OBJECTION HANDLER MODULE

This module is a part of an e-learning program which focuses on the different aspects of ADCETRIS, pivotal clinical trials with ADCETRIS, the role and approval for use in certain patient populations which include patients with relapsed or refractory Hodgkins lymphoma and patients with relapsed or refractory systemic anaplastic large-cell lymphoma.

The material presented as part of this e-learning program is strictly for internal training purposes only.

This module is aligned with the content in the Objection handler. The Objection Handler demonstrates the 4-step process to conduct a good dialogue while handling objections posed by the customer. This training will provide the supporting marketing resources and approved messages.

To begin, click on an objection you would like to explore

OBJECTION 1: I DON'T SEE WHY WE SHOULD CONTINUE TO TREAT A PATIENT WHEN THEY HAVE ACHIEVED CR EARLY IN THE COURSE OF TREATMENT

I don't see why we should continue to treat a patient when they have achieved CR early in the course of treatment

There could be many factors that lead you to end treatment in early responders. It's a critical treatment choice, so can we discuss what's important to you in this decision?

Here are some questions you may ask:

- What are the important factors that lead you to decide to take early responders off treatment; are your concerns related to tolerability, cost/time/resources, and treatment goals achieved/allogeneic stem cell transplant?
- How important is duration of response in your treatment goals?
- What are your expectations of duration of response for your early responders?

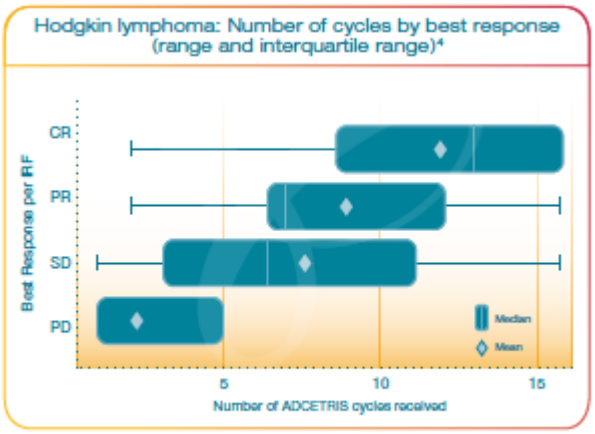
We agree there may be some important pressures on you to discontinue treatment for early complete responders, but once a response has been achieved the therapeutic goal is to maintain that response.

The medical history of these patients shows that they have relapsed after achieving a CR/PR, or have never achieved a CR/PR before. If treatment is stopped as soon as complete response with ADCETRIS is observed, there is a risk that the response will be lost.

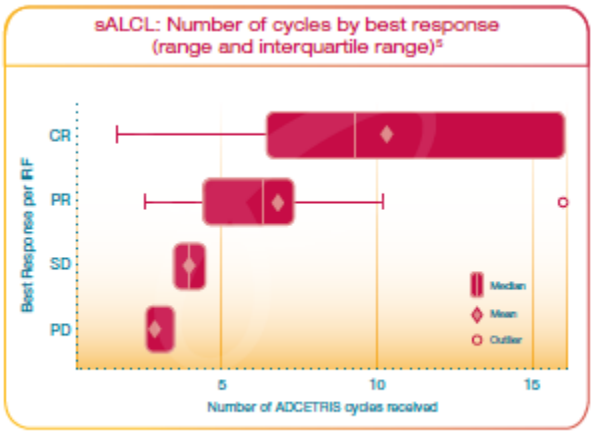
Therefore, once CR is achieved, and in accordance with the ADCETRIS label, patients should continue the recommended treatment regimen, thereby giving them the best chance of achieving a long duration of response. Treatment for fewer than 8 cycles may lead to an uncertain outcome, even if CR is achieved

In the pivotal Hodgkin lymphoma study, patients received a median of 9 cycles (range, 1 to 16) and in the pivotal sALCL study, patients received a median of 7 cycles (range, 1 to 16).

