

Practical Consideration For Successful Sequential Tumor Biopsies In First-In-Human Trials

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Abstract

Purpose: In first-in-human (FIH) trials, sequential tumor biopsies, i.e., two consecutive tumor biopsies, the first performed at baseline (pretreatment) and the second during the early treatment period (on-treatment), provide proof of concept in investigational new drugs.

Methods: We evaluated the success of sequential tumor biopsies in FIH trials, and explored approaches for improved success rates. We retrospectively reviewed the sequential tumor biopsies required in 17 of 52 FIH trials conducted from 2015 to 2020.

Results: One hundred and thirty-eight patients were identified. Success of either pretreatment or on-treatment biopsy alone, and of sequential tumor biopsies, was defined as the acquisition of viable tumor cells and as obtaining tumor cells from both biopsy specimens, respectively. The success rates of pretreatment and on-treatment biopsy were 98.6% and 94.2%, respectively, and of sequential tumor biopsies was 70.3%. Adverse events associated with the pretreatment biopsies (33.3% positive; 72.0% negative) and timing of the first imaging assessment (before on-treatment biopsy = 40.0%; after on-treatment biopsy = 82.7%) correlated with successful sequential tumor biopsies. The reasons for unsuccessful sequential tumor biopsies could be categorized into two groups: 1) patient refusal of the on-treatment biopsy (most frequently due to early disease progression); and 2) absence of tumor cells in the pretreatment or on-treatment biopsy specimen.

Conclusion: We propose an approach to achieving greater success in sequential tumor biopsies in FIH trials; the first imaging assessment during the study should be scheduled after on-treatment biopsy.

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Introduction

In recent decades, sequential tumor biopsies, i.e., two consecutive tumor biopsies, the first performed at baseline and the second during the early treatment period, have often been included in phase I trials, especially first-in-human (FIH) trials, to provide proof of concept of investigational new drugs (INDs), the biologic effect of drugs on target molecules, and to assess the tumor microenvironment [1–3]. An increasing number of FIH trials have required sequential tumor biopsies in their protocols [4]. This practice has raised a number of issues, however, including safety and ethical concerns [5–7]. In the past three decades, several studies have focused on the performance of a single tumor biopsy at baseline in clinical trials and have reported a success rate (defined as an adequate number of viable tumor cells) of 70–90% [6, 8–10]. These studies also investigated the different factors affecting successful single tumor biopsies, including biopsy site, technical procedure, size of target lesion, necrosis on imaging, and operator dependence. One study investigated the success rate of sequential tumor biopsies in clinical trials at an academic medical center [11], and reported a success rate of 41.7%. However, no study has analyzed why the success rate of sequential tumor biopsies is notably lower than that of a single tumor biopsy.

Here, we evaluated our performance in FIH trials requiring sequential tumor biopsies and analyzed the detailed reasons for unsuccessful sequential tumor biopsies. We propose an approach to achieving greater success in sequential tumor biopsies in FIH trials.

Materials And Methods

Patient data collection

We conducted a retrospective study of the 17 of 52 FIH trials that required sequential tumor biopsies at the National Cancer Center Hospital (NCCH) in Tokyo from July 2015 to December 2020. We analyzed patient characteristics, including age, gender, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and cancer type. The types of IND, biopsy site, technical procedure, and biopsy outcome (tumor cell acquisition, adverse events [AEs]) were also analyzed. We also evaluated the timing of the on-treatment biopsy and the first imaging assessment during the study.

Definition of terms

We defined the biopsy performed at baseline as the “pretreatment biopsy” and the biopsy performed during the early treatment period as the “on-treatment biopsy.” A pretreatment biopsy or on-treatment biopsy was defined as successful if the acquisition of tumor cells in the specimen was confirmed by the designated pathologist [12]. A pair of sequential tumor biopsies was defined as successful if tumor cells were obtained from both pretreatment and on-treatment biopsy specimens. This study categorized biopsy sites as follows: skin/soft tissue (skin, subcutaneous tissue, breast, and vagina), bone/internal organs (bone, pleura, peritoneum, kidney, and mediastinum), and gastrointestinal tract (stomach, esophagus, and rectum).

