Supportive Care in Cancer (2019) 27:1845–1852
https://doi.org/10.1007/s00520-018-4443-3

ORIGINAL ARTICLE

Certainty within uncertainty: a qualitative study of the experience of metastatic melanoma patients undergoing pembrolizumab immunotherapy

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Received: 26 May 2018 / Accepted: 23 August 2018 / Published online: 4 September 2018

Abstract

Objective Little is known about the lived experiences of patients with metastatic melanoma undergoing checkpoint inhibitor treatment. We conducted a feasibility study of a supportive care intervention for melanoma patients being treated with pembrolizumab. Here, we report a secondary objective of the study, which was to explore the lived experience of being on pembrolizumab treatment for advanced melanoma.

Methods Twenty-eight participants with metastatic melanoma were recruited across two cohorts, all receiving 3-weekly immunotherapy treatment. Semi-structured interviews were conducted with 26 participants once at 9 weeks. Thematic analysis using interpretative phenomenological analysis (IPA) was performed with multiple iterations of data review to achieve consensus.

Results Three overarching themes were identified; here, we report the first and most dominant theme: how metastatic melanoma patients live within uncertain spaces. Although immunotherapy increases overall survival, metastatic melanoma patients live within an uncertain spectrum. They confront uncertainty related to immunotherapy treatment, their disease trajectory, family relationships, and decision-making. Melanoma patients attempt to normalize their lives, engaging in their usual activities. Uncertainty increases prior to active treatment and intensifies during investigation phases.

Conclusions Despite progress in melanoma patient treatment and outcomes, these patients face sustained uncertainty about their disease trajectory.

Keywords Immune checkpoint inhibitor · Immunotherapy · Metastatic melanoma · Qualitative research · Uncertainty · Supportive care · Cancer · Feasibility study

Introduction

The introduction of immunotherapy, a rapidly growing therapy, to treat advanced melanoma has significantly impacted patients' lives. Checkpoint inhibitor immunotherapies prolong overall survival in patients with advanced melanoma [1–3], leaving people with advanced melanoma in considerable uncertainty.

The challenge of living with uncertainty for cancer patients has been widely explored [4–7]. Common themes are patient's desire to live "a normal life" [8], with anxiety related to medical appointments, upcoming scans, and blood tests. While anti-programmed cell death protein 1 antibody (anti-PD-1) treatment is well tolerated with minimal side effects, a minority experience rare but important side effects that may result in withdrawal of therapy [1].

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00520-018-4443-3) contains supplementary material, which is available to authorized users.

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To identify supportive care needs of this population, a qualitative component embedded in our feasibility study [9] explored patient experiences of living with advanced melanoma and receiving pembrolizumab treatment. We aimed to identify themes to guide development of supportive care and therapeutic strategies to enhance experience of patients treated with immunotherapy.

Methods

This qualitative study was nested within a feasibility study of a supportive care intervention for patients receiving immunotherapy treatment for metastatic melanoma (see Fig. 1) [9]. Ethical approval was granted by Sydney Local Health District – Concord zone Human Research Ethics Committee (HREC/15/CRGH/265) in accordance with the Declaration of Helsinki [10]. The inclusion criteria of the population were as follows: patients with advanced melanoma undergoing standard treatment with pembrolizumab, aged 18 years or older, providing informed consent, and able to complete the interview without an interpreter. The research team comprised three medical oncologists and one each supportive care medical specialist, exercise physiologist, psycho-oncology researcher, and qualitative health and illness experience researcher (four female, three male) facilitating diverse analytical perspectives.

A medical oncologist or cancer nurse purposively recruited eligible participants with metastatic melanoma undergoing 3-weekly pembrolizumab therapy to participate in the feasibility study (detail reported elsewere) [9].

Individual semi-structured interviews were conducted by one author (DL) once, either face to face or via telephone at our institution. Audiorecordings of interviews were transcribed verbatim by a professional transcribing service. Interviews were median 42 (range 19 to 80)-min duration. Participants explored their experiences of living with advanced melanoma (Supplementary file 1). As the initial data were analyzed, the interviewer employed increasingly exploratory and analytic questions to extend an understanding of participants' experiences. De-identified transcripts were managed in NVivo 11 (QSR International, Melbourne, Australia).

In accordance with IPA methodology and the interpretive theoretical framework [11], researcher preconceptions were foregrounded, ensuring concepts generated specifically captured participant experiences. Interviews were coded (DL) line by line for descriptive experiences. Transcripts were distributed for cross-coding among the team (DL, JL, AL, CM, MM, HD, and SK) expanding initial codes and facilitating a coding tree.

Data analysis explored the experience of living with advanced melanoma and response to immunotherapy, and perceived experience of the supportive care intervention. Eighty-four initial codes were generated, reflecting participant attitudes to and beliefs about metastatic melanoma and immunotherapy, experiences coping with their illness, and the impact on family relationships. Emergent themes were iteratively developed from the exploratory categories and thematic saturation achieved.

Results

A total of 28 participants (41–84 years; 57% male) took part in the feasibility study, 13 intervention and 15 usual care. Of these, 26 completed semi-structured interviews, 24 face to face and two via telephone. Two participants died prior to interview. Demographic details are depicted in Table 1.

Three major themes represented the participants' principal concerns. These were (1) living and coping within a spectrum of uncertainty, (2) navigating the immunotherapy treatment experience, and (3) the experience and subjective benefits of supportive care. These interconnected concerns were not limited to the duration of the study; rather, participants described the temporal impacts of the disease, its treatments, and adverse effects.

Here, we report only theme 1, representing the dominant concern shared by participants in both cohorts: how metastatic melanoma patients live within uncertain spaces. The remaining two themes are reported elsewhere. Participants' uncertainty experience can be divided into four sub-themes: uncertainty about immunotherapy treatment, uncertainty regarding their disease trajectory, uncertainty influencing personal relationships, and uncertainty regarding decision-making.

Uncertainty about novelty of immunotherapy

For the majority of participants, uncertainty was cyclical, accentuated before imaging scans, creating three-monthly anticipatory anxiety.

> You just don't know what the next CT [computed-tomography] scan is going to tell you … As time went on, after I started PD-1, the CT scan results were getting better. It's very easy to just suddenly live your life from one scan to the next. I try very hard not to do that, but *that is the hardest thing*. (Pt 03, M 75 years)

Despite the novelty of pembrolizumab, participants were unwilling to abandon any treatment opportunity, comparing immunotherapy to the risk of gambling:

> I worry about what's going to happen next and are we going to be playing a bit of Russian roulette, stretching it out, and waiting and watching to see. (Pt 04, F 67 years)

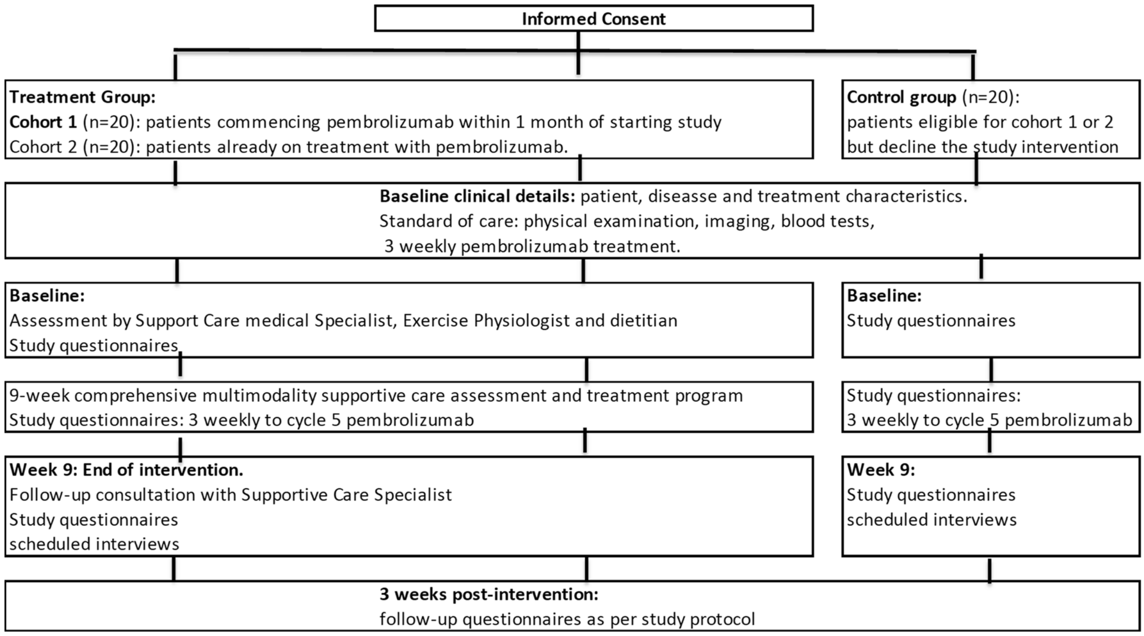

Fig. 1 Feasibility study of a supportive care intervention for patients receiving immunotherapy treatment for metastatic melanoma

A degree of uncertainty was consistent among participants. For some, uncertainty escalated the moment immunotherapy infusion commenced:

> I don't think about it. Only until I come in here. I even had a little cry today when she was putting it [cannula] in because [I'm] not here for a ham sandwich, am I? (Pt 04, F 67 years)

For others, uncertainty prevailed, tipping into a state of despair.

> With my last scan, there's a lot of activity ... a lot of uncertainty there. I'd started on [pembrolizumab], and then you start to think, "Does that mean this is working? ... Am I ever going to get rid of this thing?" (Pt 06, F 43 years)

Equally, for some, pembrolizumab was experienced as innocuous, especially among those experienced with chemotherapy:

> Joyful not to lose your hair. Never lost my appetite. Even having lost a third of my stomach, my appetite just came back ... (Pt 01, F 64 years)

> These infusions, I mean *they are child's play*. There is nothing to them. (Pt 17, M 84 years)

While others remained enthusiastic about the therapeutic capacity of immunotherapy, they balanced their uncertainty with optimism and confidence in their oncologists.

> When I first heard of my diagnosis – stage 4 – I thought I'd be on chemo for sure. But, no, this new drug they've put me on … I've had excellent results. From the neck down, the cancer is gone. It's still in my brain, though. The doctor said, "Because of that, you're on it for life." (Pt 04, F 67 years)

> I've had a fantastic response. I've had … very minimal side effects. A little bit of joint pain… fatigue. But I also put it down to running a business, running a farm, having a family … and I'm getting a little bit older. (Pt 20, F 43 years)

Regardless of the treatment benefits and optimism of participants, adverse events were present in some.

> During this treatment process, I've had other problems … I have an underactive thyroid gland … and I'm on medication for that. (Pt 03, M 75 years)

Several participants (2, 5, 11, 18) experienced dryness of the mouth (xerostomia), finding it uncomfortable and requiring treatment. For most, side effects were negligible and manageable, requiring self-monitoring.

> None whatsoever. I am just amazed. I've been waiting for it because they keep asking me the same questions all the time … I look for those similar symptoms. (Pt 04, F 67 years)

Metastatic melanoma patients inhabited a transitory space, feeling well most of the time, at least between regular

Table 1 Interviewee demographics

Participant ID	Sex	Age	Marital status	Family status	Work status	Time since diagnosis (months)	Prior immunotherapy
Pt 01	F	63	MD	A, E	p/t	153	Y
Pt 02	F	59	MD	A, E	p/t	288	Y
Pt 03	M	74	MD	A	R	177	Y
Pt 04	F	68	W	A, E	p/t	169	Y
Pt 05	F	58	MD	A, E	p/t	73	Y
Pt 06	F	43	MD	C, P	H	125	Y
Pt 07	M	58	MD	A, E	f/t	5	N
Pt 08	F	51	D	A, P	f/t	92	Y
Pt 09	M	94	MD	A	R	229	Y
Pt 10	M	61	MD	NC	f/t	169	Y
Pt 11	M	42	MD	C, P	f/t	170	Y
Pt 12	M	60	S	N	f/t	115	Y
Pt 13	F	69	W	A	R	58	Y
Pt 14	M	54	D	P	f/t	84	Y
Pt 15	F	85	S	NC	R	3	N
Pt 16	M	68	MD	A	R	181	Y
Pt 17	M	84	MD	A	R	64	Y
Pt 18	M	65	MD	A	R	48	Y
Pt 19	M	78	MD	A	R	201	Y
Pt 20	F	43	MD	C	f/t	28	Y
Pt 21	M	65	D	NC	R	74	Y
Pt 22	M	81	D	A	R	38	Y
Pt 23	M	67	MD	A, E	R	95	Y
Pt 24	F	82	W	A	R	134	N
Pt 25	M	72	MD	A	R	17	N
Pt 26	M	68	MD	A	R	99	Y
Pt 27	F	84	W	A	R	365	N
Pt 28	F	51	MD	A, E	O	89	Y

F, female; *M*, male; *MD*, married/de facto; *W*, widowed; *S*, single; *D*, divorced/separated; *p/t*, part-time; *f/t*, fulltime; *R*, retired; *h*, home duties; *O*, other; *Y*, yes; *N*, no; *NC*, no children; *C*, children < 15 years; *A*, adult children; *p*, active parents; *E*, elderly parents

melanoma assessments and immunotherapy treatments, where doubt and uncertainty about the treatment and future resurfaced and dominated.

Uncertainty regarding disease trajectory

Participants faced relentless uncertainty regarding the melanoma trajectory despite their disease response to immunotherapy. Nevertheless, many participants were too busy living—sailing, playing golf, and practicing yoga, maintaining active, and fulfilling working lives—to be thinking about death. For some, having melanoma and needing treatment were primarily an inconvenience. Their experiences reflect specific and diverse psychological coping strategies illustrated in Box 1.

Box 1 Case study illustrating balance between living and uncertainty

Pt 08, 51-year-old female, divorced, single parent lived with a diagnosis of melanoma for 7.7 years and metastatic melanoma for 5. She worked fulltime as a receptionist, managed her home, walked, and attended the gym regularly. Yet minimized her uncertainty, comparing herself with other patients displaying explicit cancer signs:

I'm not in denial knowing that I have cancer, but because I don't feel like I have cancer [like] the emaciated ones … I'm still capable of doing it all. I'm just living with cancer. I think that's probably the words you use. Not a victim, but living with it.

Living with hope and the acceptance of their limited control and uncertain trajectory resonated with many:

> I didn't think I was going to make Christmas. I bought a boat. I start my sailing again on Saturdays. That's the

> crux … I'm not buying a boat if I'm going to die, am I? (Pt 04, F 67 years)

A retired naval officer accepted the limited control over his disease:

> The future looks bright … probably all that salt air … I've got no control over the future. I can … keep myself in shape and that sort of thing, and I don't get into trouble. Like most of us, *we just go about our lives*. (Pt 21, M 66 years)

Adjusting to chronic disease including cancer is a powerful coping strategy, compensating for the uncertainty of treatment and an uncertain future. Others normalized the experience of metastatic melanoma, reflecting on similarities to living with any chronic disease.

> It's like living with heart disease. It's like living with renal failure. It's just the same, isn't it? (Pt 08, F 52 years)

Uncertainty influencing family relationships

Participants' family status reflected a variety of situations, parents with young or adult children, other adult children of elderly parents, or grandparents with large families to consider. Two participants, with nonagenarian mothers, shared the imperative to stay alive for their sake as well as for themselves. Participants expressed diverse attitudes to communicating concerns with family members. Some openly discussed decisions as a family to ensure judicious risk assessment, while others preferred to minimize family communication about the disease.

> From day one, we made decisions on things like kids. At one stage, we were trying to have another child … my melanoma returned, and I said we should really reconsider bringing another child into the world given that we don't know what is happening with my life. (Pt 11, M 42 years, diagnosed at 28 years)
> I've got a 14-year-old daughter. I told her "do not get on the internet. If you want to know anything about my disease, you come and see me" ... Mum is 76 and she's got enough of her own health issues. (Pt 20, F 43 years)

Others were more philosophical about their own life and death, being chiefly concerned how the disease affected family, which influenced the decision to have immunotherapy treatment.

> I just wanted nature to take its course. At my age I just felt I'd had enough ... But when I saw how it affected my partner, I felt I couldn't do that to him, had to make an effort … I know it's not going to be cured, but have a bit of respite so he can sort of pull himself together which he has done. (Pt 24, F 83 years, recent diagnosis)

Uncertainty in decision-making

At times, participant uncertainty coincided with ambiguity regarding how, when, and by whom treatment decisions were made. Some emphasized the importance of autonomy, while others rationalized their uncertainty by deferring decision-making to their oncologist.

> The option was put to me to suspend my infusions and go on observation. That's now been decided, and that's what I will do ... I was an accountant – so I'm able to analyze the various options. I think I handle these decision-making processes pretty well. Also, in doing that … my family were aware of what I was considering. (Pt 03, M 75 years)
> It is such a new area [immunotherapy] that, if you come to it with no particular knowledge, it's a bit hard to do anything other than say, "Yes, sir, three bags full." (Pt 04, F 67 years)

However, there was a perception of uncertainty in their physician's hesitancy regarding treatment length, creating a complex interaction between clinician and patient.

> I know it's up to her [oncologist]. I said to her, "How long am I on this [pembrolizumab] for?" She said: "We don't know" because it's only since 2013 this particular drug has been okay ... She just gave me the eye. She said, "You're on it for life". "Yes. Right. Okay". I think it's because I've got the one in the brain. (Pt 04, F 67 years)

Across the uncertainty continuum, participants expressed relief and hope regarding their disease status. For many, qualified certainty predominated, contrasting long periods of uncertainty they had endured. Most felt psychologically buoyed by tumor response, improved blood results, and improved subjective wellbeing. For several participants, intermittent comparative certainty provided respite from treatment, periods of wellbeing and normal life activities, and hope in the possible, a state of *certainty, within uncertainty.*

> There is always *uncertainty* with everything in your life anyway, but I think having that *certainty* of the next 14-16 months of treatment is one thing that puts you in a positive frame of mind. (Pt 05, F 58 years)

Favorable treatment response enhanced a sense of certainty regarding the future. Fear of cancer recurrence or progression was embedded in some participant narratives, leading to increased reliance on social media to facilitate information and decision-making.

> I've been fine right up until it all resurfaced again ... The immune therapy, you see a lot of good stories about it, and then you see a lot of stories where people are on it and then all of a sudden having recurrences. At the moment, I'm at that *unsure about everything* stage ... What's going to happen? Where am I going to be? (Pt 06 F 42 years, 3 children)

Metastatic melanoma patients cope within a spectrum of uncertainty increasing before and during cycles of treatment, monitoring, and investigations, then subsiding, allowing patients to re-engage in their lives.

Discussion: the dimensions of melanoma uncertainty

We have explored what characterizes the uncertainty of living with metastatic melanoma. Uncertainty for cancer patients is a logical response and a clinical phenomenon. Living with cancer and being a cancer survivor have become the *new normal* [12–14]. Uncertainty was cyclical, not continual in our population. Literature conceptualizing uncertainty in the cancer trajectory predominantly explores breast [15–17], prostate [18, 19], and gastrointestinal cancer patient experiences [6], not melanoma. Empirical research examining patient uncertainty in chronic disease is limited [20], including for those with metastatic melanoma [21]. Dean explored the uncertainty trajectory in BRCA-positive women anticipating a diagnosis of breast cancer undergoing 6-monthly screening [15]. Cancer survivors commonly experience some fear of cancer recurrence or progression, which may become clinically significant [22–24].

Advances in treatment mean some patients with metastatic melanoma now experience considerably longer survival [25, 26]. A corollary of improved treatment and increased survival is the shifting dimension of uncertainty. Gaining a sense of hope and enhanced quality of life, melanoma patients face uncertainty and existential anxiety [27] which intensifies at particular intervals such as during active treatment. As pembrolizumab immunotherapy is a relatively new treatment, it is conceivable the experience reflects a non-linear state of anxiety about treatment, uncertainty about managing the disease, and fear of recurrence or progression. For melanoma patients, the uncertainty experience is temporal, peaking before investigation and treatment episodes, and spatial, restricting some patients from routine activities. As uncertainty may be linked to sustained adverse outcomes such as anxiety, depression, diminished quality of life, and reduced self-efficacy [28], we sought to understand the dimensions of uncertainty for melanoma patients as a distinct sub-population.

Liminality, continuum of uncertainty

Uncertainty is not static or restricted to a single event; it is dynamic, shifting according to information received, treatment response, and disease progression. Studies indicate cancer patients try to remain positive and maintain a normal life [8, 13, 29], as did our study participants. Mishel [30] defined uncertainty in illness *as the inability to determine the meaning of illness-related events*, reflecting experiences of participants in this study, most of whom felt well rather than diseased.

Researchers examining ambiguity and uncertainty in cancer patients have explored the liminal experiences of cancer survivorship [31, 32], the continuum of uncertainty faced by people affected at all stages with cancer. Resulting from social anthropology research by van Gennep [33] and Turner [34, 35], liminality describes "an individual's attempt to deal with the disruption of life after the illness incidence and, a continual adaptation to illness by constructing its meaning through narrative" [36]. In relation to cancer, Little et al. understand liminality as "an enduring and variable state" [32, p. 1490] conceptualized in two phases: an *acute* phase when patients experience their cancer diagnosis and a *sustained* phase persisting throughout the patient's entire illness journey [32]. Living with metastatic melanoma necessitates enduring liminality, depending on the individual's disease response, coping mechanisms, and capacity to re-engage in acts of independence.

A third liminal phase, 5 years after cancer diagnosis, is theorized [37]. This phase—*transcending* sustained liminality—is characterized by relative security and yearning to become more like *ordinary people*, or, a desire to maintain *normalcy* to cope with the uncertainty of incurable disease with an uncertain future [8]. Our participants unquestionably yearned, and mostly managed, to live ordinary lives, engaged in work, travel, and social activities, while supporting children, grandchildren, and elderly parents. Among these ordinary events, they confronted 3-weekly cycles of tests, immunotherapy treatment itself, and awaiting results, each sustaining liminality.

Immunotherapy has altered survival outcomes yet paradoxically sustained the metastatic melanoma trajectory; experiences of participants in this study reflect this. Their experiences encompass periods of certainty, hope, and optimism, simultaneous with an enduring fundamental sense of uncertainty.

Limitations

Participants self-selected into the intervention and most were not experiencing rapidly progressive disease, although three died during the study. Emergent themes may have been more diverse had participants been interviewed more than once. The research team comprised individuals working in clinical care of these patients or research in this setting which may have biased their interpretation of participants comments; however, foregrounding and regular checks throughout the study processes guarded against this.

Clinical implications

Immune checkpoint inhibitors have profoundly impacted the disease trajectory of patients living with advanced melanoma. The regularity of tests and treatment reminds patients of their uncertain future. Clinical teams need to understand this and develop strategies to manage uncertainty and cyclical anxiety in metastatic melanoma patients.

Conclusions

This patient population inhabits a unique space. Despite living with a melanoma diagnosis over long periods, they now receive 3-weekly immunotherapy accompanied by regular pathology tests and scans, punctuated with waves of uncertainty to interrupt living a normal life. The longer the journey, the more this uncertain lifestyle has become the *new normal*. The impact of uncertainty and the vigilance of patients demand consideration as to how we develop comprehensive supportive interventions to address their needs.

Acknowledgments The authors would like to thank Corrinne Renton, Research Officer, Centre for Medical Psychology and Evidence-Based Decision-Making, Sydney Medical School, University of Sydney, for database design, management, and technical support; Theresa Nielsen for assistance with participant recruitment and coordination; Alex Pereira and Charlotte Davies for assistance with data entry; and Alison Sibley for administrative support and the supportive care and integrative oncology team at Chris O'Brien Lifehouse for clinical input.

Data ownership The data generated as part of this study remains the property of the investigators. It is available for inspection on request.

Funding This study was funded through an educational and research grant from MSD, administered through Chris O'Brien Lifehouse. Anna Lomax was supported by the Simon Kerr Fellowship.

Compliance with ethical standards

Ethical approval was granted by Sydney Local Health District – Concord zone Human Research Ethics Committee (HREC/15/CRGH/265) in accordance with the Declaration of Helsinki

Conflict of interest Catriona McNeil received travel, conference, and accommodation support from MSD; has sat on MSD advisory boards; and has given talks for MSD and BMS (honoraria to Chris O'Brien Lifehouse). Steven Kao received honoraria paid to his institution from Boeringher, Astrazeneca, Roche, Pfizer, BMS, and MSD. Steven Kao has had travel costs paid for by BMS, Roche, and AstraZeneca. Haryana Dhillon has received honoraria paid to her institution from MSD. Judith Lacey has received honoraria paid to her institution from TEVA and MSD.

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