In both trials patients who achieved an objective response (CR, or PR) received more cycles of therapy.



Adapted from Copal et al. 2013
Use of ASH poster as reference subject to local approval process.



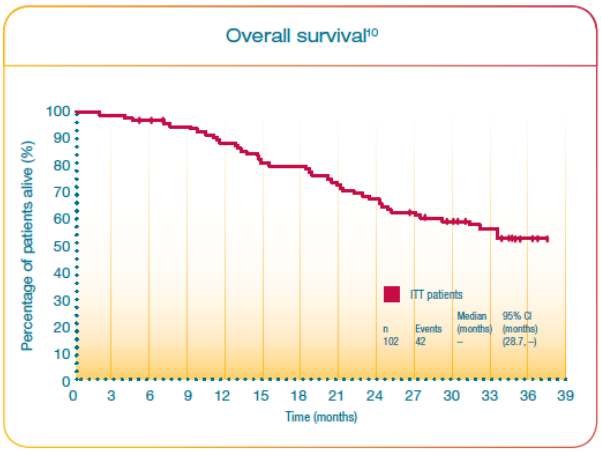
Adapted from Pro et al. 2013
Use of ASH poster as reference subject to local approval processes

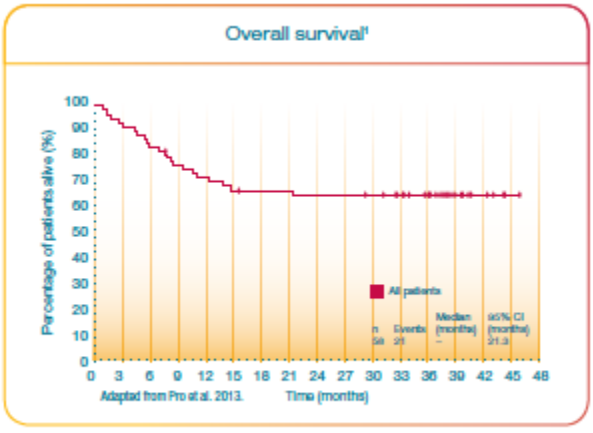
The ADCETRIS label states that patients who achieve stable disease or better should receive a minimum of 8 cycles and up to a maximum of 16 cycles (approximately 1 year). Treatment should be continued until disease progression or unacceptable toxicity.

Check to establish customer acceptance of this response, and identify any outstanding aspects of this objection to address.

Emphasise the benefits of continuing ADCETRIS when following the licensed indication.

ADCETRIS is a treatment option for patients who can achieve a long duration of survival. However, patients must be treated according to the license to give patients the best possibility of achieving optimal outcomes. Moreover, when used for the licensed period, Hodgkin lymphoma patients had a median OS of 40.5 months and for sALCL patients, median OS has not yet been met at 33.4 months.





Adapted from Pro et al. 2013.

OBJECTION 2: "THIS DOSING ISN'T REALLY CLEAR; HOW MANY CYCLES ARE NEEDED TO GET A RESPONSE? THE ADCETRIS LABEL STATES THAT PATIENTS WHO ACHIEVE STABLE DISEASE OR BETTER, SHOULD CONTINUE FOR A MAXIMUM OF 16 CYCLES. IF MY PATIENT DOESN'T RESPOND CAN I GIVE THEM MORE THAN 16 CYCLES?"

"This dosing isn't really clear; how many cycles are needed to get a response? The ADCETRIS label states that patients who achieve stable disease or better, should continue for a maximum of 16 cycles. If my patient doesn't respond can I give them more than 16 cycles?"

The licence states that a patient who achieves stable disease or better should receive a minimum of 8 and up to a maximum of 16 cycles.

While it is true that some patients do respond earlier than others, maintaining response is also important.