We calculated the success rate of sequential tumor biopsies as the number of patients in whom both the pretreatment biopsy and the on-treatment biopsy were performed successfully per the number of patients enrolled in each FIH trial. We graded biopsy-related AEs according to the NCI Common Terminology Criteria for Adverse Events version 4.0. [13].

Statistical analysis

Univariate analysis (Fisher’s exact test) and multivariate analysis (logistic regression model) were performed to examine whether any of the following three factors affected the success of sequential tumor biopsies: ECOG PS, AEs related to pretreatment biopsies, and the first imaging assessment during the study (before vs. after on-treatment biopsy). All tests were two-sided, and a P -value $< .05$ was considered statistically significant. All statistical analyses were performed using commercial software (JMP version 14.3; SAS Inc., Cary, North Carolina, USA).

Result

Patient characteristics and biopsies

A total of 138 patients were identified in the 17 FIH trials (Fig. 1). The numbers of patients who underwent pretreatment and on-treatment biopsy were 138 and 103, respectively. Patient characteristics and type of IND are shown in Table 1. In terms of cancer type, lung cancer was the most common with 70 patients, followed by colorectal cancer with 13 patients. One hundred and ten patients were enrolled in trials of immuno-oncology drugs or antibody-drug conjugates. The most common biopsy sites were lung and lymph nodes (cervical, supraclavicular, mediastinal, and hilar) in both pretreatment and on-treatment biopsies (Fig. 2a and 2b). The most common technical procedures were bronchoscopy and ultrasound (US)-guided needle biopsy in both pretreatment and on-treatment biopsies.

Table 1
a. Patient characteristics

Characteristic	N(%)
Total	138
Gender	
Male/Female	77 (55.8)/61 (44.2)
ECOG^a Performance Status	
0/1	81 (58.7)/57 (41.3)
Age, years	
> 65/≤ 65	35 (25.4)/103 (74.6)
Cancer type	
Lung cancer	60 (43.5)
Colorectal cancer	13 (9.4)
Pancreatic cancer	9 (6.5)
Ovarian cancer	7 (5.1)
Breast cancer	6 (4.3)
Melanoma	6 (4.3)
Sarcoma	6 (4.3)
Head and neck cancer	5 (3.6)
Thymic cancer	5 (3.6)
Esophageal cancer	4 (2.9)
Uterine cancer	3 (2.2)
Bile duct cancer	2 (1.5)
Kidney cancer	2 (1.5)
Neuroendocrine tumor	2 (1.5)
Stomach cancer	2 (1.5)
Other	6 (4.3)
Type of investigational new drug	

Abbreviations: ^aECOG; Eastern Cooperative Oncology Group

Characteristic	N(%)
Immuno-oncology drug	56 (40.6)
Antibody-drug conjugate	54 (39.1)
Immuno-oncology drug and cytotoxic drug	20 (14.5)
Molecularly targeted drug	8 (5.8)
Abbreviations: ^a ECOG; Eastern Cooperative Oncology Group	

Table 1

b. Adverse events related to pretreatment biopsies and on-treatment biopsies

	N, (%)
Pretreatment biopsies	138
Pneumonia (Grade ^a 3)	1 (0.7)
Mediastinal hemorrhage (Grade 2)	1 (0.7)
Biliary fistula (Grade 2)	1 (0.7)
Biopsy-related pain (Grade 2)	1 (0.7)
Hemoptysis (Grade 1)	2 (1.5)
None	132 (95.7)
On-treatment biopsies	104
Mediastinal hemorrhage (Grade 2)	1 (0.9)
Fever (Grade 1)	1 (0.9)
Hemoptysis (Grade 1)	2 (1.9)
None	100 (96.3)
Abbreviation: ^a Grade; Common Terminology Criteria for Adverse Events version 4.0 Grade	

