Breast Cancer Research and Treatment (2022) 194:171–178
https://doi.org/10.1007/s10549-022-06611-6

EPIDEMIOLOGY

Patient perspectives on window of opportunity clinical trials in early-stage breast cancer

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Received: 17 January 2022 / Accepted: 13 April 2022 / Published online: 11 May 2022

Abstract

Purpose Window of opportunity trials (WOT) are increasingly common in oncology research. In WOT participants receive a drug between diagnosis and anti-cancer treatment, usually for the purpose of investigating that drugs effect on cancer biology. This qualitative study aimed to understand patient perspectives on WOT.

Methods We recruited adults diagnosed with early-stage breast cancer awaiting definitive therapy at a single-academic medical center to participate in semi-structured interviews. Thematic and content analyses were performed to identify attitudes and factors that would influence decisions about WOT participation.

Results We interviewed 25 women diagnosed with early-stage breast cancer. The most common positive attitudes toward trial participation were a desire to contribute to research and a hope for personal benefit, while the most common concerns were the potential for side effects and how they might impact fitness for planned treatment. Participants indicated family would be an important normative factor in decision-making and, during the COVID-19 pandemic, deemed the absence of family members during clinic visits a barrier to enrollment. Factors that could hinder participation included delay in standard treatment and the requirement for additional visits or procedures. Ultimately, most interviewees stated they would participate in a WOT if offered ($N = 17/25$).

Conclusion In this qualitative study, interviewees weighed altruism and hypothetical personal benefit against the possibility of side effect from a WOT. In-person family presence during trial discussion, challenging during COVID-19, was important for many. Our results may inform trial design and communication approaches in future window of opportunity efforts.

Keywords Patient perspectives · Window of opportunity · Clinical trials · Breast cancer

Introduction

Historically, investigational cancer drugs have been tested in patients with advanced stage and heavily pretreated cancer and, if found efficacious in that population, have been moved earlier in the disease course. This approach to drug development has led to great success, but has its drawbacks: drugs may function differently at various points during tumor progression as the microenvironment changes and as treatment resistance develops [1]. Examining serial tissue samples in advanced stage patients may accelerate development and optimization of therapies [2], but may impose burden on patients [3].

An alternative approach for testing investigational cancer drugs is to enroll patients with early-stage cancer in "window of opportunity trials" (WOT). In these trials, patients with newly diagnosed early-stage cancer are given a drug

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during the time between diagnosis and the start of their standard treatment [4]. These trials are distinguished from neoadjuvant treatment trials, which are available to a similar population, in that their primary endpoints are typically translational rather than clinical—most commonly relating to cancer cell proliferation [5], biological pathway inhibition [6], or microenvironmental changes [7]—and occur before standard treatment begins. As such, they do not change the standard treatment, nor do they aim to improve the trial participant's personal outcome.

To date, WOT have provided early readouts on drug dosing [8], drug targets [5], and biomarkers of sensitivity and resistance [9]. They have also answered long-standing questions about the anti-cancer activity of repurposed drugs, such as metformin [10]. WOT could play a major role in accelerating the understanding of breast cancer biology and treatment in the decades to come, underscoring the importance of understanding the patient perspective on this unique type of clinical trial.

The window of opportunity design brings with it specific challenges and opportunities for trial participants that are distinct from other clinical trials [11]. Both phase 1 clinical trials and WOT have endpoints that do not directly translate into participant benefit, and prior research has shown that a major driver for participants in phase 1 clinical trials is altruism [12]. However in a WOT the decision about participation must be made soon after a person's cancer diagnosis and some WOT may bring delays in standard treatment [13].

Clinical trial participation among cancer patients remains very low with less than 5% of adults with cancer in the USA ever enrolling in a trial [14, 15], and a detailed understanding of patient perspectives is essential to reduce barriers [16]. While the number of WOT is rapidly increasing, with hundreds currently registered on clinicaltrials.gov, data on patient perspectives about these trials have been limited [17]. In this study, we sought to understand patient views on WOT in early-stage breast cancer using qualitative methods. We used the theory of planned behavior, a well-validated decision-making model [18] that has been used to understand cancer patients' decisions about clinical trials in prior studies [19]. Our results provide important context for WOT development and shed light on patient perspectives on barriers to participation in clinical trials, including during the COVID-19 pandemic.

