CASE AUTH/3631/4/22 and CASE AUTH/3636/4/22

COMPLAINANT v ASTRAZENECA AND DAIICHI SANKYO

Concerns about a trastuzumab deruxtecan advisory board

CASE SUMMARY

This case was in relation to the nature of a trastuzumab deruxtecan advisory board entitled 'T-DXd in the second-line setting in HER2+ mBC'.

The Panel ruled both AstraZeneca and Daiichi Sankyo in breach of the following Clause(s) of the 2021 Code due to insufficient details being provided to advisors about the advice being sought prior to them contractually agreeing to participate in the advisory board:

Breach of Clause 5.1	**Failing to maintain high standards**

The Panel ruled no breach of the following Clause(s) of the 2021 Code in relation to other allegations about the arrangements of the advisory board:

No Breach of Clause 24.2	**The requirement that the arrangements for genuine consultancy services fulfil the criteria of this Clause, including a written contract in advance of the commencement of the services which specifies the nature of the services to be provided and the basis for payment of those services**
No Breach of Clause 19.1	**The requirement that no gift, pecuniary advantage or benefit may be supplied, offered or promised to health professionals or to other relevant decision makers in connection with the promotion of medicines or as an inducement to prescribe, supply, administer, recommend, buy or sell any medicine**
No Breach of Clause 5.1	**The requirement to maintain high standards**
No Breach of Clause 2	**The requirement that activities or material must not bring discredit upon, or reduce confidence in, the pharmaceutical industry**

This summary is not intended to be read in isolation.
For full details, please see the full case report below.

FULL CASE REPORT

A complainant who described him/herself as a consultant medical oncologist, involved in the care of breast cancer patients, complained about an advisory board that he/she attended on 7

April 2022 regarding trastuzumab deruxtecan as a second line HER2+ metastatic breast cancer option.

COMPLAINT

The complainant alleged that the nature of the advisory board was completely misplaced and not a fair representation of what he/she (as well as other advisors including the chair) were advised of.

The complainant stated that since the data was released at an international congress in the previous year, he/she had been approached by representatives from both AstraZeneca and Daiichi Sankyo in late 2021; the questions he/she was asked in these meetings were identical to those of the advisory board on 7 April 2022. There had been no further developments in the second line metastatic space to change any of his/her, or his/her peers, opinions on this matter since.

It begged the complainant to believe that along with the line of questions asked on 7 April that they were being forced to think about patients that they would want to start on trastuzumab deruxtecan, and even possibly to think about prolonging patient treatments until the license had been granted, for which they were assured would be imminent.

The complainant stated that he/she did not understand why his/her, as well as his/her honourable peers time was wasted in a fad advisory board. The complainant abhorrently failed to see how the companies involved could think that this was not a waste of valuable time given that the ESMO guidelines clearly stated that trastuzumab deruxtecan could be used in second line given the data presented last year. Furthermore, the NCCN guidelines (extract provided) also stated that trastuzumab deruxtecan was a preferred regimen for the second line. He/she was staggered beyond belief that two prestigious guidelines had included this medicine in second line yet the companies thought an advisory board was necessary.

The complainant stated that he/she had previously attended numerous advisory boards with AstraZeneca, all of which wanted expert advice on uncertainty with clinical data. He/she could not say the same for this advisory board where international and national consensus was reached last year that trastuzumab deruxtecan was the new standard of care for metastatic patients in the second line.

The complainant alleged that this advisory board felt like the two companies were trying to recap the data with his/her peers in advance of the license and had left him/her feeling extremely uncomfortable.

In response to a request for information from the case preparation manager regarding the meetings with representatives referred to in his/her complaint, the complainant stated that they were one to one meetings and virtual meetings that he/she had with various representatives from both AstraZeneca and Daiichi Sankyo. The complainant stated that these representatives covered third line but also the data in second line which had just been released.

The complainant further stated that his/her initial email should have mentioned that he/she had also attended advisory boards for AstraZeneca which were with global colleagues and international peers. These happened just after ESMO 2021 and discussed all of the same

topics as in the 7 April advisory board, which again made the complainant question the nature of the 7 April meeting.

When writing to AstraZeneca and Daiichi Sankyo, the Authority asked them to consider the requirements of Clauses 2, 5.1, 19.1 and 24.2 of the Code.

RESPONSE

Case AUTH/3631/4/22 (AstraZeneca)

AstraZeneca stated that Daiichi Sankyo was the marketing authorisation holder for trastuzumab deruxtecan (T-DXd) working in partnership with AstraZeneca for the development and promotion of T-DXd. For the named advisory board meeting, Daiichi Sankyo was the lead marketing company with AstraZeneca supporting. Daiichi Sankyo was responsible for the contracting process for the chair and advisors and selected agency. AstraZeneca and Daiichi Sankyo co-led on all briefings (including chair briefings), formulated the objectives, agenda and jointly approved the meeting and associate materials. The approval of materials was a shared responsibility between Daiichi Sankyo and AstraZeneca with both companies reviewing and approving materials in the Daiichi-Sankyo owned platform. Daiichi Sankyo certified the materials on behalf of both companies and were responsible for notifying the PMCPA and MHRA of details for medical signatories acting on behalf of both companies.

The complainant's allegations (as AstraZeneca believed) could be broken down as follows:

1 Mismatch between the intent of advisory board communicated to participants and the actual advisory board meeting and the appropriate use of health professionals.
2 Similarities between questions asked by sales representatives from AstraZeneca and Daiichi Sankyo and those asked in the advisory board meeting.
3 Unnecessary advisory board meeting and data presentation.

AstraZeneca stated that it would address each of the complainant's allegations according to the relevant clauses of the Code.

Allegation 1: Mismatch between the intent of advisory board communicated to participants and actual advisory board meeting and appropriate use of health professionals

On 24 February 2022, an invitation was sent to participants who had expressed interest in attending the advisory board meeting. The invitation included the topic (metastatic breast cancer), the requirements for participation and the logistics for confirming participation. On 29 March 2022, the confirmed participants were sent further communication highlighting the purpose of the advisory meeting which was to 'understand the practical implications of using T-DXd in the second line setting as well as identify any data gaps that could be addressed in future analyses to increase the confidence of HCPs when deciding the treatment sequence for patients with HER2+ mBC' and the time commitment required. The pre-reads and the pre advisory board meeting survey were also included. The pre work survey reiterated the same intent .