Performance of tumor biopsy sampling

Pretreatment biopsy specimens from two patients did not contain tumor cells (Fig. 2a). The pretreatment biopsy in one patient was performed in the liver, while the on-treatment biopsy was performed in the lung because the pretreatment biopsy specimen did not contain tumor cells. The technical procedures used in on-treatment biopsy of three patients were changed from those used in pretreatment biopsies because of AEs related to the pretreatment biopsies: from US-guided needle biopsy to bronchoscopy ($N = 1$), from US-guided needle biopsy to percutaneous biopsy ($N = 1$), and from computed tomography (CT)-guided

needle biopsy to percutaneous biopsy ($N = 1$). Thirty-three patients did not undergo on-treatment biopsies. On-treatment biopsy specimens from six patients did not contain tumor cells, and specimens from three of these patients contained only necrotic cells, most likely due to the efficacy of the INDs (Fig. 2b).

Table 1a shows the details and AE rates related to pretreatment and on-treatment biopsies. The AE rates for pretreatment biopsy and on-treatment biopsy were 4.3% and 3.9%, respectively. Lung was the biopsy site with the highest frequency of AEs for both pretreatment (7.1%) and on-treatment biopsy (8.3%). Bronchoscopy was the technical procedure with the highest frequency of AEs for both pretreatment (7.6%) and on-treatment biopsies (7.5%).

Performance of sequential tumor biopsies

The success rate of sequential tumor biopsies was 70.3% (95% CI = 62.2–77.3) (Fig. 3a). The number of patients who had successful and unsuccessful sequential tumor biopsies is shown according to each cancer type in Fig. 3b. Pretreatment biopsies were performed in 138 patients, and the biopsy specimens from 136 patients contained tumor cells. Thirty-three patients refused on-treatment biopsy for the following reasons: early disease progression ($N = 21$), *deteriorated* physical condition due to AEs with INDs ($N = 8$), AEs related to the pretreatment biopsies ($N = 3$) and absence of a biopsiable lesion due to tumor shrinkage ($N = 1$). On-treatment biopsies were performed in 103 patients, and the biopsy specimens from 97 patients contained tumor cells.

Timing of the first imaging assessment on successful sequential tumor biopsies

We examined whether the timing of the first imaging assessment during the study affected successful sequential tumor biopsy in Fig. 3c. The first imaging assessments were performed before on-treatment biopsies in 40 patients (6 patients according to the protocol schedule and 34 patients for the purpose of evaluating AEs). Of these 40 patients, successful sequential tumor biopsy was performed in 16 patients (40.0% [95% CI = 26.3–55.4]). Nineteen patients refused on-treatment biopsy due to early disease progression confirmed on imaging ($N = 17$) or clinical symptoms ($N = 2$). Four patients refused on-treatment biopsy for the following reasons: *deteriorated* conditions due to AEs with INDs ($N = 3$) and mediastinal hemorrhage (Grade 2) related to the pretreatment biopsy ($N = 1$). The first imaging assessments were not performed between pretreatment biopsy and on-treatment biopsy in 98 patients. Of these 98 patients, successful sequential tumor biopsy was performed in 81 patients [82.7% (95% CI = 74.0 to 88.9)]. Ten patients refused on-treatment biopsy for the following reasons: *deteriorated* condition due to AEs from INDs ($N = 5$), early disease progression confirmed on clinical symptoms ($N = 2$), the AE of biopsy-related pain (Grade 2) and pneumonia (Grade 3) related to the pretreatment biopsy ($N = 2$), and absence of a biopsiable lesion due to tumor shrinkage ($N = 1$).

Factors correlating with success of sequential tumor biopsies and tumor biopsy sampling

Patient characteristics, including ECOG PS, did not affect successful sequential tumor biopsy (Table 2). AEs related to pretreatment biopsy (33.3% positive; 72.0% negative) did not affect successful sequential tumor biopsy in univariate analysis ($P = 0.0639$), but did in multivariate analysis ($P = .0057$). The timing of the first imaging assessment during the study (before on-treatment biopsy = 40.0%; after on-treatment biopsy = 82.7%) had a major impact on successful sequential tumor biopsies in both univariate and multivariate analysis, with $P < .0001$ in both.