Methods

Study design

Working with subject experts and patient advocates, we designed a semi-structured interview guide. The interview guide included a description of WOT, which was revised by three medical oncologists with expertise in clinical trial research and three patient advocates to ensure accurate and clear language. The interview guide included open-ended questions tailored to address the three constructs of the theory of planned behavior: attitudes about the behavior (attitudes), beliefs about the normative expectation of others (normative factors), and beliefs about factors that may hinder the performance of the behavior (perceived behavioral control). Prior to study start, the interview guide was piloted on two women with a personal history of breast cancer and further refined for clarity. The first 10 interviews were completed prior to the onset of the COVID-19 pandemic and afterward, additional questions were added to explore the impact of the pandemic on patient perspectives in subsequent interviews. The final version of the semi-structured interview guide is attached in the Appendix. This study is reported in accordance with the Standards for Reporting Qualitative Research (SRQR) reporting guidelines [20].

Patient sampling

We recruited and enrolled patients from a single-academic medical center, Stanford Cancer Center, with treatment centers in Palo Alto and San Jose, California. A research coordinator identified eligible patients by chart review who met the following inclusion criteria: adults at least 18 years of age, English-speaking, with a diagnosis of clinical anatomic stage I or II breast cancer, and awaiting treatment (no prior therapy for breast cancer). Patients who were recently diagnosed and awaiting treatment are intentionally chosen to capture perspectives in the window period as depicted in Fig. 1. The research coordinator reviewed the study information with the patient, obtained oral consent, and provided the patient with a research information form. All participants were offered a $25 gift card as compensation for their time and were scheduled for a one-on-one phone interview. After the first 20 interviews, the research coordinator screened to increase the racial/ethnic diversity of the subsequent participants in order to increase the potential for the study's findings to be applicable to other contexts and populations. The Stanford University Institutional Review Board approved all methods prior to study start.

Data collection and analysis

An investigator trained in qualitative research (DP) conducted all interviews using the semi-structured interview guide. Questions were only asked if that topic was not discussed organically when participants responded to prior open-ended questions. No follow-up interviews were conducted to clarify or obtain additional information. The interview was audio recorded and transcribed verbatim on an encrypted computer, and the document

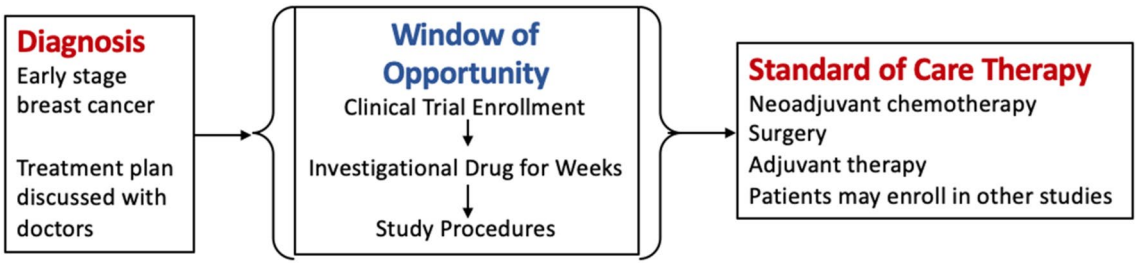

Fig. 1 Window of opportunity depiction

was de-identified with the removal of all protected health information by the interviewer. The transcript was imported into qualitative data management software (Dedoose 8.0.35) [21].

The interviewer read samples of the transcribed text and created codes under the constructs of the theory of planned behavior. The research team (DP, LK, SB, DH, VL), including three breast cancer patient advocates, convened to review the codes and associated quotations. Through an inductive process, we created a codebook that was used by two experienced coders (DP, AA) who independently and consecutively coded full transcripts and discussed discrepancies. We calculated a Cohen's kappa to measure coder consistency with the minimum standard of Cohen's kappa 0.7, achieving a Cohen's kappa of 0.97 [22]. The research team then inspected excerpts across all major codes to identify emergent patterns, repetitions, and opportunities for comparison. We performed thematic analysis of the unique 285 quotations and reached thematic saturation (when further analysis revealed no new themes). We conducted content analysis to determine the number of times each theme emerged.