The virtual advisory board meeting took place on 7 April 2022. The meeting objectives and agenda which were part of the meeting showreel clearly outlined the four objectives of the meeting as follows:

1 To gain expert insights and feedback on the efficacy profile of T-DXd in the second line (2L) setting as reported in the DESTINY-Breast03 trial, including the pre-specified subgroup analysis.
2 To understand UK expert perceptions on the safety profile of T-DXd, as well as adverse event management strategies.
3 To explore how health professionals might prescribe T-DXd in the 2L setting in UK clinical practice, including how the patient pathway might change when this treatment option becomes available for use.
4 To identify potential data gaps that, if addressed, would support the use of T-DXd in the 2L treatment of patients with HER2+ mBC.

The agenda outlines these objectives again and highlights that each session would cover each objective. The agenda also highlighted the timings of the session and the participants for each session.

AstraZeneca stated that it believed that the information provided above sufficiently demonstrated that the advisors were informed of the nature of the meeting a number of times and that this information was consistent throughout its engagement with the advisors. In addition, all the advisors chosen were practising health professionals. In line with the 2021 version of the Code, health professionals were permitted to act as advisors in advisory board meetings and the contracting company could provide appropriate remuneration and hospitality. In this case, the advisory board meeting was a virtual meeting and therefore, no hospitality was provided.

Each participant was given a contract which was signed before the meeting took place. It clearly specified the nature of the services that AstraZeneca and Daiichi-Sankyo were engaging advisors to undertake and the basis for payment of those services. The honorarium was in keeping with fair market values.

AstraZeneca therefore denied the alleged breach of Clause 5.1 and 24.2 in addition to Clauses 2 and 19.1 of the Code 2021.

Allegation 2: Similarities between questions asked by representatives from AstraZeneca and Daiichi Sankyo and those asked in the advisory board meeting

AstraZeneca stated that T-DXd was licensed as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who had received two or more prior anti-HER2-based regimens (3rd Line setting). Thus, AstraZeneca and Daiichi Sankyo did have sales representatives co-promoting within this license. AstraZeneca were not privy to the details of discussions that had taken place between sales representatives and health professionals or the anonymous complainant. AstraZeneca's sales representatives were briefed to only have discussions on the licensed indication.

The SOP outlining field medical conduct was provided, which clearly defined the reactive nature of their role. AstraZeneca could confirm that Daiichi Sankyo and AstraZeneca UK had not organised any other advisory board meetings on this topic. Global AstraZeneca and Daiichi

Sankyo did hold an advisory board meeting to ascertain the Global clinical implications of the DB03 results on treatment paradigm. There were two UK advisors present out of a total of 10 advisors.

AstraZeneca stated that it could confirm that there was no overlap between the attendees of the Global advisory board meeting and the UK advisory board meeting on 7 April 2022.

The UK advisory board meeting was to provide UK-specific advice on the practical implications of using T-DXd within the 2L setting, as well as identifying data gaps that could be addressed to increase the confidence of UK HCPs in creating treatment regimens. This also included obtaining feedback from devolved nations not represented at the Global advisory board meeting and to assist the UK Marketing Companies for AstraZeneca and Daiichi Sankyo to inform strategic and tactical planning. This business need could not be met by a Global advisory board meeting.

AstraZeneca therefore denied the alleged allegations made by the complainant and denied alleged breach of Clauses 2, 5.1, 19.1 and 24.2 of the Code 2021.

Allegation 3: Unnecessary advisory board and data presentation

Confirmed participants were sent pre reads which included full published articles outlining trial rationale, methodology & results from Destiny Breast 3: T-DXd versus Trastuzumab emtansine in unresectable / metastatic breast cancer patients. This was AstraZeneca's registration study which was supporting AstraZeneca's application for earlier line use of T-DXd in metastatic breast cancer patients. The show reel had summarised the key elements of the papers shared in the pre reads and was used by the Chair as an aide memoire for the participants to support the discussion. There was no didactic presentation of the slides. A detailed briefing document for the Chair of the meeting was provided and within the briefing the use of meeting slide deck was clearly outlined ie, Meeting slides for the facilitation of this meeting will be shared with you for your approval prior to the meeting and will include prompts to cover all the questions listed above.

The briefing document also outlined the total presentation and discussion time for each session in addition to the discussion points that had to be covered in each session. It was clear from the document that approximately 27 minutes were allocated to presentation and 143 minutes to discussion. The 16/84 % split between presentation and discussion, coupled with the detailed briefing to the Chair, clearly showed that the advisory board meeting was structured to gain advise for documented and communicated unanswered business questions.

This was consistent with the concept form that was required to be completed and approved before any advisory board meeting. The concept form also highlighted that the slides were to be used as a reference to aid discussion.

AstraZeneca had reviewed the advisory board meeting report, which highlighted that the chair communicated the salient data points on the slides to base the discussion on. The length of the report was testament to the depth and breadth of the discussion that took place at the advisory board meeting.

The complainant referred to the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) guidelines, highlighting that both these

guidelines had been updated and recommend earlier use of T-DXd in eligible patients ie, 2L instead of 3L. This was based on the results of the published Destiny Breast 03 trial. Whilst the NCCN guidelines might be referred to by some UK clinicians, it was the ESMO guidelines that the majority of UK clinicians would consult for guidance. However, the guidelines were there to provide a level of direction and the clinician had the autonomy to interpret and implement the guidance as they felt was appropriate for their patient(s). The objective of the advisory board meeting (as stated above) was to explore how health professionals might prescribe T-DXd in the 2L setting in UK clinical practice. ESMO guidance was created by a panel of European experts for a European population. As such, it might not be an accurate reflection of how UK clinicians might treat their patients due to several reasons. This was echoed in the advisory board meeting report, where it was clear that the UK clinicians did not agree with all the guidance within the ESMO guidelines and in particular, the recommendation for patients with active brain metastasis as advisors felt that there was not sufficient evidence to support T-DXd use in this setting.