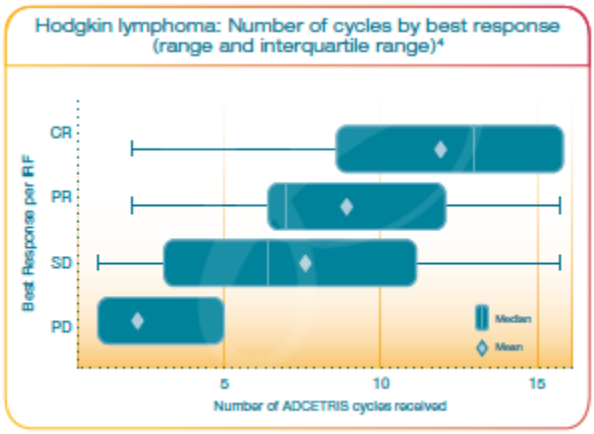
You can get a better understanding of the customer's inquiry by trying to gain insight into their particular concern. The following are a few questions you may ask

- How does the licensed dosage of 8-16 cycles fit in with your expectations and treatment pathway?
- What concerns do you have about keeping patients on the treatment for between 8 and 16 cycles?
- Would you like to look at data exploring why the licensed treatment period is 8-16 cycles?

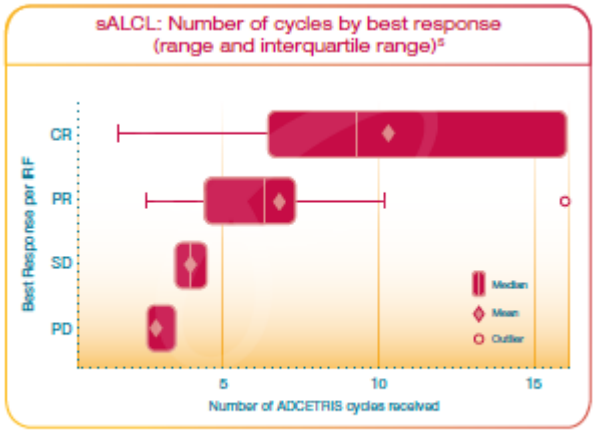
To answer your question, let's look at the licence. The licence states that treatment should be continued until disease progression or unacceptable toxicity. If a patient achieves stable disease or better, they should receive a minimum of 8 cycles and up to a maximum of 16 cycles.

Let us take a look at data from the pivotal clinical trials and examine the number of cycles needed to get a response

In the trial with patients with Hodgkin lymphoma the time to individual response ranged from 5.1 to 56 weeks. Although the majority of responses did occur early in the course of treatment, at least one instance of complete remission (CR) was initially documented approximately 1 year after initiation of therapy.



Adapted from Gopal et al. 2013
Use of ASH poster as reference subject to local approval process.



Adapted from Pro et al. 2013
Use of ASH poster as reference subject to local approval processes

Similarly, in the pivotal sALCL study, the median time to OR was 5.9 weeks and the time to individual responses ranged from 4.3 to 14 weeks. Also, the last instance of CR in this study was observed almost 1 year after initiation of therapy.

Patients received a median of 7 cycles in the Hodgkin lymphoma trial and a median of 9 cycles in the sALCL study. In both trials patients who achieved an objective response (CR, or PR) received more cycles of therapy.

In summary, responses were seen in the pivotal trials following up to 1 year of therapy, highlighting the importance of continuing treatment up to 16 cycles which is approximately equivalent to 1 year of treatment.

Regarding the possibility of continuing treatment beyond 16 cycles for patients who do not achieve SD or better, Takeda cannot endorse a regimen that differs from that specified in the licence.

ADCETRIS was well tolerated in patients with either HL or sALCL, and most drug-related adverse events were managed through standard supportive care. The most common events were typically grade 1 or 2.

The optimal duration of therapy should strike a balance between maintaining tumour control and minimising toxicity, which may be best achieved with rational application of dose delays and dose reductions if toxicity develops.