Results

Patient characteristics

A total of 89 patients who were seen for a new patient visit at Stanford Cancer Center between January 2020 and September 2021 were offered the interview of which 33 patients consented (37%) and ultimately 25 (28%) completed the study interview. The 25 interview participants were of age range 31–71 (mean 56.79, SD 10.38). All interviewed patients were female ($N=25$, 100%) and the majority were of White race ($N=16$, 64%), with Asian ($N=3$, 12%), Black ($N=3$, 12%), Hispanic ($N=2$, 8%), and American Indian ($N=1$, 4%) patients also represented. All patients were diagnosed with early-stage breast cancer, 52% Stage I ($N=13$) and 48% ($N=12$) Stage II, and the majority were diagnosed with hormone receptor-positive, HER2-negative breast cancer ($N=21$, 84%). The majority of patients were awaiting their surgery as their first definitive treatment ($N=22$, 88%). A summary of patient demographic and clinical characteristics is depicted in Table 1.

Table 1 Demographic and clinical characteristics of participants

Demographic/clinical factor	*n*	%
Gender		
Male	0	0
Female	25	100
Age		
< 40	1	4
40–50	6	24
51–60	9	36
60–70	8	32
> 70	1	4
Race/ethnicity		
Non-Hispanic white	16	64
Black	3	12
Hispanic	2	8
Asian	3	12
American Indian	1	4
Highest education		
High school	4	16
College	10	40
Masters	7	28
Doctorate	4	16
Stage (AJCC 7)		
Stage I	13	52
Stage II	12	48
Molecular subtypes		
HR-positive/HER2-negative	21	84
HER2-positive	2	8
TNBC	2	8
First definitive treatment		
Surgery	22	88
Neoadjuvant chemotherapy	3	12

Understanding window of opportunity clinical trials

Only one participant reported having been offered a clinical trial in the past, and none had prior experience with a WOT. After participants heard the prepared description of WOT, they were asked "Do you have any questions about this clinical trial design?" and all questions were answered by the interviewer. All participants were able to answer the follow-up question "What is your understanding about how this (WOT) might differ from a standard clinical trial?".

"The clinical trial is happening before treatment, so the patient would still get the planned surgery or treatment." (Participant #2).

"The window trial happens before any other treatments, so there isn't anything in the patient's system to confuse things and the doctors can better see the effects of the trial treatment." (Participant #12).

Decision-making factors in window of opportunity trial participation

The theory of planned behavior proposes three constructs that together predict decision-making, including initial attitudes about the implications of a behavior (attitudes), beliefs about the normative expectation of other people (normative factors), and beliefs about the presence of factors that may further or hinder the performance of the behavior (perceived behavioral control) (Fig. 2). In our analysis, we identified 17 themes related to these three constructs of the theory of planned behavior. After the 23rd interview, there were no new themes generated from the interviews, and it was therefore deemed that the data collection had reached a saturation point. There was considerable interaction and overlap between the initial 17 themes and we further classified them into seven overarching themes. This thematic framework with frequencies is shown in Table 2.

Attitudes

The majority of participants ($N=23$) identified at least one positive attitude toward WOT, most commonly a desire to contribute to research ($N=22$) and a hope for personal benefit ($N=16$).

Participants noted research is important to improve future breast cancer treatments and expressed a willingness to participate in a WOT because of an altruistic desire to advance science ($N=16$). Some participants reported they would want to contribute to cancer research to help future generations ($N=8$), and some highlighted that doing so would provide meaning to their cancer diagnosis ($N=5$).

"If there's a drug that has to be tested the only way is through research on people like myself, and the more research we do the better the treatments for cancer will be. So I guess it's important for people like myself, to take a chance and give doctors more technology to help other patients." (Participant #1).

"I think that if we contribute by participating in this type of clinical trial it's going to help future generations and that's very important. I have cancer now, there's nothing I can do about that, but if I can help along the way… I think that's meaningful." (Participant #3).