AstraZeneca stated that it believed that the information outlined above provided sufficient evidence that the advisory board meeting held April 7 2022 was needed to address outstanding UK business questions.

AstraZeneca therefore denied the alleged allegations made by the complainant and denied alleged breach of Clauses 2, 5.1, 19.1 and 24.2 of the Code 2021.

Summary of AstraZeneca's position

It was AstraZeneca's position that the objections and need for the advisory board meeting held on 7 April 2022 were clearly communicated to the advisors through a number of written channels. AstraZeneca were also of the firm belief that it conducted the advisory board meeting in a manner that enabled depth and breadth of discussion to address specific business questions. AstraZeneca strongly denied the alleged breaches that had been put forward by the complainant. AstraZeneca hoped that the evidence it had provided was sufficient to address these allegations.

AstraZeneca stated that it subscribed fully to the high ethical and moral spirit of the Code and took its responsibilities under the code very seriously.

Further information

The Panel requested further details from the complainant regarding the one to one meetings with company representatives and the AstraZeneca global advisory board meetings referred to in his/her complaint. The complainant did not respond.

The Panel therefore requested additional information from AstraZeneca in relation to any global trastuzumab deruxtecan advisory board meetings that took place in 2021, around the time of, or following, ESMO, which were attended by at least one of the same UK advisors present at the 7 April 2022 UK advisory board.

In response, AstraZeneca submitted that there was one global trastuzumab deruxtecan advisory board that took place virtually on 30 August 2021 just before the ESMO 2021 congress, however, this was not attended by any of the same UK advisors present at the 7 April 2022 UK

advisory board. AstraZeneca also submitted that there were no other global trastuzumab deruxtecan advisory board that took place around the time of, or following, ESMO 2021.

RESPONSE

Case AUTH/3636/4/22 (Daiichi Sankyo)

Daiichi Sankyo denied all breaches.

Background Information

Daiichi Sankyo stated that this advisory board was run under the terms of its Alliance agreement with materials being examined under the code by signatories from both companies and final examination being carried out within the Daiichi Sankyo electronic approval system to which AstraZeneca alliance colleagues had full access.

This advisory board was also run in accordance with both company SOPs always using the stricter requirement where the SOPs differed and wherever possible using a stricter approach than required in either SOP. See final section on the technical elements of this advisory board.

Trastuzumab deruxtecan as monotherapy was currently indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who had received two or more prior anti-HER2-based regimens (so called third line treatment). It was reimbursed and actively promoted in this indication in all four home nations.

Trastuzumab deruxtecan was being investigated in other indications and was likely to be granted a licence extension later this year in an earlier line of treatment (so called second line). The subject of this advisory board was the proposed new indication.

Allegation 1

Daiichi Sankyo submitted that the content, aims, and nature of this advisory board were extremely clear to advisors prior to the meeting. In Daiichi Sankyo's initial invitation email to establish advisors' availability Daiichi Sankyo did not mention the specific indication or medicine to be discussed but in subsequent communications with confirmed advisors well in advance of the meeting, including in the contract signed by all advisors, the title of the advisory board and the area Daiichi Sankyo was going to be seeking advice on (the use of the medicine in the second line setting) was imparted very clearly.

Ahead of the advisory board Daiichi Sankyo sent pre-reading material as well as a pre-work questionnaire. This was all detailed in a cover email in which Daiichi Sankyo stated:

> 'We look forward to your participation in the upcoming advisory board on the use of trastuzumab deruxtecan▼ (T-DXd) for the second-line treatment of human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (mBC). The purpose of this advisory board meeting is to understand the practical implications of using T-DXd in the second-line setting* as well as to identify any data gaps that could be addressed in future analyses to increase the confidence of HCPs when deciding the treatment sequence for patients with HER2+ mBC.'

In addition, Daiichi Sankyo had several discussions with the external chair, an expert in breast cancer based at the [named London hospital], where Daiichi Sankyo again went over the agenda and aims and objectives. These were set out very clearly in a briefing document to the chair. The [named doctor] was happy to chair the meeting and his/her subsequent feedback to Daiichi Sankyo after the meeting had been very positive suggesting he/she had a very different opinion on the nature and legitimacy of this advisory board than the complainant.

The content of the complaint suggested that the complainant did not think there were any outstanding issues to discuss regarding the use of this medicine in the second line setting. While Daiichi Sankyo disagreed with that and would outline why below, it was important at this point to state that none of the advisors (and so therefore the complainant) asked for any additional clarity at any stage during the several communications that happened before the meeting despite knowing the area Daiichi Sankyo would be covering. Daiichi Sankyo did not see how the complainant could have been in any doubt ahead of time as to the subject or nature of this advisory board or why they would agree to attend and signed the contract if they had such doubts.

Allegation 2

Daiichi Sankyo stated that no commercial representatives from either company had been authorised to discuss second line data and product related briefings on materials for current promotional campaigns include specific instructions not to discuss the use of trastuzumab deruxtecan in unlicensed indications (Enhertu Updated Sales Aid briefing document (ADC/22/0088).

At the time of the advisory board being planned, the UK signatories from both companies checked what other advisory activity had occurred as was required in concept documents from both companies. The information Daiichi Sankyo sought in this advisory board was not available and the rationale for proceeding with this advisory board (including all previously conducted and future planned activity above country) was set out in the attached concept approval form.

Importantly as far as this complaint was concerned, when all global and regional advisory activity was checked at concept stage there was no record of any of the UK clinicians who attended the advisory board having attended any other advisory boards run recently by either Daiichi Sankyo or AstraZeneca. Daiichi Sankyo had checked again in light of the complaint and could still find no record of any advisory board activity having taken place, arranged either by Daiichi Sankyo or AstraZeneca, which included any of the advisors who attended its advisory board. Daiichi Sankyo therefore did not know what advisory board the complainant was referring to in his/her follow up email to the PMCPA.