Table 2

Univariate and multivariate analysis of successful sequential tumor biopsy by ECOG Performance Status, adverse events related to pretreatment biopsy, and timing of the first imaging assessment

Factor	Successful sequential tumor biopsy <i>N</i> , (%)	Univariate analysis	Multivariate analysis
ECOG^a Performance Status		$P = .248$	$P = .259$
0	60/81 (74.1%)		
1	37/57 (64.9%)		
Adverse events related to pretreatment biopsy		$P = .0639$	$P = .0057$
Yes	2/6 (33.3%)		
No	95/132 (72.0%)		
Timing of the first imaging assessment		$P < .0001$	$P < .0001$
Before on-treatment biopsy	16/40 (40.0%)		
After on-treatment biopsy	81/98 (82.7%)		
Abbreviations: ^a ECOG; Eastern Cooperative Oncology Group			

Discussion

Sequential tumor biopsies in FIH trials play a key role in providing proof of concept of the mechanism of action of INDs. The difficulty of achieving success with sequential tumor biopsies has been reported [11, 14]. However, no report has suggested approaches to overcome this difficulty. We evaluated our performance of sequential tumor biopsies in the FIH trials and explored approaches for a higher success rate.

Our study shows that the success rate of sequential tumor biopsies in FIH trials was as high as 70.3%. The fact that all patients underwent pretreatment biopsy after enrollment in the FIH trials suggests that these patients were prepared to undergo tumor biopsy sampling as required in the protocols, and that none revoked an earlier agreement to participate on learning of the protocol necessity for biopsy, as has

been reported elsewhere [6, 10, 15]. In both pretreatment and on-treatment biopsies, the success rate of tumor biopsy sampling was considered to be higher than that generally reported, and the rate of biopsy-related AEs was considered lower [9, 11, 14]. AEs related to the pretreatment biopsies were negatively associated with the completion of successful sequential tumor biopsies (Table 2). In selecting biopsy site and type of technical procedure, it is important to maximize the possibility of tumor cells being obtained in the biopsy specimen, but also to minimize the possibility of biopsy-related AEs [16, 17]. The success rate of on-treatment biopsy (94.2%) was slightly lower than that of pretreatment biopsy (98.6%) ($P = .0763$). This was partly related to necrosis in the on-treatment biopsy specimens due to the efficacy of the IND in three patients.

There was a discordance between our success rate in sequential tumor biopsies (70.3%) and the success rate of pretreatment (98.6%) and on-treatment biopsies (94.2%), respectively. The major reason for this discordance was the patients' refusal of on-treatment biopsy ($N = 33$), and 21 out of 33 refusal (63.6%) were related to early disease progression. On-treatment biopsies could not be performed when the patients felt distressed due to early disease progression, even though the biopsy target lesions were larger and easier to biopsy [8, 9]. The American Society of Clinical Oncology has published clear guidelines on tumor biopsy sampling in early-phase clinical trials [18], with the core ethical principles of minimizing risk for participants.

Liquid biopsy is less invasive to the patient than tissue biopsy [19, 20]. Patients would most likely be willing to consent to a blood draw, instead of a painful biopsy procedure, even in the presence of early disease progression. As the number of phase I trials in which patients can participate based on the results of liquid biopsy is increasing, liquid biopsy may be able to replace invasive tumor biopsies [21]. However, liquid biopsy faces barriers in completely replacing tissue biopsy as a means of elucidating the proof of concept of an IND, since it cannot be used to evaluate the microenvironment around the tumor [22].

The success rate of sequential tumor biopsies was significantly lower when the first imaging assessment was performed before the on-treatment biopsy (40.0%) compared to when it was performed after the on-treatment biopsy (82.7%). Patients inevitably refused on-treatment biopsies once the imaging assessments reveal early disease progression. In our study, the first imaging assessments were performed in 40 patients before on-treatment biopsies, and revealed early disease progression confirmed on imaging in 17 patients. All 17 of these patients refused on-treatment biopsies. The first imaging assessment during the study should be scheduled after on-treatment biopsy in the protocol. The first imaging assessments were actually performed before on-treatment biopsy in 6 patients according to the protocol schedule in our study. If imaging assessment was scheduled after on-treatment biopsy in the protocol, the success rate of sequential tumor biopsies could be estimated to improve from 70.3–74.6%. Selecting patients on similar IND protocols but on different imaging schedules would have been a technique to eliminate imaging schedule as a variable.