OBJECTION 3: "THIS DOSING ISN'T REALLY CLEAR; HOW MANY CYCLES ARE NEEDED TO GET A RESPONSE? THE ADCETRIS LABEL STATES THAT PATIENTS WHO ACHIEVE STABLE DISEASE OR BETTER, SHOULD CONTINUE FOR A MAXIMUM OF 16 CYCLES. IF MY PATIENT DOESN'T RESPOND CAN I GIVE THEM MORE THAN 16 CYCLES?"

"What are the main criteria for continuing ADCETRIS treatment in the 8-16 dosage cycles stated in the licence? Is there any evidence that continuation of ADCETRIS will lead to a better response?"

Clearly, it is important that the criteria meet your treatment goals and practice needs. So let's look at this in more detail.

You can seek further clarification to better understand the query. The following are a few questions you may ask

- What treatment goals are most important to you and your patient?
- What criteria are most important to you when deciding on continuing treatment?
- What barriers are there to continuing therapy into the licensed minimum period of 8 cycles, up to the maximum of 16 cycles?
- What sort of response or duration of response are you looking for from a treatment?

To answer your question, let's look at how the criteria in the licence for ADCETRIS fit in with your patient's treatment pathway and goals.

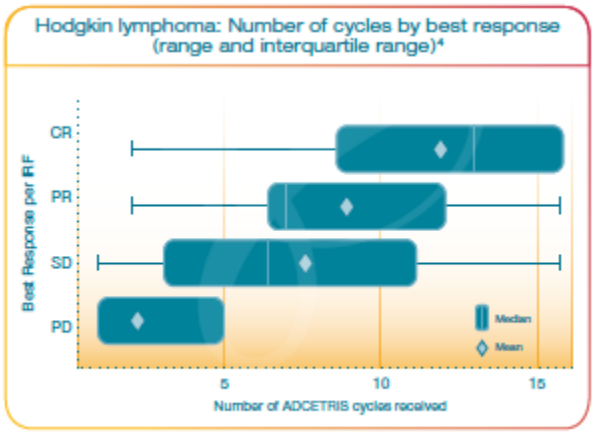
The licence for ADCETRIS states that treatment should be continued until disease progression or unacceptable toxicity.

Patients who achieve stable disease or better should receive a minimum of 8 cycles and up to a maximum of 16 cycles.

Patients should continue the recommended treatment regimen, thereby giving patients the opportunity to achieve a response and maintain that response.

In the two pivotal trials with HL and sALCL patients, the median time to CR was 12 weeks and 11.9 weeks respectively and there was a wide range of time to CR – up to one year after treatment had started.

While many patients showed a relatively fast response to treatment, some were shown to respond later, which reinforces the rationale of continuing treatment for at least 8 cycles, and up to 16 cycles (approximately 1 year treatment time) if no progression is detected and there is no unacceptable toxicity.



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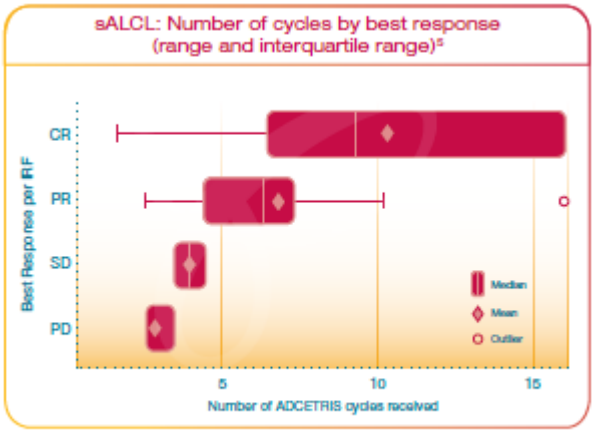

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There has been no formal evaluation of the number of treatment cycles and level or duration of response, and the use of regimens with a minimum of fewer than 8 cycles is of uncertain outcome.