Allegation 3

Daiichi Sankyo strongly refuted the suggestion that this was a fad advisory board. There were many issues on which companies seek advice beyond clinical uncertainty.

All of the detailed aims and objectives of the advisory board were set out in in the chair's briefing document and were communicated at the beginning of the advisory board meeting. In high level summary, the objectives of this advisory board were:

- To gain insights and feedback on the efficacy profile of trastuzumab deruxtecan in the 2L setting particularly in pre-specified subgroups and to understand whether subgroups of patients might be treated differently depending on certain characteristics.
- To understand perceptions of the safety profile of trastuzumab deruxtecan as well as adverse event management strategies.
- To explore how health professionals may prescribe trastuzumab deruxtecan in the 2L setting in UK clinical practice including how the patient pathway might change when this treatment option became available for use given this interplay of opinion on the relevant efficacy versus safety profile.
- To explore whether there were additional things Daiichi Sankyo needed to do to answer any outstanding questions in the data.

In terms of the efficacy profile, the complainant suggested that the advisory board was not necessary because the medicine was now included in the NCCN and ESMO guidelines. This was simply not correct. The NCCN guidelines were issued by the National Comprehensive Cancer Network in the United States of America. These guidelines were not implemented in UK practice and indeed very often differ significantly from UK practice due to issues of different marketing authorisations and reimbursement situations for medicines in the US.

The ESMO (European Society for Medical Oncology) guidelines were often more reflective of UK practice, but they were again a European level set of guidelines written by a panel of experts from across Europe and were subject to interpretation and implementation by individual countries based on a number of issues, not least reimbursement status of medicines.

The current ESMO guidelines included by the complainant highlight that the current gold standard in second line was TDM-1 treatment and that trastuzumab deruxtecan showed greater efficacy and so 'it is reasonable to consider trastuzumab deruxtecan the new standard second-line therapy in regions where this drug is available [I, A], moving T-DM1 to a later-line setting.' However, it was not at all clear that T-DM1 therapy would be reimbursed in the UK in a later line of therapy, and it was not at all clear to Daiichi Sankyo ahead of the advisory board whether clinicians in the UK felt that the ESMO guidelines would reflect practice for all patients in the UK. Trastuzumab deruxtecan was currently licensed in 3rd line after T-DM1 so maintaining the current approach allows patients to get both treatments (TDM-1 first and trastuzumab deruxtecan subsequently). Moving trastuzumab deruxtecan earlier in the treatment path as per the proposed new indication might mean patients losing a line of therapy and being overall disadvantaged. Indeed, there were groups highlighted by the advisors for whom that might be the case and some of the data they would want to see to include those more marginal groups of patients in a new treatment paradigm were discussed.

Finally, the ESMO clinical practice guidelines were discussed. There was disagreement by advisors on the day regarding some of the recommendations in the ESMO clinical practice guidelines, especially regarding treatment of patients with active brain metastases. There was also a discussion around sequencing of treatments and an acknowledgement that this would not become fully clear until it was understood what medicines were reimbursed in what lines of treatment. It was very clear from the feedback at the advisory board that the ESMO guidelines may not be adopted wholesale as is suggested by the complainant. The full advisory board report was provided.

Discussing the safety profile of this medicine was also very important for Daiichi Sankyo. Trastuzumab deruxtecan was a black triangle medicine and had known safety issues including causing interstitial lung disease (ILD) (inflammation of the lung) which could progress rapidly and had resulted in fatal outcomes in clinical trials and in real world experience. Although Daiichi Sankyo did have a suite of risk management materials, the company had seen cases of ILD in the UK including fatal cases. On the day, Daiichi Sankyo were able to gain insight from the clinicians on the other elements of the adverse event profile that concerned them as well as suggestions around more work that Daiichi Sankyo could and should be doing to help even more effectively define the adverse event profile and potentially help to mitigate the impact of adverse events (and ensure better outcomes for patients) through work with the UK clinical community.

In summary, Daiichi Sankyo felt that it discussed in great detail a number of crucially important areas of uncertainty for the company and the information Daiichi Sankyo received would be crucial in guiding its strategy and forecasting (and resourcing) in the future. Daiichi Sankyo submitted that this was a bona fide advisory board to answer legitimate outstanding business questions. Therefore, Daiichi Sankyo refuted a breach of Clause 24.2.

Allegation 4

Daiichi Sankyo stated that it had largely addressed why this was a legitimate advisory board. But this specific allegation was probably worth addressing in detail.

Daiichi Sankyo stated that its current expectation was that marketing authorisation would be granted in September 2022. NICE submission would be in parallel but Daiichi Sankyo was expecting to gain reimbursement in November 2022 at the earliest and probably sometime in the first few months of 2023. It would be even later than this in Scotland.

The delay from this advisory board to reimbursement and commercial availability of trastuzumab deruxtecan was likely to be at least 7 months and possibly as long as a year. Certainly, this was not 'imminent' as the complainant suggested and would absolutely not be of a timescale Daiichi Sankyo would encourage people to hold off on treating patients who had metastatic breast cancer and would become unwell very quickly.

Technical elements of the advisory board

Daiichi Sankyo outlined some technical elements of the advisory board and how it considered these met the requirements of both the Code and the company's SOPs:

- This advisory board included 9 advisors. These were all expert breast cancer oncologists likely to be very familiar with the data and with the likely impact of the data on clinical practice. They were also all expected to be experienced in the use of trastuzumab deruxtecan in the existing indication and finally they were chosen to represent a broad range of geographies across the UK to allow for any potential regional variation in clinical practice.
- Two company employees from medical departments were in attendance, one from Daiichi Sankyo and from Astra Zeneca. This was to ensure representation from both companies, to assist the chair in guiding the discussion and answer any medical and technical questions on the medicine. A third medical colleague was proposed in the concept form as a back up but he/she did not attend the advisory board.