In conclusion, our research showed that the success rate of sequential tumor biopsy in FIH trial was as high as 70.3%. We analyzed the detailed reasons for unsuccessful sequential tumor biopsy. We propose a reasonable approach to achieve greater success in sequential tumor biopsy in FIH trials; the first imaging assessment during the study could be recommended to be scheduled after on-treatment biopsy.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional Review Board of National Cancer Center Hospital (approval no: 2014-148) and with the 1964 Helsinki declaration and its later amendments or with comparable ethical standards. Informed consent was obtained in the form of optout on the website and bulletin board of our hospital.

Consent for publication

Not applicable.

Availability of data and material

The datasets supporting the conclusion of this article are included within the article.

Competing interests

All authors declare neither financial interest that is relevant to the submitted work.

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Author contributions

TK, TS, JS, YK, and NY: Conceptualization, methodology, investigation, writing the original draft, and revising the manuscript.

SI, SK, TY, KS, MN, YT, and KY: Investigation and revision of the manuscript.

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Compliance with Ethical Standards

Disclosure of potential conflicts of interest

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Research involving Human Participants and/or Animals

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional Review Board of National Cancer Center Hospital (approval no: 2014-148) and with the 1964 Helsinki declaration and its later amendments or with comparable ethical standards.

Informed consent

Informed consent was obtained in the form of optout on the website and bulletin board of our hospital.

