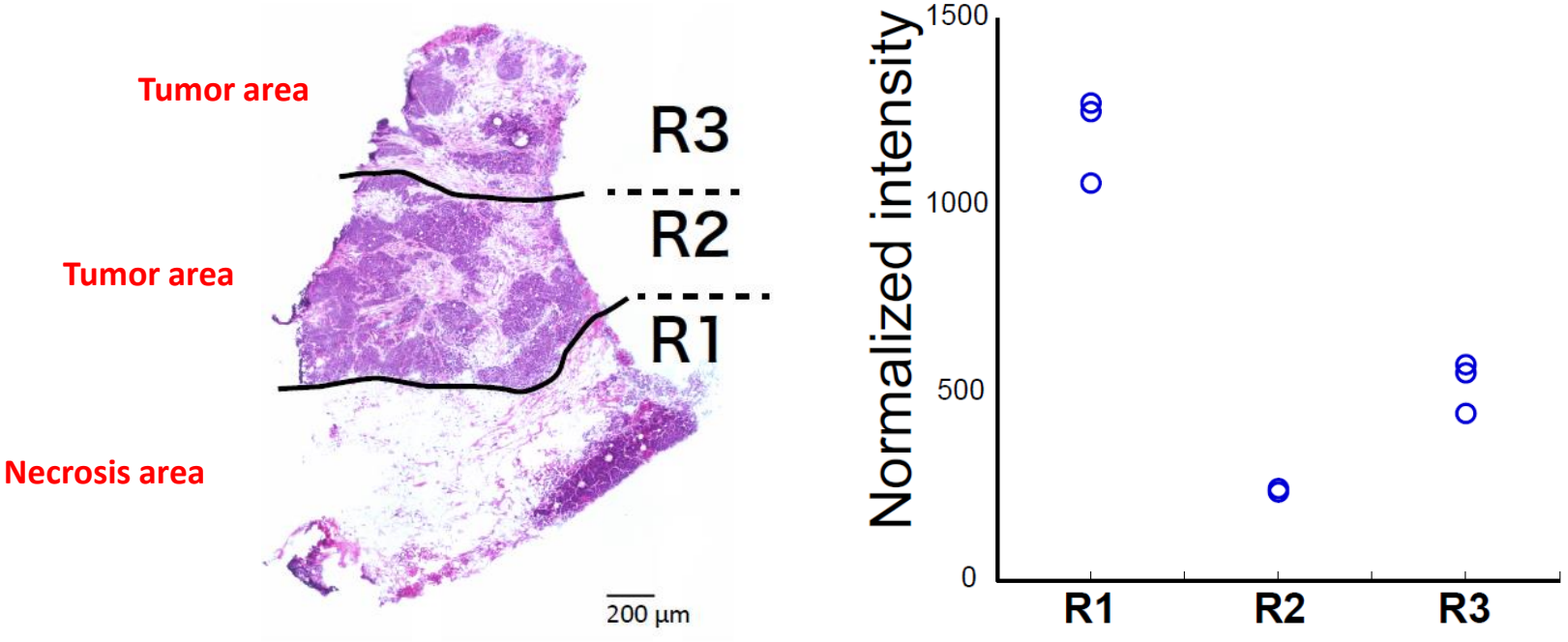
sample H&E stained Olaparib (MS/MS) Reference substance

Sample size
Width 0.5mm
Length 2 mm



Result No.2

Administration: 9:30 (May 31, 2013), Sampling: 13:45 (4h 15 min after dosing)



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