- Further, Daiichi Sankyo had two colleagues from its agency managing logistics and minute taking. The ratio of staff to advisors was below the 2:1 ratio required in the companies SOPs.
- The final agenda timings were detailed in the chair briefing document.
- In addition to the initial invitation email, a pre-work email was also sent. In this, a pre-meeting questionnaire was given (which Daiichi Sankyo confirmed ahead of time was completed by all the advisors in advance) which helped guide some of the discussions. A document outlining the pre-reading was also sent with all of the pre-reading materials included in full. That document made it clear that these data would form the basis of the advisory board discussions and that, advisors should come along having familiarized themselves with the material.
- Since all relevant data were sent as pre-read, the final powerpoint deck for this advisory board was not given as a didactic presentation. As could be seen from the advisory board report, although all slides were available to advisors and were navigated by the chair, because of the engagement with pre-read by the advisors only 18 slides were looked at in detail on the day. The concept form also highlights that the slides were to be used as a reference to aid discussion. In the agenda, there were 27 minutes of introductions and presentation scheduled and 148 minutes of discussion. This was a ratio of 85% discussion to 15% introductions and presentation. This was well within the requirements of Daiichi Sankyo's SOP (which recommends a minimum 70% discussion) and reflected its desire to maximise discussion time at advisory boards.
- All attendees were contracted in advance and remunerated for their time in line with Daiichi Sankyo fair market value guidance in the UK in keeping with the requirements of Clause 24.2. That remuneration was set out clearly, including time for Pre-reading (one hour) and for the advisory board attendance itself (3 hours virtually).

Summary and conclusions

Daiichi Sankyo submitted that this was a thoroughly planned and well conducted advisory board with legitimate aims and objectives which would not only help it to ensure appropriate patients receive the right treatment options for their breast cancer but would also help it plan activities to mitigate the challenges Daiichi Sankyo saw from adverse events with this medicine. Daiichi Sankyo engaged effectively with the chair throughout the planning and execution. The communication before the advisory board to all advisors was clear and unambiguous in detailing the aims and objectives of the meeting and Daiichi Sankyo did not feel there was any space for the misunderstanding that the complainant alleged. Daiichi Sankyo had only positive and constructive feedback from other advisors and was unaware of any others who felt the way the complainant did. Daiichi Sankyo therefore did not accept the suggestion that this advisory board breached Clause 5.1

Daiichi Sankyo submitted that this was a necessary and valuable advisory board where it had gained very helpful advice; it was contracted and arranged properly in accordance with the requirements of the code and its SOPs. It was absolutely not Daiichi Sankyo's intention that any of the advisors would be subsequently any more likely to prescribe trastuzumab deruxtecan and therefore Daiichi Sankyo did not accept that this advisory board breached Clause 19.1.

Daiichi Sankyo submitted that this advisory board met all the requirements of Clause 24.2 and the evidence for this, including contracts, was provided. Daiichi Sankyo therefore denied a breach of Clause 24.2. Daiichi Sankyo further denied a breach of Clause 2.

PANEL RULING

The Panel noted that the advisory board at issue took place on 7 April 2022 and focussed on a proposed new indication for trastuzumab deruxtecan for the second-line treatment of HER2+ metastatic breast cancer. At the time of the advisory board, trastuzumab deruxtecan was licensed in the third line setting.

The Panel noted that the case preparation manager initially asked AstraZeneca to respond to the matter. The Panel noted AstraZeneca's submission that Daiichi Sankyo was the marketing authorisation holder, working in partnership with AstraZeneca for the development and promotion of trastuzumab deruxtecan. For the named advisory board meeting, Daiichi Sankyo was the lead company with AstraZeneca supporting. Daiichi Sankyo was responsible for the contracting process with the chair, advisors and agency. AstraZeneca and Daiichi Sankyo co-led on all briefings (including chair briefings), formulated the objectives, agenda and jointly approved the meeting and associate materials. The approval of materials was a shared responsibility between Daiichi Sankyo and AstraZeneca with both companies reviewing and approving materials in the Daiichi Sankyo platform. The Panel noted that the contracts for advisors were provided by Daiichi Sankyo in its response to the Panel and appeared to have been signed on behalf of Daiichi Sankyo.

As such, in addition to AstraZeneca (Case AUTH/3631/4/22), Daiichi Sankyo was asked to respond to the complaint under Case AUTH/3636/4/22. Whilst the Panel made its rulings for each company separately, as set out below, the Panel utilised documents and submissions from both companies noting AstraZeneca and Daiichi Sankyo were jointly involved in the advisory board.

The Panel noted that the complainant did not respond to a request for further information, regarding the one-to-one meetings with company representatives and the AstraZeneca global advisory board meetings referred to in his/her complaint. In accordance with the introduction to the Constitution and Procedure, complaints were judged on the evidence provided by the parties. Complainants had the burden of proving their complaint on the balance of probabilities.

Case AUTH/3631/4/22

The Panel noted that the complainant was an advisor at the 7 April 2022 advisory board and alleged that the nature of the meeting itself was not a fair representation of what he/she was advised of.

It appeared to the Panel that an email invitation was sent on 24 February 2022 to participants who had expressed interest in attending the advisory board meeting; it was not clear how this initial expression of interest was obtained and AstraZeneca made no submission in this regard.

The email invitation template provided stated:

> 'We are pleased to invite you to <Chair/participate in> the virtual advisory board meeting on 7th April between 3 and 6pm. The topic will be on metastatic breast cancer and is a non-promotional meeting organised by Daiichi Sankyo and AstraZeneca. You have been asked specifically to participate in this advisory board because of your expertise in breast cancer. This email is to confirm your availability.'

The email listed the time investment required by the advisors, including for pre-work, and stated that a contract would be sent upon confirmation of participation. Those who had responded to the email invite confirming their willingness to participate were sent contracts to sign.

The Panel noted that AstraZeneca had not provided any contracts for the advisors; the contracts were submitted as part of Daiichi Sankyo's response (Case AUTH/3636/4/22) and the contracts all appeared to be between the advisors and Daiichi Sankyo.

The Panel noted that 'Attachment A – Services and Fees' of the contracts listed the services for advisors as, 'The Consultant will participate in a DS Ad Board entitled T-DXd in the second-line setting in HER2+ mBC', or similar wording. The Panel noted that whilst the amount of preparation time varied depending on the role, the contract did not state whether the participant was an advisor or chair. Furthermore, the contracts did not state what the aims or objectives of the advisory board were nor did they state the nature of the advice being sought.

The Panel noted that on 29 March, prior to the advisory board, a pre-work cover email was sent to advisors who had contractually agreed to participate, which included a link to an online questionnaire to help understand initial thoughts, along with a pre-reading attachment which included 8 publications that would 'form the foundation for discussion on the day'. The email stated, *inter alia*:

> 'We look forward to your participation in the upcoming advisory board on the use of trastuzumab deruxtecan▼ (T-DXd) for the second-line treatment of human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (mBC). The purpose of this advisory board meeting is to understand the practical implications of using T-DXd in the second-line setting* as well as to identify any data gaps that could be addressed in future analyses to increase the confidence of HCPs when deciding the treatment sequence for patients with HER2+ mBC.'

The asterisk (*) led to a footnote which stated: 'T-DXd as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens'.

The Panel considered that the invitation of 24 February and the contracts contained limited details about the advisory board; neither detailed the purpose (as stated in the email of 29 March) nor the aims or objectives of the advisory board. Whilst the pre-reading material, sent on 29 March, included a questionnaire and cover email, which detailed the purpose of the advisory board meeting, the Panel considered that this material was only sent to advisors after they had signed the contract and thus had already contractually confirmed participation. The Panel thus queried the concept of contractually agreeing to be an advisor without important information such as the objectives of the meeting being understood.

Clause 24.2 stated, *inter alia*, that a written contract or agreement must be agreed in advance of the commencement of the services which specifies the nature of the services to be provided and the basis for payment of those services.

The Panel considered that, on balance, there was sufficient detail in the contract to decipher that the service required of the health professional was an advisory board in relation to

trastuzumab deruxtecan for the second-line treatment of HER2+ metastatic breast cancer and in that regard no breach of Clause 24.2 was ruled.

However, the Panel considered the limited details in the contract, which referred to 'Trastuzumab Deruxtecan (T-DXd) for second line treatment of HER2+ Metastatic Breast Cancer', and the even more limited details within the invite, were insufficient for an advisor to decipher what the actual advice being sought from him/her was prior to contractually agreeing to participate; the contract made no reference to the aims nor objectives of the advisory board. Whilst noting that the contracts were signed by Daiichi Sankyo, the activity was joint between Daiichi Sankyo and AstraZeneca and therefore AstraZeneca also had responsibility to ensure that advisors had sufficient information prior to contractually agreeing to participate. In this regard, the Panel considered that AstraZeneca had failed to maintain high standards and a breach of Clause 5.1 was ruled.

The complainant alleged that he/she had been asked identical questions to those of the advisory board by AstraZeneca and Daiichi Sankyo representatives in late 2021. The complainant also allegedly attended advisory boards for AstraZeneca, just after ESMO 2021, which discussed all of the same topics as in the 7 April advisory board, which made the complainant question the nature of the 7 April meeting.

The Panel noted AstraZeneca's submission that it was not privy to the details of discussions that had taken place between sales representatives and health professionals or the anonymous complainant and that AstraZeneca's sales representatives were briefed to only have discussions on the licensed indication. AstraZeneca also submitted that field medical conduct was reactive in nature. The Panel further noted AstraZeneca's submission that there was one global trastuzumab deruxtecan advisory board that took place virtually on 30 August 2021 just before the ESMO 2021 Congress, however this was not attended by any of the same UK advisors present at the 7 April 2022 UK advisory board. AstraZeneca also submitted that there were no other global trastuzumab deruxtecan advisory board that took place around the time of, or following, ESMO 2021.

The Panel noted that the parties' accounts differed in this regard.

A judgement had to be made on the available evidence bearing in mind the extreme dissatisfaction usually necessary on the part of an individual before he/she was moved to actually submit a complaint. The Panel noted that the complainant bore the burden of proof and did not consider that he/she had established that there were advisory boards that discussed the same topics as the meeting of 7th April at issue, nor that the meeting was not a *bona fide* advisory board meeting. The Panel ruled no breach of Clauses 19.1 and 24.2 in that regard.

With regard to the complainant's allegation that advisors were being forced to think about patients that they would want to start on trastuzumab deruxtecan, and even possibly to think about prolonging patient treatments until the license had been granted, for which they were assured would be imminent, the Panel noted that AstraZeneca made no submission in this regard.

The Panel noted that the pre-work questionnaire included the questions 'How do you envisage the future patient pathway for 1, 2 and 3L treatment of HER2 mBC and where would you position T-Dxd?' and 'Which patient characteristics/clinical factors would alter the pathway you propose?'. A summary of these results had been presented at the meeting for discussion.

Whilst the Panel could not be sure exactly what was said at the meeting, it noted that the pre-work questionnaire, meeting slides and report did not appear to support the complainant's allegation that advisors were being forced to think about patients that they would want to start on trastuzumab deruxtecan or think about prolonging patient treatments until the licence was granted as alleged, and no breach of Clause 5.1 was ruled in that regard.

With regard to the complainant's allegation that the advisory board was 'a waste of valuable time' and an attempt to recap data, the Panel noted the complainant referred to the ESMO and NCCN guidelines and stated international and national consensus was reached in 2021 that trastuzumab deruxtecan was the new standard of care.

The Panel noted AstraZeneca's submission that whilst the NCCN guidelines may be referred to by some UK clinicians, the majority of UK clinicians would consult ESMO guidelines and that the guidelines were there to provide a level of direction and the clinician has the autonomy to interpret and implement the guidance as they feel is appropriate for their patient(s). AstraZeneca submitted that the objective of the advisory board meeting was to explore how healthcare professionals may prescribe T-DXd in the 2L setting in UK clinical practice. The Panel noted AstraZeneca's submission that ESMO guidance is created by a panel of European experts for a European population and as such, it may not be an accurate reflection of how UK clinicians may treat their patients due to several reasons; this was echoed in the advisory board meeting report where UK clinicians did not agree with all the guidance within the ESMO guidelines and in particular, the recommendation for patients with active brain metastasis as advisors felt that there was not sufficient evidence to support T-DXd use in this setting.

The Panel noted that the objectives of the advisory board as stated in the slides were:

- To gain expert insights and feedback on the efficacy profile of T-DXd in the 2L setting as reported in the DESTINY-Breast03 trial, including the pre-specified subgroup analysis.
- To understand UK expert perceptions on the safety profile of T-DXd, as well as adverse event management strategies.
- To explore how healthcare professionals may prescribe T-DXd in the 2L setting in UK clinical practice, including how the patient pathway may change when this treatment option becomes available for use.
- To identify potential data gaps that, if addressed, would support the use of T-DXd in the 2L treatment of patients with HER2+ mBC.

The Panel noted AstraZeneca's submission that approximately 27 minutes were allocated to presentation and 143 minutes to discussion; AstraZeneca submitted that the split between presentation and discussion showed that the advisory board meeting was structured to gain advise for documented and communicated unanswered business questions.

The Panel noted the above four objectives and the advice obtained as provided in the post meeting report and considered that the complainant had not established that the meeting was not a *bona fide* advisory board, nor that AstraZeneca had used the advisory board as an attempt to recap the data. The Panel therefore ruled no breach of Clauses 19.1 and 24.2 in that regard.

Clause 2 was a sign of particular censure and was reserved for such use. The Panel noted its ruling of Clause 5.1 above, which it considered adequately covered the matter, and no breach of Clause 2 was ruled.

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The Panel noted that the complainant was an advisor at the 7 April 2022 advisory board and alleged that the nature of the meeting itself was not a fair representation of what he/she was advised of.

It appeared to the Panel, according to the submission provided by AstraZeneca, that an email invitation was sent on 24 February 2022 to participants who had expressed interest in attending the advisory board meeting; it was not clear how this initial expression of interest was obtained and AstraZeneca made no submission in this regard.

The email invitation template provided stated:

> 'We are pleased to invite you to <Chair/participate in> the virtual advisory board meeting on 7th April between 3 and 6pm. The topic will be on metastatic breast cancer and is a non-promotional meeting organised by Daiichi Sankyo and AstraZeneca. You have been asked specifically to participate in this advisory board because of your expertise in breast cancer. This email is to confirm your availability.'

The email listed the time investment required by the advisors, including for pre-work, and stated that a contract would be sent upon confirmation of participation. Those who had responded to the email invite confirming their willingness to participate were sent contracts to sign.

The contracts submitted by Daiichi Sankyo were between the advisors and Daiichi Sankyo.

The Panel noted that 'Attachment A – Services and Fees' of the contracts listed the services for advisors as, 'The Consultant will participate in a DS Ad Board entitled T-DXd in the second-line setting in HER2+ mBC', or similar wording. The Panel noted that whilst the amount of preparation time varied depending on the role, the contract did not state whether the participant was an advisor or chair. Furthermore, the contracts did not state what the aims or objectives of the advisory board were nor the nature of the advice being sought.

The Panel noted, according to the submission provided by AstraZeneca, that on 29 March, prior to the advisory board, a pre-work cover email was sent to advisors who had contractually agreed to participate, which included a link to an online questionnaire, to help understand initial thoughts, along with a pre-reading attachment which included 8 publications that would 'form the foundation for discussion on the day'. The email stated, *inter alia:*

> 'We look forward to your participation in the upcoming advisory board on the use of trastuzumab deruxtecan▼ (T-DXd) for the second-line treatment of human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (mBC). The purpose of this advisory board meeting is to understand the practical implications of using T-DXd in the second-line setting* as well as to identify any data gaps that could be addressed in future analyses to increase the confidence of HCPs when deciding the treatment sequence for patients with HER2+ mBC.'

The asterisk (*) led to a footnote which stated: 'T-DXd as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens'.

The Panel considered that the invitation of 24 February and the contracts contained limited details about the advisory board; neither detailed the purpose (as stated in the email of 29 March) nor the aims or objectives of the advisory board. Whilst the pre-reading material, sent on 29 March, included a questionnaire and cover email, which detailed the purpose of the advisory board meeting, the Panel considered that this material was only sent to advisors after they had signed the contract and thus had already contractually confirmed participation. The Panel thus queried the concept of contractually agreeing to be an advisor without important information such as the objectives of the meeting being understood.

Clause 24.2 stated, *inter alia*, that a written contract or agreement must be agreed in advance of the commencement of the services which specifies the nature of the services to be provided and the basis for payment of those services.

The Panel considered that, on balance, there was sufficient detail in the contract to decipher that the service required of the health professional was an advisory board in relation to trastuzumab deruxtecan for the second-line treatment of HER2+ metastatic breast cancer and in that regard no breach of Clause 24.2 was ruled.

However, the Panel considered the limited details in the contract, which referred to 'Trastuzumab Deruxtecan (T-DXd) for second line treatment of HER2+ Metastatic Breast Cancer', and the even more limited details within the invite, were insufficient for an advisor to decipher what the actual advice being sought from him/her was prior to contractually agreeing to participate; the contract made no reference to the aims nor objectives of the advisory board. In this regard, the Panel considered that Daiichi Sankyo had failed to maintain high standards and a breach of Clause 5.1 was ruled.

The complainant alleged that he/she had been asked identical questions to those of the advisory board by AstraZeneca and Daiichi Sankyo representatives in late 2021. The complainant also allegedly attended advisory boards for AstraZeneca, just after ESMO 2021, which discussed all of the same topics as in the 7 April advisory board, which made the complainant question the nature of the 7 April meeting.

The Panel noted Daiichi Sankyo's submission that no commercial representatives from either company had been authorised to discuss second line data and product related briefings on materials for current promotional campaigns included specific instructions not to discuss the use of trastuzumab deruxtecan in unlicensed indications. According to Daiichi Sankyo, at the time of the advisory board being planned, the UK signatories from both companies checked what other advisory activity had occurred as was required in concept documents from both companies; the information sought from the advisory board in question was not available and the rationale for proceeding with the advisory board was captured in the concept approval form.