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Figures

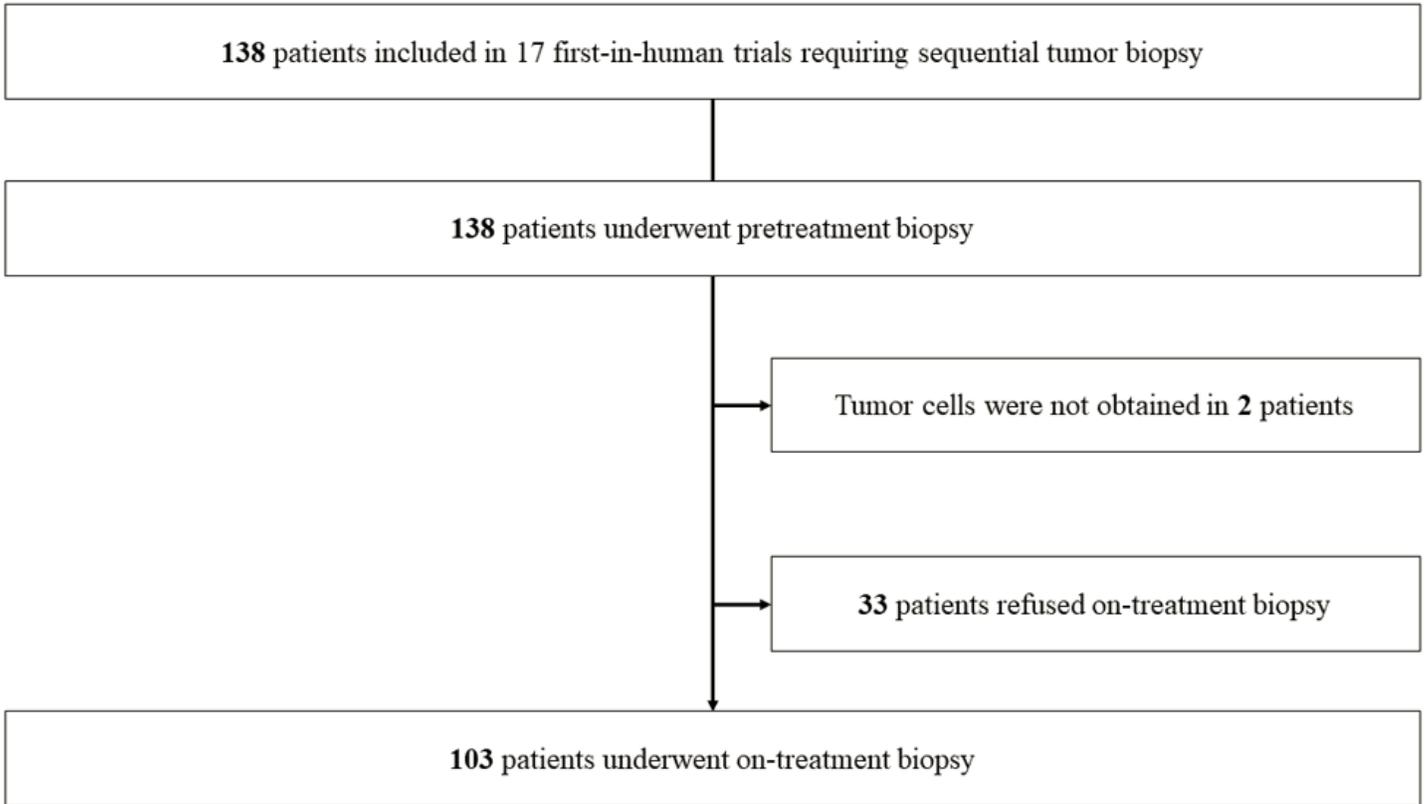


Figure 1

Patient flow diagram

All 138 patients who were enrolled in 17 oncology first-in-human trials that required sequential biopsies underwent pretreatment biopsies. Two patients had no tumor cells in the pretreatment biopsies. Thirty-three patients refused on-treatment biopsy, with 103 patients undergoing on-treatment biopsies.

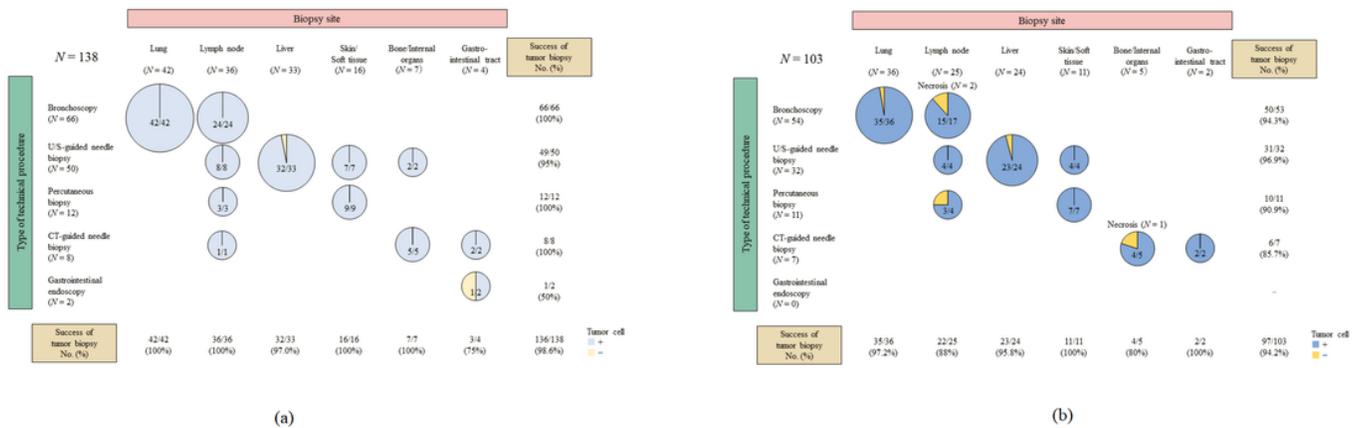


Figure 2

a Biopsy site and technical procedure in pretreatment biopsy

Each pretreatment biopsy and on-treatment biopsy were defined as successful if the acquisition of adequate tumor cells in the specimen were confirmed by the designated pathologist. This study categorized biopsy sites as follows; skin/soft tissue (skin, subcutaneous tissue, breast, and vagina), bone/internal organ (bone, pleural membrane, peritoneal membrane, kidney, and mediastinum), and gastrointestinal tract (stomach, esophagus, and rectum). The success rate of tumor biopsy sampling in the pretreatment biopsy was 98.6%.

b Biopsy site and technical procedure in on-treatment biopsy

The success rate of tumor biopsy sampling in the on-treatment biopsy was 94.2%. On-treatment biopsy specimens from six patients did not contain tumor cells, and specimens from three of these patients contained only necrotic cells, most likely due to the efficacy of the INDs revealed necrosis based on evaluation of H&E-stained slides by pathological diagnosis.