Participants were coached at the beginning of the interview that any personal benefit of the experimental drug in a WOT is unlikely because of the short duration of treatment. Despite this information, many participants remained hopeful that a clinical trial drug could provide personal benefit ($N=16$). Some participants expressed interest in genomically targeted treatments ($N=3$) and many felt any additional treatment might shrink their cancer ($N=14$).

"I think you'd feel like at least something was being done rather than being in a holding pattern, and if you're taking something that has an even a small possibility of shrinking or doing something to the tumor before surgery, that feels positive." (Participant #20).

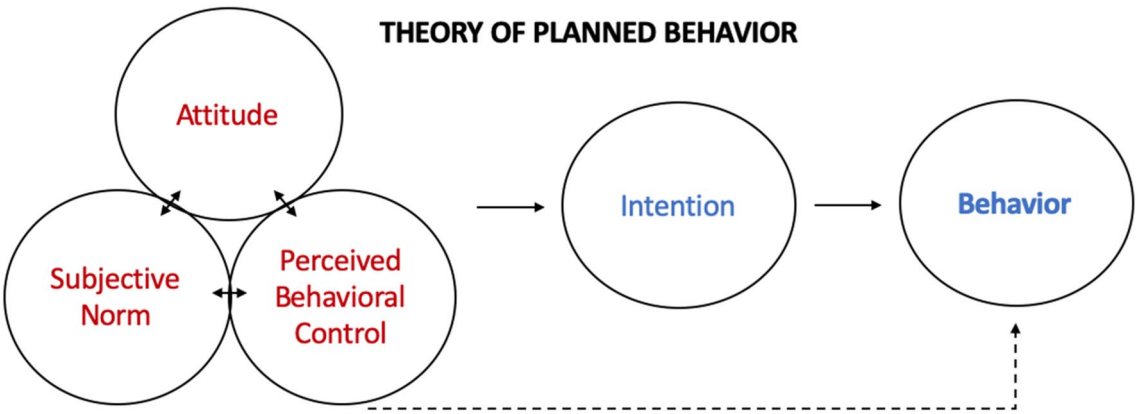

Fig. 2 Theory of planned behavior

Table 2 Themes, subthemes, and content analysis

Theory of planned behavior construct	Theme subtheme	Number of patients ($n=$)	Percent of patients (%)
Attitudes	**Desire to contribute to research**	22	88
	To help advance science	16	64
	To help future generations	8	32
	To provide meaning to cancer diagnosis	5	20
	Personal benefit	16	64
	Shrink my cancer	14	56
	Access to a targeted drug	3	12
	Drug side effects	21	84
	Impact on future treatment plan	17	68
	Long-term side effects	6	24
	Unknown side effects	5	20
	Mistrust in research		
	Historical deception of African Americans	1	4
Normative factors	**Support of other people**	20	80
	Family members important	19	76
	Oncologist recommendation	1	4
	COVID-19 restricts support system	7	47
Behavioral control	**Delays**	23	92
	Any delay causes distress	20	80
	Short delay acceptable	3	12
	Clinical trial procedures	18	72
	Additional time required	10	40
	Additional biopsies	13	52
	Costs of trial procedures	4	16
	Appreciation for COVID-19 modifications	10	67
	COVID-19 screening questionnaires	8	53
	Virtual visits	2	13

"I think especially if the clinical trial was for a targeted drug without chemotherapy I would be interested because it could be one of those miracle drugs and shrink my tumor. I think this would be a great opportunity while waiting anyways." (Participant #4).

Although many participants had favorable initial attitudes about WOT, the most common negative attitude toward WOT identified was participants' concern about how the side effects from the investigational therapy could affect them ($N=21$). Participants were particularly worried about how therapy side effects might impact their fitness and ability to get other planned treatments ($N=17$), about long-term side effects ($N=6$), and about unknown side effects of an experimental therapy ($N=5$).

"I would worry about long-term side effects. You know I have a curable cancer and if I were to walk away with a long-term side effect because of a clinical trial that would not sit well with me." (Participant #6).

"I would not want to experience a side effect that could make my upcoming surgery more difficult. I want to be in the best physical state I can be for my surgery." (Participant #12).