The Panel further noted Daiichi Sankyo's submission that when all global and regional advisory activity was checked at concept stage, and again following the complaint, Daiichi Sankyo could find no record of any recent advisory board activity having taken place, arranged either by Daiichi Sankyo or AstraZeneca, which included any of the same advisors who attended the

advisory board in question. Daiichi Sankyo therefore did not know what advisory board the complainant was referring to in his or her follow up email to the PMCPA.

The Panel noted that the parties' accounts differed in this regard.

A judgement had to be made on the available evidence bearing in mind the extreme dissatisfaction usually necessary on the part of an individual before he/she was moved to actually submit a complaint. The Panel noted that the complainant bore the burden of proof and did not consider that he/she had established that there were advisory boards that discussed the same topics as the meeting of 7th April at issue, nor that the meeting was not a *bona fide* advisory board meeting. The Panel ruled no breach of Clauses 19.1 and 24.2 in that regard.

With regard to the complainant's allegation that advisors were being forced to think about patients that they would want to start on trastuzumab deruxtecan, and even possibly to think about prolonging patient treatments until the license had been granted, for which they were assured would be imminent, the Panel noted Daiichi Sankyo's submission that its expectation at the time was that marketing authorisation would be granted in September 2022 with the expectation of NICE reimbursement in November 2022 at the earliest and probably some time in the first few months of 2023; it would be later in Scotland.

The Panel noted Daiichi Sankyo's submission that the delay from the advisory board in question to reimbursement and commercial availability of trastuzumab deruxtecan was likely to be at least 7 months and possibly as long as a year; this was not 'imminent' as suggested by the complainant and would absolutely not be of a timescale Daiichi Sankyo would encourage people to hold off on treating patients who have metastatic breast cancer and would become unwell very quickly.

The Panel noted that the pre-work questionnaire included the questions 'How do you envisage the future patient pathway for 1, 2 and 3L treatment of HER2 mBC and where would you position T-Dxd?' and 'Which patient characteristics/clinical factors would alter the pathway you propose?'. A summary of these results had been presented at the meeting for discussion.

Whilst the Panel could not be sure exactly what was said at the meeting, it noted that the pre-work questionnaire, meeting slides and report did not appear to support the complainant's allegation that advisors were being forced to think about patients that they would want to start on trastuzumab deruxtecan or think about prolonging patient treatments until the licence was granted as alleged, and no breach of Clause 5.1 was ruled in that regard.

With regard to the complainant's allegation that the advisory board was 'a waste of valuable time' and an attempt to recap data, the Panel noted the complainant referred to the ESMO and NCCN guidelines and stated international and national consensus was reached in 2021 that trastuzumab deruxtecan was the new standard of care.

The Panel noted Daiichi Sankyo's submission that the NCCN guidelines, issued by the National Comprehensive Cancer Network in the United States of America, were not implemented in UK practice and often differed significantly from UK practice due to issues of different marketing authorisations and reimbursement situations in the two countries. Daiichi Sankyo submitted that the ESMO (European Society for Medical Oncology) guidelines were more reflective of UK practice but were a set of guidelines written by a panel of experts from across Europe and subject to interpretation and implementation by individual countries based on a number of

issues, not least reimbursement status of medicines. Daiichi Sankyo submitted that the ESMO guidelines, included by the complainant, highlighted that the current gold standard in second line was TDM-1 treatment and that trastuzumab deruxtecan showed greater efficacy and so *'it is reasonable to consider trastuzumab deruxtecan the new standard second-line therapy in regions where this drug is available [I, A], moving T-DM1 to a later-line setting.'* However, Daiichi Sankyo submitted that it was not at all clear that T-DM1 therapy would be reimbursed in the UK in a later line of therapy, and it was not at all clear ahead of the advisory board whether clinicians in the UK felt that the ESMO guidelines would reflect practice for all patients in the UK. At the time, Daiichi Sankyo submitted that trastuzumab deruxtecan was licensed in 3rd line after T-DM1 so maintaining the current approach allowed patients to get both treatments (TDM-1 first and trastuzumab deruxtecan subsequently). Moving trastuzumab deruxtecan earlier in the treatment path as per the proposed new indication might have meant patients losing a line of therapy and being overall disadvantaged. Indeed, there were groups highlighted by the advisors for whom that may be the case and some of the data they would want to see to include those more marginal groups of patients in a new treatment paradigm were discussed.

The Panel further noted Daiichi Sankyo's submission that there was disagreement by advisors on the day regarding some of the recommendations in the ESMO clinical practice guidelines and that it was clear from the advisory board that the ESMO guidelines may not be adopted.

The Panel noted Daiichi Sankyo's submission that it felt it discussed in great detail a number of crucially important areas of uncertainty and that the information will be crucial in guiding its strategy and forecasting (and resourcing) in the future.

The Panel noted that the objectives of the advisory board as stated in the slides were:

- To gain expert insights and feedback on the efficacy profile of T-DXd in the 2L setting as reported in the DESTINY-Breast03 trial, including the pre-specified subgroup analysis.
- To understand UK expert perceptions on the safety profile of T-DXd, as well as adverse event management strategies.
- To explore how healthcare professionals may prescribe T-DXd in the 2L setting in UK clinical practice, including how the patient pathway may change when this treatment option becomes available for use.
- To identify potential data gaps that, if addressed, would support the use of T-DXd in the 2L treatment of patients with HER2+ mBC.

The Panel noted Daiichi Sankyo's submission that there were 27 minutes of introductions and presentation scheduled and 148 minutes of discussion which was a ratio of 85% discussion to 15% introductions and presentation and reflected its desire to maximise discussion time at advisory boards.

The Panel noted the above four objectives and the advice obtained as provided in the post meeting report and considered that the complainant had not established that the meeting was not a *bona fide* advisory board nor that Daiichi Sankyo had used the advisory board as an attempt to recap the data. The Panel therefore ruled no breach of Clauses 19.1 and 24.2 in that regard.

Clause 2 was a sign of particular censure and was reserved for such use. The Panel noted its ruling of Clause 5.1 above, which it considered adequately covered the matter, and no breach of Clause 2 was ruled.

Complaint received **11 April 2022**

Case completed **10 March 2023**