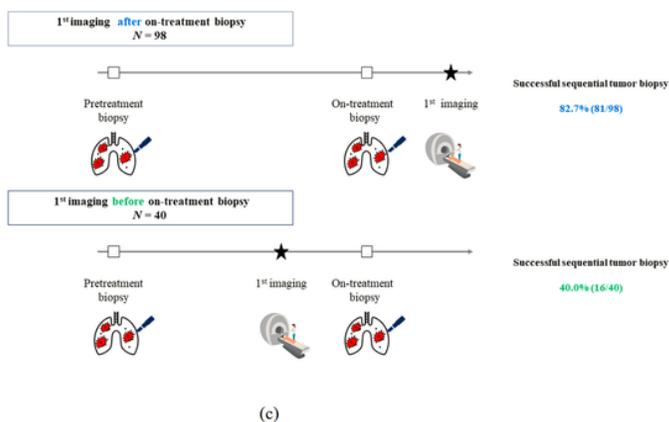
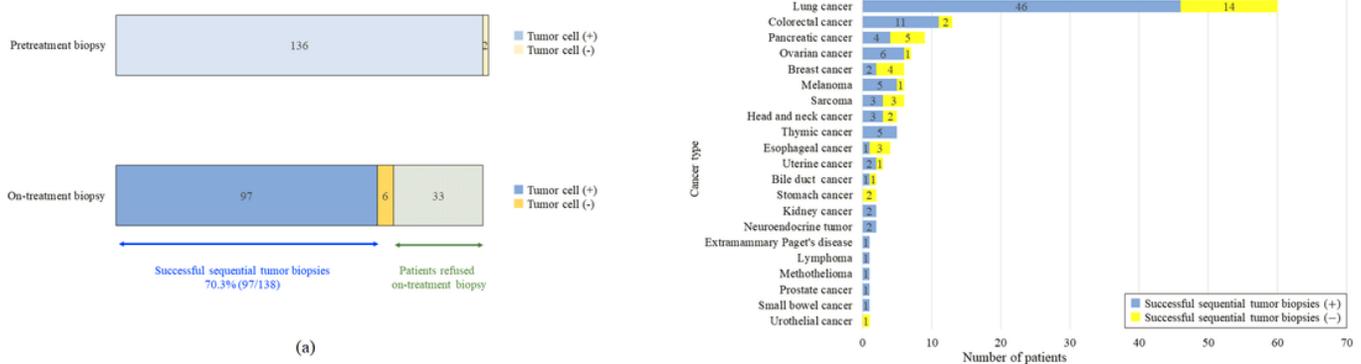


Figure 3

a Success of sequential tumor biopsy

The sequential tumor biopsies were defined as successful if tumor cells were obtained from both pretreatment and on-treatment biopsy specimens. The success rate of sequential tumor biopsies was 70.3%. All 138 patients who were enrolled in 17 first-in-human trials underwent pretreatment biopsy ($N=138$). An on-treatment biopsy was not carried out in 33 patients because of the patients' refusal. A total of 103 underwent on-treatment biopsy, with 97 biopsies considered successful.

b Successful sequential tumor biopsy by cancer type

The number of patients who had successful sequential tumor biopsies and the number of patients who did not have successful sequential tumor biopsies by cancer type are shown.

c Impact of 1st tumor imaging timing on successful sequential tumor biopsy

Of the forty-three patients undergoing the first imaging assessment before on-treatment biopsy, 16 patients subsequently underwent on-treatment biopsy (41.0%). The first imaging assessments were not performed between pretreatment biopsy and on-treatment biopsy in 95 patients. Of these 99 patients, successful sequential tumor biopsies were performed in 81 patients (81.8%).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementsequentialtumorbiopsy.pdf](#)