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Clinical factors influencing retreatment with anti-PD-(L)1 therapies after treatment in early-stage cancers: a modified Delphi consensus study

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ABSTRACT

Anti-programmed death (ligand) 1 (anti-PD-(L)1) therapies were first introduced in the metastatic setting and have since been approved and reimbursed for treating early-stage cancers in the adjuvant, perioperative, and neoadjuvant settings in many cancer types. Current evidence supporting anti-PD(L)-1 retreatment after relapse with prior neoadjuvant and/or adjuvant anti-PD(L)1 therapy is limited and inconclusive. There is no guidance for clinicians on how and when to retreat with anti-PD-(L)1 therapies when anti-PD-(L)1 therapy was administered in the neoadjuvant and/or adjuvant setting. This study aimed to reach consensus on factors to guide decision-making regarding retreatment with anti-PD-(L)1 therapies after prior therapy with an anti-PD-(L)1 agent. This modified Delphi study consisted of a clinician survey across 10 countries followed by three real-time virtual Delphi panels involving clinical experts who had completed the survey. Clinical experts were experienced in using anti-PD-(L)1 treatments in early-stage cancers and/or as retreatment of patients with recurrences following early-stage treatment with anti-PD-(L)1 therapies. Of 28 clinicians providing survey responses, 20 participated in one of three Delphi panels. There was consensus that retreatment can be defined as 'repeated treatment with the same therapeutic class following relapse after or during neoadjuvant and/or adjuvant treatment.' All three panels agreed that decisions around retreatment should consider 'prior immune-related adverse events/toxicity,' 'time-related factors' (eg, time since completion of full treatment course and since discontinuation) and 'previous patient response' (often referred to by clinicians as tumor response, which may have reflected their experience with metastatic disease). Other factors identified as important included country-specific practices, treatment availability, and reimbursement. Generally, the clinical experts considered that retreatment could be considered from ≥3 to 6 months after stopping initial anti-PD-(L)1 treatment, or from ≥6 months after relapse/recurrence. In conclusion, clinicians across different regions recognized a role for retreating patients with anti-PD-(L)1 therapies after initial anti-PD-(L)1 treatment for early-stage cancers. Consensus was reached on some factors to consider regarding whether and when to retreat, although differences in clinical practice between countries/geographical regions made it difficult to achieve consensus for some more nuanced elements of retreatment. Further evidence could help better inform retreatment decisions.

BACKGROUND

Immunotherapy, or immuno-oncology (IO), has changed the oncology treatment landscape, significantly improving patient outcomes across tumor types.[1] IO treatment with anti-PD-(L)1 therapy was first introduced in the metastatic setting, with the initial treatment duration limited to 2 years or until disease progression or unacceptable toxicity for most anti-PD-(L)1 therapies in most cancer types.[2–14] Due to the successful use of anti-PD-(L)1 therapy and IO combination therapies in metastatic cancers, there has been an interest in understanding whether treating again after prior anti-PD-(L)1 treatment in the metastatic setting (ie, rechallenge) may be beneficial.[10 15–36] More recently, anti-PD-(L)1 therapies have also been approved and reimbursed for the treatment of early-stage cancers in the adjuvant, perioperative, and neoadjuvant settings.[2–4 11–13 37–45] Despite the reductions in recurrence rates with the inclusion of anti-PD-(L)1 drugs, a subset of these patients with early-stage cancers will relapse, and currently, no randomized clinical trial has assessed the efficacy of retreatment after relapse with prior neoadjuvant and/or adjuvant anti-PD(L)1 therapy.[22 25 46] Retreatment differs from rechallenge in that it refers to retreating a patient with the same

class of drug (eg, anti-PD-(L)1) that they have received for early-stage cancer, following a relapse. Rechallenge refers to treating the patient with another course of immunotherapy (combination or monotherapy) in the metastatic setting.[18 47]

Anti-PD-(L)1 therapies, as neoadjuvant and/or adjuvant treatment in conjunction with surgical resection to treat early-stage cancers, have shown overall survival benefit in non-small-cell lung cancer (NSCLC), renal cell carcinoma (RCC), triple-negative breast cancer, and cervical cancer;[48–51] recurrence-free/event-free survival benefit in resectable metastatic melanoma,[52 53] and distant metastasis-free survival and recurrence-free survival benefit in early-stage melanoma.[54 55] However, there is a lack of guidance for clinicians on how and when to retreat patients who have received prior anti-PD-(L)1 therapies and are now experiencing disease relapse.[56] Also, there are few published payer decisions regarding retreatment, or payers have provided insufficient detail or instead noted specific restrictions regarding reimbursement for retreatment with anti-PD-(L)1 therapies, resulting in uncertainty around retreatment options for patients.

Single-arm studies and case series suggest that the common clinical scenarios for retreatment include (1) discontinuation of initial therapy due to toxicity and (2) recurrence after completion of treatment with a set number of courses.[26 57 58] A change in anti-PD-(L)1 treatment strategy from what was used for early-stage disease (eg, switching to a different therapy or from monotherapy to combination therapy) may also be required to obtain benefit from retreatment after relapse.[26 57 58] However, it is difficult to draw conclusions about the extent to which retreatment should be used, and overall, there is no consensus on what clinical factors should be considered to identify patients who may benefit from retreatment, such as the treatment-free interval to consider after the patient was treated with an anti-PD-(L)1 therapy (as monotherapy or combination therapy) in the early-stage setting. Additionally, it is difficult to determine the patient benefits of retreatment due to the retrospective nature and small sample sizes of current studies. It is also unknown whether the benefit of retreatment in different scenarios varies according to specific clinical and patient factors.[59 60]

Given the gaps identified in the published literature and guidelines, a modified Delphi study with international clinicians was conducted with the aim of reaching consensus on the factors that should guide decision-making regarding whether, when, and how to retreat with anti-PD-(L)1 therapies after patients have already been treated with those therapies in an early-stage setting.[61]

METHODS

Study design

This study used a modified Delphi methodology to capture expert clinician insights around definitions of retreatment as well as an understanding of how clinicians could approach making retreatment decisions following anti-PD-(L)1 treatment in an early setting. The Delphi method is an iterative process used to yield consensus on issues of importance and to establish clinical guidelines.[62] It involves a group of clinical experts and a series of sequential questionnaires; after each round of questions, the responses are aggregated and shared with the group, which allows the clinical experts to adjust their answers based on how they interpret the group response. Our modified approach, while maintaining the traditional Delphi principles,[61] included more interaction between participants through real-time discussions using video conferencing. The first round of questionnaire responses was sent to a larger group of experts than just those participating in the consensus panels; participation in the panels was based on clinicians' willingness to participate, along with availability, and the consensus process was done in real time through a series of virtual meetings.

The study, which took place from February 2023 to April 2024, consisted of an initial clinician survey across 10 countries to gather insights from the potential Delphi panel participants to inform subsequent discussions at the following series of three real-time virtual Delphi panels involving clinical experts from the USA, Canada, France, Germany, Italy, Spain, and the UK (North America-Europe (NA-EU) panel); South Korea and Australia (KR-AU panel); and Japan (Japan panel). All panels comprised exclusively a subgroup of clinicians who had completed the survey.

All survey participants and expert panelists gave written informed consent for research participation and received honoraria from the study sponsor for their participation. Survey participants and panel members were blinded to the sponsor of the study (and vice versa) until completion of the survey responses (for those who only participated in the survey) or completion of the Delphi panel (for those who participated in both the survey and the Delphi panel). To maintain the blinding, remuneration from the sponsor was given to participants indirectly via Avalere Health. The team moderating the panels was made aware of the Delphi panel participants' identity shortly before the panel meetings. To preserve anonymity from the study sponsors and to follow Delphi methodology, all responses from the survey and Delphi panel were reported in aggregate form only. All participants agreed to complete the survey in English, aside from participants in Japan, where the survey was translated to Japanese. The survey (in SmartSurvey) and the panel materials (including questions in Vevox (vevox.com)) were evaluated independently by members of the research team (JM, CK, and AK) before they were sent to the participants.

Setting and participants

Recruitment of clinicians aimed to involve up to 30 clinical experts across 10 different countries to support the survey and 3 geographically based panels. The sample size was based on previously published consensus

panels[63–67] and in recognition of the availability of potential participants for both a survey and real-time virtual panel, although there is no agreement in the literature on the optimum size of Delphi panels.[62] The survey was sent to more than the intended panel numbers based on an anticipated ~10%–20% response rate and to allow flexibility, as it was expected some potential survey participants may not subsequently be able to attend the real-time Delphi panels.[68–70] A total of 388 potential clinician participants (NA-EU and KR-AU regions: 288; Japan: 100) were selected by a third-party vendor who emailed and invited them to participate in the study on the basis of their background and experience. Inclusion criteria were as follows:

- Had worked in their current role for at least 2 years.
- Had been treating patients in oncology for at least 5 years.
- Had spent more than 50% of their time in patient care (or were disease-focused experts).
- Were experienced in using anti-PD-(L)1 treatments (monotherapy or combination) to treat patients with early-stage cancers and/or as retreatment of recurrences after or during immunotherapy for early-stage cancers.

Experts were asked to respond within 2 weeks if they wished to participate in the study, and the survey took approximately 45 min to complete. All participating clinicians were asked to indicate the tumor type with which they had the most experience of anti-PD-(L)1 retreatment, except in Japan, where all clinicians recruited were experts in RCC. Options for tumor specialty included melanoma, NSCLC, triple-negative breast cancer, and RCC, where IO treatments are used in early-stage cancers, thereby ensuring participants were familiar with treating early-stage cancer.

For the Delphi panels, clinicians who completed the online questionnaire were invited to be part of the panels, with the aim of recruiting up to 10 clinicians from the NA-EU region, up to 6 clinicians from the KR-AU region, and up to 5 clinicians from Japan. Clinicians who expressed interest and confirmed their availability were included in the panel. All panels were moderated by one of the research team members (JM) experienced in this methodology.

Data collection

Background research

A targeted literature review (TLR) was conducted in 2022 to ensure the most up-to-date understanding of anti-PD-(L)1 therapy for the treatment of early-stage cancers and retreatment on relapse. Due to the limited number of articles identified when the TLR search was restricted to early-stage oncology, the final scope was broadened to ensure that enough information was captured to inform the questionnaires and Delphi panel. Therefore, while the focus of this current study is retreatment on relapse after prior anti-PD(L)1 treatment for early-stage disease, the scope of the TLR included retreatment across all stages of cancer, including rechallenge for metastatic disease.

The TLR identified no clinical guidance on whether and how to retreat or rechallenge patients with anti-PD-(L)1 therapies and no consensus on which patient and disease characteristics are optimal for retreatment after previous treatment for early-stage disease or rechallenge after treatment in the metastatic setting. The very limited data for retreatment after anti-PD(L)1 treatment in early-stage cancer indicates that the most common clinical scenarios for retreatment include anti-PD-(L)1 discontinuation due to toxicity or completion of treatment with finite duration.[47] However, determining the minimum treatment-free interval before retreatment and understanding how to identify the patients who will benefit most remain key challenges for clinicians.[59 60]

Online survey

The questionnaire was developed to explore retreatment definitions, clinical factors influencing whether to retreat, how the timing of clinical events influences retreatment decisions, and factors influencing how to retreat with an anti-PD-(L)1 therapy (table 1). Questions were categorical, with either binary, ordinal, or descriptive response options, with free-text fields to capture additional details where there was a response option of 'other.'

Seven hypothetical clinical scenarios were constructed to reflect a range of possibilities of how anti-PD-(L)1 retreatment is used in practice, and these scenarios were used as stimuli for some questions in the clinician survey and Delphi panel (figure 1). After the survey was pretested by members of the research team, the survey was 'soft launched' to 10 respondents to ensure the responses were as expected. Following a review of the data collected, no changes were made to the survey questionnaire. Participating clinicians completed the online questionnaire in SmartSurvey, sent via an email link, between February and July 2023 (NA-EU and KR-AU) or between February and March 2024 (Japan). The survey was designed to be completed within a 45 min period at a time that suited each respondent. Responses for each question were summarized in a Microsoft Excel database, maintaining the anonymity of each clinician to the sponsor and the other participating clinicians.

Expert clinician panels

A subgroup of clinicians who completed the questionnaire was included in the Delphi panels, which took place on August 23, 2023 (KR-AU panel); September 18, 2023 (NA-EU panel); and April 4, 2024 (Japan panel). The focus of the panels was on exploring consensus around whether and when to retreat, with discussions held based on the survey responses. Survey responses were used to develop a series of additional questions and potential consensus statements for the panels with predefined response options, which were either descriptive or ordinal in nature. The panels then further explored the topics from the survey along with more specific details on factors

Table 1 Topics explored by the modified Delphi study (survey+Delphi panel)

Theme	Survey	Delphi discussion
Context	Establish views on a definition of retreatment Identify the clinical perceptions around the ease/difficulty of retreatment	Establish retreatment definition Establish level of difficulty in decision-making
Whether	Establish the top clinical factors influencing whether or not to retreat	Identify the most important factors and establish if they are essential, useful but not essential, or not useful Establish differences between tumor types
When	Establish the events and factors that influence the timing of retreatment for seven hypothetical clinical scenarios: (1) discontinuation due to locoregional recurrence, (2) discontinuation due to metastatic recurrence, (3) discontinuation due to irAE, (4) locoregional recurrence off anti-PD-(L)1*, (5) metastatic recurrence off anti-PD-(L)1*, (6) long-term relapse†, and (7) recurrence during or after intervening treatment	Establish the timing of clinical events for seven hypothetical clinical scenarios and how that influences decisions. around retreatment Establish differences between tumor types
How	Identify the factors considered when deciding to add on another therapy to anti-PD-(L)1 retreatment (add-on therapy) for the seven different clinical scenarios Identify the factors considered when deciding to switch or use the same anti-PD-(L)1 for retreatment for the seven different clinical scenarios	Establish the scenarios in which clinicians select different treatment strategies (ie, switching vs using the same anti-PD-(L)1 therapy for retreatment) Identify the top factors that influence the decision to add on to the original anti-PD-(L)1 therapy or use the same one Identify the top factors that most influence clinicians to either switch or use the same therapy when retreating with an anti-PD-(L)1 therapy Establish differences between tumor types
Evidence needs	Identify gaps in current evidence/additional evidence needs	Discuss for context/clarification

*Recurrence off anti-PD-(L)1 refers to recurrence that occurs after the patient has completed anti-PD-(L)1 treatment for early-stage cancer after receiving the full regimen (1 year).
†Long-term relapse was the term used to indicate disease returning after an extended period of remission, although the specific duration defining 'long term' was not explicitly stated; this has also been referred to as 'late relapse' in the literature.[79–83]
anti-PD-(L)1, anti-programmed death (ligand) 1; irAE, immune-related adverse event.

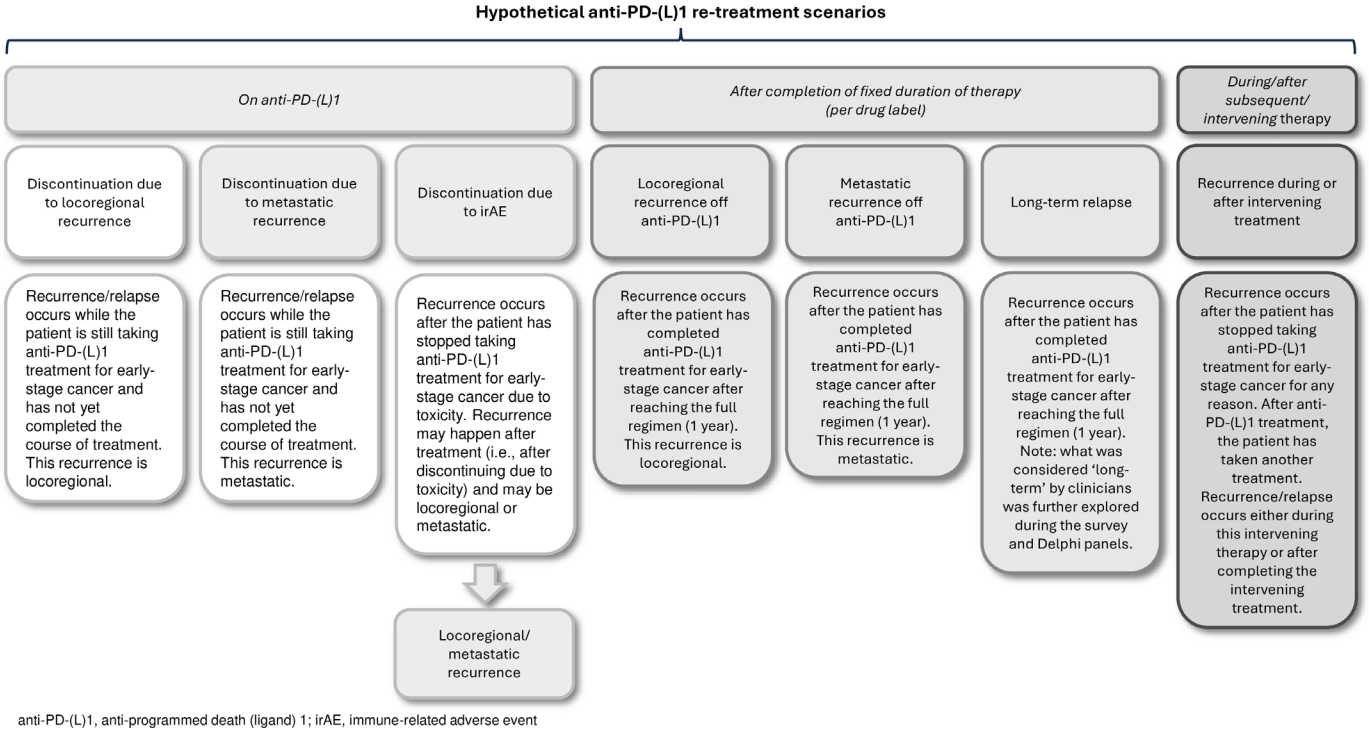
considered when deciding to add on to a previous anti-PD-(L)1 therapy when retreating and factors considered when deciding to switch or use the same anti-PD-(L)1 therapy when retreating.

Delphi panel methodology

In published Delphi studies, definitions of consensus vary widely, from 50% to 100%.[71] In this study, consensus was defined as 80% agreement for categorical questions based on the thresholds set in previous Delphi panels of similar size.[66] For each panel, geographically relevant quantitative survey responses were presented in an aggregated, anonymized manner, along with insights gained from qualitative responses, and were discussed to gain an understanding of the context for the results, regardless of whether or not there was consensus based on survey results. If consensus had already been obtained on a question/statement based on survey responses, no further responses were collected from the panel, in line with Delphi methodology. For survey questions lacking an initial consensus response, or where additional questions/statements were generated specifically for the panel to consider, anonymized responses were captured in real-time and displayed in an aggregate form using Vevox, followed by a discussion with Delphi panel participants. For questions lacking a consensus response after two rounds of voting and discussion (with the survey responses being considered as round 1 where appropriate) and where discussion suggested further voting would not achieve consensus, this outcome was noted, and no further iterations took place.

Data analysis

Data analysis for the survey was performed in Microsoft Excel and was descriptive in nature to reflect the non-comparative design of the study, with no formal statistical hypotheses tested. All data collected were included and summarized to reflect both consensus and divergence of opinion, with all analyses (of both survey and panel data) conducted separately for the three panels. The number and percentage of respondents were calculated for each category of response (for questions with binary or multiple response options), and data were also summarized per tumor type where relevant. Any free-text fields



anti-PD-(L)1, anti-programmed death (ligand) 1; irAE, immune-related adverse event

Figure 1 Hypothetical clinical scenarios for retreatment and the minimum time elapsed before considering retreatment.

were reviewed to identify recurring themes and provide context for the quantitative data collected. Where appropriate, the themes were treated as categorical data, and the number and percentage of respondents in each category were summarized.

Analyses for the data collected during the panels were conducted (in real time) through the Vevox application.

RESULTS

Participants

Across the panels, a total of 28 clinicians (from the 388 initially emailed) provided eligible survey responses (NA-EU: 17, KR-AU: 6, Japan: 5) (online supplemental table 1), of whom 20 participated in the Delphi panels (NA-EU: 10, KR-AU: 5, Japan: 5). The aim was to include 30 clinicians to participate in the survey (and some to also participate in the panels). In South Korea, the plan was to recruit five clinicians for the survey with the view that as many of these as possible would participate in the panel; however, only three were able to be recruited in the timeframe of the survey fieldwork. Self-reported primary tumor expertise of the clinicians who completed the survey included NSCLC (n=9/28), melanoma (n=8/28), RCC (n=6/28; including all Japanese clinicians), genitourinary cancers, breast cancer, and non-melanoma skin cancers (online supplemental table 1). The NA-EU Delphi panel included five experts in NSCLC, three experts in melanoma, one expert in triple-negative breast cancer, and one expert in genitourinary cancers (RCC and bladder cancer). The KR-AU panel included three panelists from Australia and two panelists from South Korea. Among the Australian panelists, all treated melanoma, and one also treated NSCLC, while another also treated breast cancer. Among the Korean panelists, one mainly treated NSCLC and the other treated genitourinary cancers (including RCC) and upper gastrointestinal cancers.

Definition and perceptions of retreatment

There was consensus that retreatment can be defined as 'repeated treatment with the same therapeutic class following relapse after or during neoadjuvant and/or adjuvant treatment' (survey results: NA-EU: 88%, 15/17; KR-AU: 100%, 6/6; Japan: 100%, 5/5). Participants indicated that the decision to retreat was at least moderately difficult (survey results: NA-EU: 94%, 16/17; KR-AU: 83%, 5/6; Japan: 100%, 5/5). Although the survey responses for two NA-EU participants did not select 'yes' when asked if they agreed with the definition provided for retreatment, when probed to provide their rationale, their written feedback suggested that they agreed with the overall principle: one considered this definition to be a very virtual concept, and the other noted that retreatment can also refer to a situation whereby a patient had discontinued treatment due to intolerable toxicity, and the provider is considering rechallenging the patient due to a lack of other therapeutic options. This latter response reflects one of the specific scenarios within the overall definition of retreatment provided in the survey.

Clinical factors influencing whether to retreat

There was a range of opinions around which factors, from a list of 12 provided, were most likely to influence the decision to retreat a patient with an anti-PD-(L)1 therapy (table 2; Supplementary Figure 1 in online supplemental appendix 1). Although there were some differences in

Table 2 Factors which influence decisions around retreatment with anti-PD-(L)1 therapy

Clinical factor	NA-EU panel (N=10)	KR-AU panel (N=5)	Japan panel (N=5)
Prior irAEs/toxicity*	✔✔✔	✔	✔✔✔
'Time'†	✔✔	✔✔	✔✔✔
Previous patient response	✔✔	✔✔	✔✔✔
Reason for stopping	✔✔✔	NE	✔✔✔
Availability of alternative treatments	✔✔✔	✔✔	NE
Patient preference	✔✔✔	NE	NE
Likelihood of expected retreatment response	NE	✔✔	NE

✔✔✔=Consensus that the factor was essential to inform decision-making.
✔✔=Essential or useful, but no consensus on whether essential or useful.
✔=Consensus that factor was useful but not essential.
NE=Not explored in that panel as not identified as a 'common' factor in the clinician survey for that geography (factors chosen in the top 3 by at least 20% of clinicians in each tumor type) nor an additional common factor identified in the panel discussion for that panel. 'Likelihood of expected treatment response' was an additional factor identified only by the KR-AU panel.
*When discussing the influence of irAEs on the decision to retreat, the KR-AU panel discussed this in terms of a more general concept of 'toxicity.' No clear reasons emerged from the KR-AU panel regarding why there was a preference of using the term 'toxicity' over 'irAEs'.
†Includes 'time since completion of full treatment course' and 'time since discontinuation'.
anti-PD-(L)1, anti-programmed death (ligand) 1; irAE, immune-related adverse events; KR-AU, Korea-Australia; NA-EU, North America-Europe; NE, not explored.

thinking around precise definitions, the factors that emerged from the survey as being potentially important for the NA-EU and KR-AU panels, reported by the highest proportion of clinicians, were:

- 'Previous patient response (ie, previous patient response to anti-PD1/PDL1) (NA-EU: 59%; KR-AU: 67%).
- 'Reason for stopping anti-PD-(L)1' (NA-EU: 47%; KR-AU: 50%).
- 'Time to recurrence or next event' (NA-EU: 47%; KR-AU: 50%).

In Japan, the survey data showed a consensus that 'previous patient response' (often referred to as tumor response) and the 'reason for stopping anti-PD-(L)1' were the important factors that would most likely influence the decision to retreat (in patients with RCC).

All factors which were considered important by greater than 20% but less than 80% of survey participants were discussed individually by each of the expert panels to establish their importance and were categorized as 'essential,' 'useful but not essential,' or 'not useful' to support clinical decision-making.

Across the panels, seven factors emerged to be considered when making retreatment decisions, although with variation across the panels about their level of importance (table 2). There was agreement that decisions around retreatment with anti-PD-(L)1 therapy should consider 'prior immune-related adverse events (irAEs)/toxicity,' 'time since completion of full treatment course,' 'time since discontinuation,' and 'previous patient response' as factors. All of these were considered 'essential' in the Japan panel and either useful or essential in the NA-EU and KR-AU panels.

Clinicians noted that 'previous patient response' in early-stage disease only applies to therapies given preoperatively (ie, neoadjuvant) or perioperatively (ie, neoadjuvant followed by adjuvant treatment) where response can be assessed; it should be noted that some of the clinicians may have been reflecting on their experience with metastatic disease to provide their opinion on previous patient response. In the NA-EU and KR-AU panels, clinicians stated 'previous patient response' would only apply to tumor types where the initial anti-PD-(L)1 treatment was in the neoadjuvant setting, and there was potential for heterogeneity (with respect to the type of response or timing of recurrence), with some panelists noting the specific type of response (complete response, stable disease, progressive disease) or details on when recurrence occurred (as an indication of a patient's response) would have different implications for whether clinicians would retreat. The discussions also noted that the timing of relapse (as an indication of a patient's response) could have implications on whether clinicians would retreat.

In the NA-EU and Japan panels, the reason for stopping the initial anti-PD-(L)1 therapy was considered essential. The role of 'patient preference' to inform retreatment decisions was discussed at all panels, and in the NA-EU panel, it was considered an essential factor. The NA-EU and KR-AU panels agreed that the availability of other treatments should influence clinical decision-making, and additionally, the KR-AU panel agreed that the likelihood of retreatment response should also be considered.

Therefore, overall, there were four 'essential' and two 'useful' factors that the NA-EU panel believed clinicians should take into account when deciding on retreatment with an anti-PD-(L)1 therapy after using similar agents in the early-stage setting; in the KR-AU panel, there were four factors considered at least 'useful' without consensus on the factors being 'essential' and two additional factors that were 'useful'; and in the Japan panel, there were four factors that were all considered 'essential' (table 2).

How the timing of clinical events influences retreatment decisions

The survey collected information on the time frame that needs to have elapsed before considering retreatment with anti-PD-(L)1 therapies for the seven clinical scenarios (figure 1), addressing both disease-free interval

and time since completion of prior anti-PD-(L)1 therapy. Analysis of the survey responses indicated a wide range of views, which warranted additional discussion to identify how the timing of events would help inform clinical decision-making.

In the Delphi panels, the clinical experts considered the timing of different clinical events and how that influenced their decisions around retreatment for each of the seven clinical scenarios (table 3; online supplemental table 2).

Retreatment after recurrence/relapse during anti-PD-(L)1 therapy

When there is metastatic or locoregional recurrence after anti-PD-(L)1 therapy for early-stage cancer, the clinical experts agreed that retreatment should be considered when there is at least 3–6 months treatment-free interval (ie, time between the discontinuation of adjuvant anti-PD-(L)1 therapy and recurrence): the NA-EU panel agreed that 3–6 months was an acceptable time frame, 80% of the KR-AU panel agreed that 6 months would be the minimum time frame, and in Japan, there was consensus for at least 3 months (3 months: 60%; 6 months: 20%).

The duration of neoadjuvant and/or adjuvant therapy before recurrence should also be considered when deciding whether to retreat; however, in Japan, the clinical experts suggested that response to the initial anti-PD-(L)1 therapy was a more important consideration than the duration of initial treatment.

Retreatment after discontinuation of anti-PD-(L)1 therapy due to irAEs

Clinicians agreed for patients who have had treatment discontinued due to irAEs/toxicity, retreatment could be considered at least 3–6 months after treatment discontinuation. In this clinical scenario, additional considerations included the severity of irAEs, whether the irAEs had resolved, the timing of irAE resolution, the timing of recurrence, and the duration of initial immunotherapy. The panel experts felt that retreatment with anti-PD-(L)1 therapy may be considered if the irAE was not 'serious' (based on the clinician's own judgment) or if symptoms of the irAE have resolved.

Recurrence/relapse after the completion of an anti-PD-(L)1 treatment course

For patients experiencing recurrence/relapse after the completion of a fixed duration of therapy, retreatment could be considered at least 6 months after the last cycle of anti-PD-(L)1 treatment. Clinicians considered that recurrence within 6 months could reflect resistance to the initial anti-PD-(L)1 therapy, likely making the patient unsuitable for retreatment.

Recurrence during or after intervening treatment

No specific recommendations were made on when anti-PD-(L)1 retreatment could be recommended for patients experiencing recurrence during or after intervening treatment (received after completing an initial neoadjuvant and/or adjuvant course of anti-PD-(L)1 therapy). NA-EU panelists placed greater importance on the timing of clinical events relative to the use of anti-PD-(L)1 therapy than to the intervening therapy and suggested that decisions on retreatment would be informed by the duration of initial anti-PD-(L)1 therapy and the duration and type of the intervening treatment. The KR-AU panel experts were aligned that retreatment should be considered at least 6 months from the last cycle of anti-PD-(L)1 therapy; for this panel, this scenario implied that there had been a previous disease recurrence because intervening therapy would have only been needed if there had been evidence of disease recurrence. The Japanese panel agreed that the timing of retreatment would depend on when the intervening tyrosine kinase inhibitor (TKI) monotherapy for RCC started; 80% of the panel experts agreed that there should be at least 3 months duration

Table 3 Recommendations on the timing of retreatment for all seven hypothetical clinical scenarios

Scenario	Time to retreatment	After which event*
On anti-PD-(L)1		
After discontinuation due to locoregional recurrence on anti-PD(L)1	≥3–6 months	Recurrence/discontinuation
After discontinuation due to metastatic recurrence on anti-PD(L)1	≥3–6 months	Recurrence/discontinuation
After toxicity/immune-related adverse event	≥3–6 months	Discontinuation of anti-PD-(L)1
After completion of fixed duration of therapy (per drug label)		
Locoregional recurrence off anti-PD-(L)1	≥6 months	Last cycle of anti-PD-(L)1 treatment
Metastatic recurrence off anti-PD-(L)1	≥6 months	Last cycle of anti-PD-(L)1 treatment
After long-term recurrence/relapse (disease-free interval)	≥6 months	Last cycle of anti-PD-(L)1 treatment
During/after subsequent intervening therapy		
Recurrence during or after intervening therapy	Varied responses	No agreement

*The event from which the time to retreatment is counted; for example, after discontinuation of anti-PD-(L)1 due to locoregional recurrence on anti-PD-(L)1, retreatment may start ≥3–6 months after discontinuation.
anti-PD-(L)1, anti-programmed death (ligand) 1.

of, or since, TKI therapy before retreatment with an anti-PD-(L)1 therapy. There was no consensus on the specific time (panel results: 3 months: 60%; 12 months: 20%).

Factors influencing the treatment approach for anti-PD-(L)1 therapy for retreatment

Choice of retreatment strategy

When a decision is made to retreat a patient with an anti-PD-(L)1 therapy, various approaches are possible, including retreating with the original anti-PD-(L)1 therapy alone or in combination with another therapy, or switching to a different anti-PD-(L)1 therapy as monotherapy or as combination treatment. Given the associated regulatory and disease-specific complexities and the heterogeneity in the survey responses, no consensus methodology was applied, but the relevant issues were discussed in the panels.

Based on the survey results, using the same anti-PD-(L)1 therapy for retreatment was a strategy more commonly employed when the initial course of treatment was a fixed-dose anti-PD-(L)1 regimen that had been completed; switching of therapy was a more common strategy where the initial anti-PD-(L)1 treatment was discontinued (online supplemental figures 2–4).

Retreatment strategy: anti-PD(L)1 monotherapy versus combination therapy

The survey indicated that 'previous patient response,' 'time to recurrence or next event,' and 'time since discontinuation' were the factors that would most likely influence the clinicians to consider adding another therapy to anti-PD(L)1 retreatment (add-on therapy)—these factors were selected by ≥60% of clinicians as one of their top three factors from a list of 12 in at least one regional survey (online supplemental figure 1).

This decision differed by tumor type and was influenced by available treatment options for specific indications and by differences in evidence status (NA-EU and KR-AU panels). For example, in breast cancer, the choice of adding an add-on therapy to anti-PD-(L)1 monotherapy was not appropriate because the only approved indication in the USA at the time the study was conducted was an anti-PD-1 agent plus chemotherapy. Biomarker profile was raised as a factor that may influence retreatment decisions for NSCLC by five clinicians in the NA-EU panel (online supplemental figure 1).

Retreatment strategy: switch from previous anti-PD-(L)1 therapy

There was no clear agreement on which factors are most likely to influence a decision to switch or use the same anti-PD-(L)1 therapy, although the Japanese panelists all agreed that for patients with RCC, 'previous patient response' and 'time-related factors' (such as short time to recurrence) would influence this decision. There were some specific clinical situations in which switching the anti-PD-(L)1 therapy may be considered preferable, including (1) when the initial anti-PD-(L)1 therapy was not licensed for treatment of relapsed disease; (2) if the patient experienced an anaphylactic reaction to the original anti-PD-(L)1 infusion and (3) when the efficacy of retreatment with the initial anti-PD-(L)1 therapy was uncertain (NA-EU panel and Australian clinicians).

DISCUSSION

This study has provided insight from expert clinicians to help guide clinical decision-making in situations where retreatment with anti-PD-(L)1 therapy may be considered following its use in early-stage cancer. Given that the data to support clinical decision-making in this field evolved to different levels across different tumor types, clinical guidelines lack specificity in how to approach retreatment with anti-PD(L)1 therapy, despite this becoming an increasingly frequent clinical challenge. It is clear that clinicians consider a range of factors when making decisions about retreating patients. The difficulty expressed by clinicians in making retreatment decisions reflects the need for additional studies and evidence-based guidance in this area.

The design of our study, with an online survey followed by real-time Delphi panels, allowed systematic exploration of the issues around retreatment. The variability in the survey data ensured that there were several topics for discussion at the Delphi panels, where the rationale for the responses was explored in more detail. The modified Delphi method allowed for consensus development on some aspects of clinical decision-making that cannot be readily deduced from the existing literature. The use of hypothetical clinical scenarios was valuable in eliciting differences of opinion and how decision-making is influenced by specific clinical features.

The panels were established to include experts in oncology who were familiar with the challenges of retreatment and experienced in decision-making surrounding anti-PD-(L)1 therapies. In both survey responses and panel discussions, there were areas of consensus among the participants and areas with considerable variation in opinions, leading to some findings being more descriptive than consensus-based. Discussions also allowed the sharing of different clinical and tumor-specific experiences in IO retreatment between experts from different countries and healthcare settings. The survey respondents included mostly NSCLC (n=9/28), melanoma (n=8/28), and RCC (n=6/28) specialists due to the wider use of IO treatments in these settings. The approach was to identify areas where there were common themes across tumor types and countries, and identify areas where there may be differences which could be explored further with additional research.

All three panels agreed that decisions around retreatment with anti-PD-(L)1 therapy should consider 'prior irAEs/toxicity,' 'time-related factors' (eg, time since completion of full adjuvant anti-PD-(L)1 therapy or time since discontinuation of treatment), and 'previous patient response.' While each of these factors was considered important, the clinicians emphasized that these

factors could not be considered as individual elements and would all be collectively considered during decision-making. Differences in tumor experience across the panels and the availability of alternative treatment options for specific tumors also contributed to different opinions on the relative influence of clinical factors. In all panels, there was a comprehensive discussion around treatment approaches for patients who experienced irAEs while receiving anti-PD-(L)1 therapy in the neoadjuvant and/or adjuvant setting. Clinicians commented that the occurrence of 'disabling' irAEs, such as neurological or cardiovascular irAEs, is a contraindication to retreatment due to limited management options, compared with irAEs such as transient transaminitis and colitis or manageable endocrinopathies. Although there was discussion of retreatment with anti-PD-(L)1 therapy possibly being considered if the irAE was not 'serious,' no clear definition of 'serious' was discussed, and it was also noted in discussion that the level of importance given to irAEs is also dependent on the alternative treatment options for specific tumor types. This warrants further tumor-specific research regarding irAEs to provide more nuanced guidance for specific tumors. Panel members were more likely to consider retreatment when there was a lack of effective alternative treatment options for the patient. Biomarker profile was also raised as a factor that may influence retreatment decisions by five NA-EU clinicians in relation to NSCLC, and additional research is needed to explore this further.

Although clinicians in the panels considered that retreatment strategies may differ between tumor types (and recurrence and metastasis characteristics), consensus was achieved for several aspects relating to retreatment. There was broad agreement across the panels about the timing of retreatment, but it first required addressing more nuanced and specific questions during panel discussions. The included scenarios described distinct clinical scenarios, although there appeared to be some potential overlap between 'long-term relapse,' sometimes referred to as 'late relapse,' and metastatic or locoregional recurrence after completion of the anti-PD(L)1 treatment course in the early-stage setting. Additionally, although the long-term relapse scenario referred to disease returning after an extended period of remission, the specific duration defining 'long term' was not explicitly stated, potentially leading to overlap with the locoregional and metastatic recurrence scenarios. Discussions around the scenario in which a patient experiences recurrence during or after an intervening treatment reached no consensus, which underscores the complexity of this scenario where the timing of retreatment may be influenced by variability in the duration of the initial anti-PD-(L)1 therapy, as well as the duration and type of the intervening treatment.

There was also broad agreement on different preferred strategies when considering situations where a previous course of treatment had been completed rather than discontinued (regardless of the reason for treatment discontinuation). Using the same anti-PD-(L)1 therapy for retreatment would be more common when the initial course of treatment with a fixed-dose anti-PD-(L)1 regimen had been completed, whereas switching was a more common strategy for scenarios in which the initial anti-PD-(L)1 treatment was discontinued; however, there were varied opinions on specific factors which would influence that decision and on the appropriate strategy to use in different situations.

The NA-EU and KR-AU panels included clinicians across different tumor types, which allowed for the sharing of experiences and perspectives but also led to more challenges in gaining consensus on certain topics. The Japan panel only included urologists with experience in RCC, and unlike in many other countries, urologists in Japan manage all aspects of RCC, including performing surgery and administering systemic therapies for advanced cancer, including adjuvant therapies; this broader perspective on patient management is likely to be reflected in some of the responses to the survey and panel questions.

This study highlighted the importance of considering previous patient response when evaluating the potential for anti-PD-(L)1 retreatment in early-stage disease. However, an important knowledge gap remains in understanding how different types of patient responses (complete response, stable disease, progressive disease) in the neoadjuvant setting influence retreatment decisions. Future studies could investigate whether initial response to neoadjuvant therapy affects the likelihood or effectiveness of subsequent anti-PD-(L)1 retreatment. Additionally, the current study did not distinguish between patients who received anti-PD-(L)1 therapy in the neoadjuvant and adjuvant setting vs the adjuvant-only setting; this may have implications for clinical outcomes and warrants further research.

It was acknowledged that differences in the availability of treatments between countries exist. In part, this is related to the reimbursement status of different treatment options across the treatment pathway, as well as a lack of specific guidance on how and when retreatment is reimbursed. In a survey of national payers conducted in North America, Europe, and Australia, less than half (35%–47%) of the respondents reported that retreatment for early recurrent cancer was reimbursed, and most payers perceived a 'lack of comparative efficacy/effectiveness data over retreatment' as the most important access challenge/barrier to retreatment.[40] As specific examples of this, in Japan, the use of an anti-PD-(L)1 combination as a second-line treatment is not currently approved and consequently not reimbursed, but if it were, clinicians indicated that they would be more likely to switch to a different anti-PD-(L)1 therapy than use the same initial anti-PD-(L)1 therapy (monotherapy or combination) when recurrence occurred during/after the intervening therapy. Similarly, clinical experts from South Korea noted that switching the anti-PD-(L)1 therapy at the point of retreatment was currently

not reimbursed, but that they would consider switching if that option was available.

Given the limited evidence and guidance specific to retreatment after the use of neoadjuvant and/or adjuvant therapy, some discussions were based on clinical experience with later stage use of anti-PD-(L)1 treatment. There is likely to be a growing focus on anti-PD-(L)1 retreatment in early-stage cancers as more anti-PD-(L)1 treatments are granted regulatory approval in early lines of therapy, and as the regulatory and reimbursement landscape evolves, different anti-PD-(L)1 retreatment approaches may be considered in clinical practice. The panel recognized the evolving landscape, including the recent approvals of perioperative durvalumab based on the AEGEAN trial, perioperative pembrolizumab based on the KEYNOTE-671 trial, and perioperative nivolumab based on the CheckMate 77T trial, which could inform emerging strategies for anti-PD-(L)1 retreatment.[6 72–78] Although clinical guidelines will likely evolve to take changes such as these into account, the current Delphi study has helped identify ways in which clinical practice can be guided by patient characteristics and, more importantly, disease-related and treatment-related factors already considered in clinical practice in other settings, such as in metastatic disease. The findings of this Delphi study also point to areas where future research could help specifically inform treatment approaches.

This study identified clinician consensus on factors that should be considered for decisions around retreatment with anti-PD-(L)1 therapy, a gap not currently addressed in clinical guidelines; however, it is subject to some limitations. First, the clinicians noted that there was a limited evidence base outside of the melanoma, NSCLC, and RCC tumor types and that there were often limits on the use of retreatment in clinical practice as a result. Therefore, it may have been sometimes difficult for the survey and Delphi panel participants to extrapolate beyond their clinical experience and the available evidence—this resulted in some discussions being based on experience in later-line use of anti-PD-(L)1 treatment. The limited available literature on the use of anti-PD-(L)1 retreatment after initial anti-PD-(L)1 treatment in early-stage cancer was the reason this study was conducted. The participants recognized this, and in the Delphi panels, discussions were broader and facilitated in a way which aimed to elicit opinions specific to early-stage treatment. Second, there was the potential for selection bias as clinicians were paid to take part in the study. However, the study sponsor and participants remained blinded during study implementation, which may have helped mitigate the potential bias. Third, as the study used a modified Delphi panel methodology, anonymity among Delphi panelists was not maintained during the live panel discussions to facilitate dynamic discussion and clarification of perspectives, although panelists' responses were collected and reported in an anonymized manner. While this deviation from the traditional Delphi methodology may introduce bias such as peer influence, such bias was minimized through expert facilitation, which ensured all participants had equal opportunity to provide their perspectives during the live panel discussions. Fourth, as the Delphi panels took place in real time, some of the clinicians who completed the survey were unavailable to join the panels at the proposed times; however, the use of real-time panels allowed valuable discussions with participants, and the use of a survey beforehand also gathered the experiences of those who were unable to join the panels. The anticipated time requirement for participation in Delphi panels, along with the time period given to indicate willingness to complete the survey, may also help explain the response rate to the request to participate in the study. However, this level of response was not unexpected for busy expert clinicians and was in line with published literature. The Delphi panel size was at the lower end of published ranges, which may have been due to the requirement for real-time participation. Additionally, the aim was to conduct the Japan Delphi panel in English, which led to a higher number of participants declining to participate; the panel was eventually conducted in Japanese. Of note, all eventual participants reflected the level of experience necessary to discuss the topic as required by the inclusion criteria. There are also practical considerations to consider when using virtual real-time panels, such as technology limitations and ensuring panels are small enough to ensure all participants are able to contribute to discussions. Finally, as reported for other Delphi panels,[66 67] although we recruited a geographically diverse group of clinical experts, the experiences reported by this number of people may not reflect those of other clinicians (including those treating patients with other tumor types) in an evolving treatment landscape across different healthcare settings. Due to the number of participants in the Delphi panels, no general statements can be generated based on tumor type by country.

CONCLUSIONS

This modified Delphi study highlighted that clinicians across different regions recognized a potential role for retreating patients with anti-PD-(L)1 therapies after initial anti-PD-(L)1 treatment for early-stage cancers. Multiple factors were considered when deciding on retreatment with anti-PD-(L)1 therapy, specifically 'prior irAEs/toxicity,' 'time-related factors,' and 'previous patient response.' Generally, the clinicians considered that retreatment would be considered from at least 3–6 months after discontinuing initial anti-PD-(L)1 treatment, or when relapse/recurrence occurs at least 6 months after completing neoadjuvant and/or adjuvant treatment, although no prospective randomized clinical trials have evaluated this. Appropriate retreatment strategies were also considered to vary by clinical scenarios, and differences in clinical practice between countries/geographical regions made it difficult to achieve consensus for some of the more nuanced elements of retreatment. Additional studies with larger cohorts of patients could help better

inform retreatment decisions, including the scenarios for which retreatment could be appropriate, and retreatment strategies for different tumor types.

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