One participant's initial attitude about WOT was grounded in her mistrust in clinical trial research due to historical deception of African Americans in research ($N=1$).

"What makes me uncomfortable is historically people of color have been taken advantage of in clinical trials, like I know all about the Tuskegee Syphilis clinical trials. I don't think I am alone because many African American people might be reluctant to participate because of the past history." (Participant #23).

Normative factors

Participants were asked to reflect on external factors, including people who would impact their decision to participate in a WOT. Most participants identified family members such as a sibling, a partner, or children who would play an important role in helping them decide ($N=19$). By contrast, only one

patient identified their oncologist as a key person in their decision-making process.

"Well I have two very intelligent young daughters who have been very involved and they're very good at asking questions. When I don't understand something related to my cancer treatment plan, they are very helpful at explaining it or being an advocate for me to get the answers." (Participant #5).

Of the fifteen participants interviewed after the onset of the COVID-19 pandemic (from March 2020 to November 2020), seven pointed out that during the COVID-19 pandemic, Stanford Cancer Center restricted family presence at clinic visits as an infectious precaution. They identified this as a barrier because not having a support person present could make it more difficult to decide to enroll in a WOT.

"These days you can't have an advocate with you unless you have a disability, which I totally understand but to enroll on a clinical trial would be very difficult when you don't have your support system with you whether they're actively involved in the conversation or they're just sitting next to you." (Participant #19).

Perceived behavioral control

Two themes emerged regarding factors that might further hinder participation in a WOT: delay in standard treatment and the requirement for additional visits or procedures.

Nearly all participants expressed a sense of urgency to get treatment for their cancer, either surgery or neoadjuvant chemotherapy, and most stated any delay in treatment would be difficult to accept ($N=20$). A few participants who had been informed that their tumors were slow growing expressed comfort with delays up to 2 weeks ($N=3$).

"Since the time I got diagnosed I have wanted to get surgery as soon as possible, and it has taken some time to schedule, so I would not want any delay." (Participant #16).

"I think I would be okay with a delay of 1–2 weeks because I don't think it's going to grow that fast in that timeframe. But again, I do have a little bit of anxiety about any delay and would wonder—is it spreading?" (Participant #18).

Some participants reacted to additional visits or procedures by commenting on the inconvenience of the time required ($N=10$) and few highlighted the potential costs associated with the additional visits and procedures ($N=4$). Many participants reflected on the need for additional biopsies and the discomfort they experienced with their initial biopsies ($N=13$). However, of the 18 participants who raised concerns about trial procedures, only 2 volunteered that this might change their decision to participate.

"I am very conscious about the time that I have to put aside for regular treatments. So, if I have to put in extra time to do extra testing…that could become annoying." (Participant #1).

"I didn't like the biopsies but I think I'd be willing to do another one for testing. I don't know how many more I would like to do, because they are quite painful." (Participant #9).

Participants who were interviewed after the onset of the COVID-19 pandemic did not express concerns about contracting COVID-19 as a result of healthcare exposure during a WOT. Participants described adjusting to medical care during the pandemic and an appreciation for the virtual visits ($N=2$) and infectious precautions, such as screening questionnaires ($N=8$) in the hospitals.

"I can imagine that having more visits and seeing more people could be unsettling for some people, but for me, that's not a big concern because I wear a mask and take precautions. I know other people who are visiting the hospital are also taking precautions and I like that the hospital is doing questionnaires at the front door." (Participant # 18).

Willingness to participate in a window of opportunity clinical trial

At the end of the interview, all participants were asked "If you were offered a window of opportunity trial today based on our conversation and anything you have learned, would you or would you not consider participation?" The majority stated they would participate ($N=17$). Those participants who stated they would not participate identified the following factors as major reasons: drug side effects ($N=7$), delays ($N=5$), additional visits and procedures ($N=2$), and inability to have family support during the pandemic ($N=2$).

There was no difference in the proportion of patients willing to participate before and after the start of the COVID-19 pandemic ($N=7/10$ and $N=10/15$, respectively). When participants were asked "Has the COVID-19 pandemic impacted your willingness to participate in a window of opportunity clinical trial?" the majority stated their decision was not affected ($N=13/15$). The two patients who stated it was affected referenced restrictions in family presence as a major reason.

Discussion

Window of opportunity clinical trials represent a powerful opportunity to accelerate cancer therapeutic development; however, compared to other types of clinical trials, they also pose unique challenges. In this study, we performed in-depth interviews of 25 women newly diagnosed with early-stage breast cancer at a single-academic institution during the time period in which they would be eligible for a WOT to learn patient perspectives on WOT. Our interviews revealed

several key themes around patient decision-making that may help oncologists who are designing or discussing WOT.

Most participants expressed positive attitudes about trial participation, and the most common positive attitude was regarding the opportunity to contribute to research in order to advance science, to help future generations of cancer patients, and to provide meaning to their own diagnosis. Thus, this study supports the idea that altruism plays a major role in decision-making even early after diagnosis [23]. Interestingly, while participants were coached that WOT are not thought to provide personal benefit because of the short duration of treatment, several participants pointed to the possibility that the drug could outperform investigators' expectations. This result is consistent with what has been observed in studies of patient perspectives of early-phase clinical trials, where patients will often hope for personal benefit beyond what is communicated [24].

Our study also highlighted potential barriers to participation in WOT that should be carefully considered in study design and communication. Chief among these was concern about study drug toxicity and its possible impact on their fitness for other standard treatments. Other concerns included delay in treatment, with a delay of more than 2 weeks deemed unacceptable by nearly all. This time course of 2 weeks fits with a standard WOT design [25], as it may take a few weeks to schedule standard treatment and most WOT include an intervention of approximately 2 weeks [7, 9]. However, as biomarker-driven trials and longer interventions are considered, this perspective must be considered. Finally, one African American participant expressed mistrust in research as a significant barrier to participating, highlighting the importance of improving diversity in clinical trial engagement.

During the COVID-19 pandemic, concern about increased contact with the medical system bringing risk of exposure to the virus did not have an impact on decision-making. Interestingly, what did matter during the COVID-19 pandemic was the absence of support persons during clinic visits. Indeed, the burden placed on patients during the pandemic to make decisions without in-person support may be very great [26], highlighting the importance of involving family and friends in decisions about clinical trial participation going forward.

Our study has several limitations. Firstly, the interviewed patients may represent a group of individuals especially altruistic or interested in research, given the high rate of agreement to participate in the interview study. Thus while the majority of these patients stated they would be willing to participate in a WOT, this may be an overestimation from the real world. Also, the population of women interviewed came from a single institution and does not reflect the diversity of women in the USA; additional studies would be useful to understand how the themes identified here apply and vary across different geographies, ages, races/ethnicities, and other socioeconomic factors. This study highlights several factors that may influence participation in WOT, but given the small sample size does not characterize which factors matter most. Further assessments of patients with breast cancer are needed to inform WOT development.

Despite these limitations, our results provide the first qualitative, in-depth information on patient perspectives on an increasingly common type of clinical trial characterized by unique challenges. These results provide important context for oncologists developing or communicating about WOT, as well as a framework for continued study of patient decision-making around altruistic clinical trials.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10549-022-06611-6.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by DAP, LK, JLC, and GWS. The first draft of the manuscript was written by DAP and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding This study was funded by the Department of Defense Congressionally Directed Medical Research Programs (Grant No. W81XWH1910739 to GWS and CC). This project was also supported by the Agency for Healthcare Research and Quality (Grant No. T32HS026128 to DAP); the content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality.

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Conflict of interest DAP, LK, SB, DH, VL, MK, IW, and GWS have no conflicts of interest to disclose. CC is a scientific advisor and consultant for Genentech, Grail, NanoString, DeepCell, Ravel, and ResistanceBio and has stock at Grail, Ravel, and DeepCell. MP is a consultant for Celgene and an advisor for Pacific Business Group. JLC has received research funding from QED Therapeutics and eFFECTOR Therapeutics to her institution.

Ethical approval Stanford Institutional Review Board approval was obtained for all methods and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from all participants in this study.

Consent for publication Not applicable.

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