Regarding the possibility of continuing treatment beyond 16 cycles for patients who achieve stable disease or better, Takeda cannot endorse a regimen that differs from that specified in the licence.

In the absence of unacceptable toxicity, ADCETRIS should always be continued for at least 8 cycles, up to a maximum of 16 cycles, as some patients will show a late response.

The optimal duration of therapy balances maintaining disease control and maximising tolerability. ADCETRIS is generally well-tolerated, with adverse events primarily grade 1 or 2, and peripheral neuropathy manageable through dose modification.

OBJECTION 4: "EUROPEAN TREATMENT GUIDELINES FOR HODGKIN LYMPHOMA INDICATE SEVERAL MULTI-AGENT REGIMENS FOLLOWED BY ASCT, GEMCITABINE-BASED CHEMOTHERAPY, NOVEL SINGLE AGENTS AND/OR REGIONAL RADIOTHERAPY: ADCETRIS IS NOT INCLUDED."

"European treatment guidelines for Hodgkin lymphoma indicate several multi-agent regimens followed by ASCT, gemcitabine-based chemotherapy, novel single agents and/or regional radiotherapy: ADCETRIS is not included."

As a new treatment, ADCETRIS is not currently included in the European treatment guidelines for Hodgkin lymphoma. Let's look into why.

You need to find out if your customer is unwilling to prescribe ADCETRIS until it is included in the guidelines.

You may want to confirm your local treatment guidelines and also ask further questions to clearly identify the concerns. The following are a few questions you may ask.

- As this is a new treatment, what is the main unmet need you have for your difficult-to-treat patients?
- What is your main interest in this new treatment?
- What is your main area of concern?

To answer your question, let's understand why ADCETRIS is not yet included in the European treatment guidelines.

The European Society for Medical Oncology (ESMO) examines evidence based on published data.

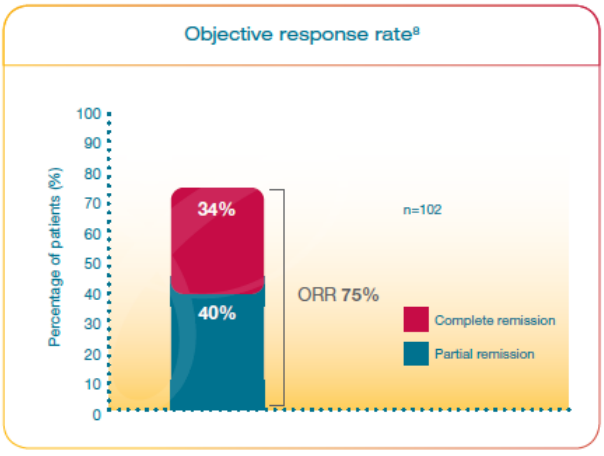
The current ESMO guidelines for Hodgkin lymphoma were produced in 2011. This was before published data for ADCETRIS was available, and so ADCETRIS is not included. An update can be expected in the next months.

However, the National Comprehensive Cancer Network (NCCN) guidelines published in 2012 and later recommend treatment with ADCETRIS for both relapsed/refractory Hodgkin lymphoma and sALCL. All other guidelines were prepared before ADCETRIS data were available.

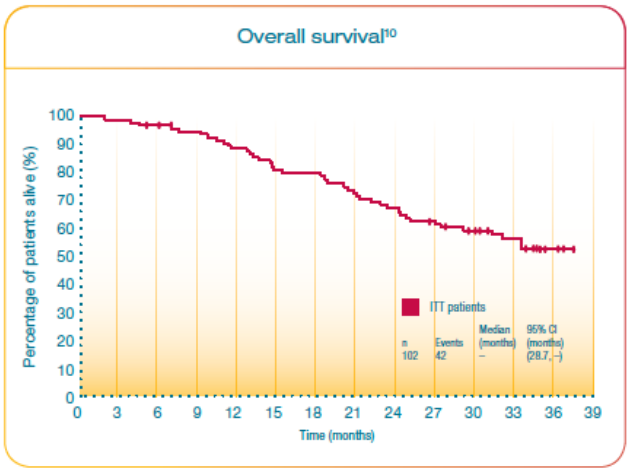
Also, other current treatment options, including chemotherapy, radiotherapy and allogeneic-SCT, are associated with high rates of toxicity or are limited by donor availability and the high risk of treatment-related mortality.

In the pivotal Hodgkin lymphoma study, an overall response rate (ORR) of 75% and complete response of 34% was observed in patients that were heavily pre-treated and highly refractory.

After three years' follow-up, median OS was 40.5 months.



Confidence interval: 95% CI for ORR: 64.9%, 82.6%; 95% CI for CR: 25.2%, 44.4%; 95% CI for PR: NA. ORR does not appear to equal CR plus PR due to rounding of numbers. Number of patients achieving responses: ORR n=76; CR n=35; PR n=41.
ORR = objective response rate.



Adapted from Chen et al. ASH 2012.

So, even though ADCETRIS is under annual review and not yet on ESMO guidelines, it has been granted a marketing authorisation as it fulfils an unmet medical need, and the benefits of immediate availability outweigh the risk of waiting for additional data.

OBJECTION 5: "THERE APPEARS TO BE A CLEAR BENEFIT FROM ACHIEVING CR IN TERMS OF DURATION OF BENEFIT IN HODGKIN LYMPHOMA PATIENTS. HOWEVER, PATIENTS WITH PR HAD ONLY A SHORT DURATION OF RESPONSE: IS THERE VALUE IN TREATING THESE PATIENTS USING MY BUDGET?"

"There appears to be a clear benefit from achieving CR in terms of duration of benefit in Hodgkin lymphoma patients. However, patients with PR had only a short duration of response: is there value in treating these patients using my budget?"

Yes, the progression free survival is different depending on whether the patient achieved a CR or a PR. What does that mean for your patient?

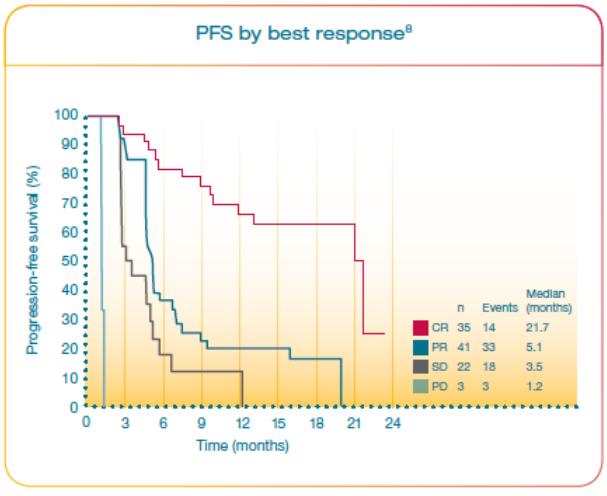
Establish the treatment goals of your customer. His/her query may relate to an older patient with comorbidities, or a young patient with fewer comorbidities: therefore the duration of response, from the doctor's perspective, may represent differing levels of benefit and value for each patient.

You may consider asking the following questions to clarify and understand

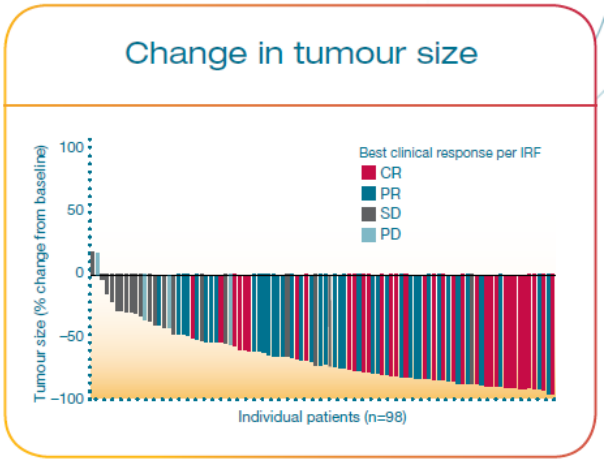
- What type of patient are you thinking of?
- What are the treatment goals you set for your patient?
- Which sort of patient would you consider as being most appropriate for this treatment?

ADCETRIS is indicated for patients who have disease that has not responded to previous treatments, and for whom limited treatments remain. These patients may also have a poor quality of life. High rates of clinical response and PFS have been observed with use of ADCETRIS in such patients.

The partial response (PR) achieved with ADCETRIS may likely be the first time the patient achieved a response. A median PFS of 5.1 months, as observed in the pivotal trial with HL, for a patient who achieves PR may be a long time for that particular patient.



Adapted from Younes et al. 2012.
CR: complete remission, PR: partial remission, SD: stable disease, PD: progressive disease.



Adapted from Younes et al. 2012.

It is also worthy to note that, in a significant number of patients in the pivotal HL trial, clinical responses were associated with a reduction in disease symptoms and a reduction in tumour size. 77% patients who experienced B-symptoms at baseline achieved resolution of symptoms.

These observations associated with ADCETRIS can help with quality of life for your patients.

So, in a significant number of patients, ADCETRIS offers a durable response. In addition, ADCETRIS is not associated with high levels of toxicity, treatment-related mortality or the use of supportive treatments. If you are trying to prolong the life of your patient with the best possible quality of life during that time, ADCETRIS has a benefit over high-dose chemotherapy here.

OBJECTION 6: "CAN WE EXPECT TO SEE THE SAME RESPONSE RATES IN REAL LIFE OR WAS THE DATA/PATIENT SELECTION BIASED?"

"Can we expect to see the same response rates in real life or was the data/patient selection biased?"

I understand you are interested to see how ADCETRIS has performed in real life, to reflect the experiences of your patients.

Establish your customer's concerns and belief in the data.

You may consider asking the following questions to clarify and understand

- What type of difficult-to-treat patients are you most focused on in your question?
- Would you be interested in the context of these data, as we have experience closer to real life through the named patient programme (NPP)?

In addition to the clinical trials conducted for marketing authorisation, Takeda made ADCETRIS available from 2010 to the medical community through named patient programs (NPPs).

The aim of NPPs is to provide access to a drug to patients who may benefit from the drug and have few other options. The NPPs are independent and cannot be influenced by Takeda.

The patients included in an NPP would rarely meet the criteria for a clinical trial, and so NPPs can provide an indication of how ADCETRIS will behave in real life.

Let's look at the data that have been published by the NPPs

In an NPP in the UK, 24 patients; 19 with Hodgkin lymphoma and 5 with sALCL, were treated with ADCETRIS. Efficacy data were reported for all patients and at a median follow-up of 12.9 months, 16 out of 24 of patients were still alive.

The overall response rate (ORR) for HL was 72% and median PFS was 5.1 months. A CR rate of 25%, independent of prior ASCT status, was reported.

In a German study, Hodgkin lymphoma patients achieved an ORR of 60% and the median PFS was 8 months. These results compare well with the data from the ADCETRIS clinical trials that showed an ORR of 75% and a median PFS of 5.6 months.

In summary, the data suggest that you can expect to see responses in real life that are comparable with the clinical trial data, and of considerable benefit to your patients.

So, the efficacy outcomes in published NPPs and the pivotal trials of ADCETRIS were comparable.

In addition, in both the UK and German NPP published results, the toxicity profile of ADCETRIS was also reported to be very similar to the published data, which provides confidence for both you and your patients

OBJECTION 7: "THE DATA FOR TRANSPLANT-INELIGIBLE PATIENTS ARE INCONCLUSIVE. WHY SHOULD I TRUST THE DATA?"

"The data for transplant-ineligible patients are inconclusive. Why should I trust the data?"

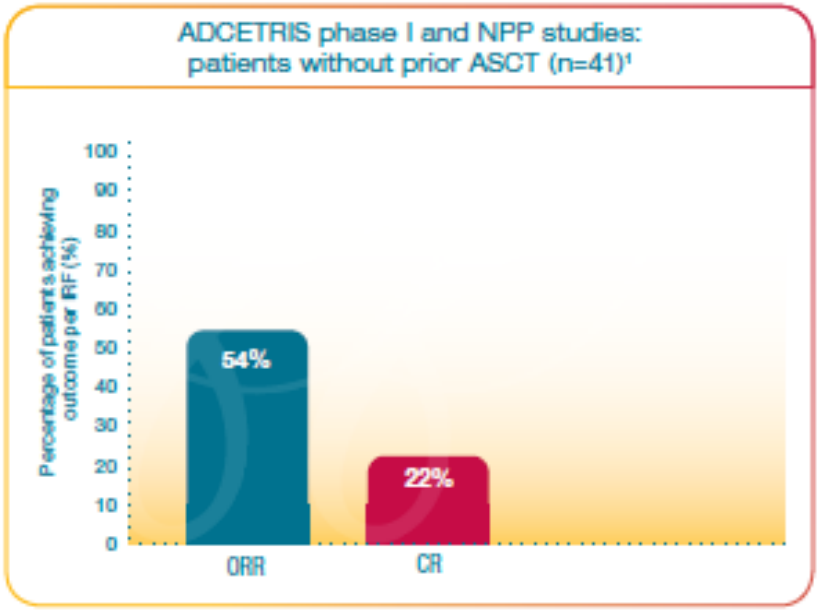
I understand your concern; however, ADCETRIS is an orphan drug and the data are based on a pivotal Phase II trial.

Establish why the customer mistrusts the data to better understand their concern

You may consider asking the following questions to clarify and understand

- What specific concerns do you have about the data?
- Would you like to look at the data for this group of patients?
- What are your treatment goals for your patients considered ineligible for transplant?

Let's look at the ADCETRIS results from the transplant-ineligible patients submitted to the regulatory authority for marketing authorisation.



NPP: named patient programme; ORR: objective response rate; CR: complete remission; IRF: Independent Review Facility

In a phase I trial and NPP, 41 patients received the recommended ADCETRIS dosing regimen, 54% (22/41) of the patients achieved an OR and 22% (9/41) achieved CR.

In addition, 8 (19%) patients went on to receive a subsequent SCT which indicates the potential for durable response in this subset of patients, who were unable to receive a transplant prior to treatment with ADCETRIS.

The regulatory authority scrutinised the study data and considered that an ORR of 54% and a CR of 22% in patients not suitable for ASCT may be considered clinically relevant in itself.

The regulatory authority is an independent assessor that has looked at that data and believes that ADCETRIS is a suitable treatment option for these patients.

So, clinically significant results have been achieved, even with transplant ineligible patients. Further data will be available in 2016 from a single arm study conducted as part of the fulfilment of a post-approval commitment.

OBJECTION 8: "THE SALCL PATIENT GROUP IS VERY SMALL."

"The sALCL patient group is very small."

The sALCL patient group is small, and our data on sALCL show that there is now the opportunity to have access to a viable targeted treatment.

You can get a better understanding of the customer's inquiry by trying to gain insight into their particular concern. The following are a few questions you may ask

- Are you referring to the general number of patients with sALCL, or the number of patients in the ADCETRIS study?
- What are your treatment goals with your sALCL patients?
- So I can answer your question fully, do you have any concerns about using ADCETRIS with sALCL patients that would prevent you from using it with appropriate patients?

As you know, from an epidemiological perspective, the Hodgkin lymphoma group is larger than the sALCL group.

The ADCETRIS pivotal sALCL study included 58 patients and was an international trial in heavily pre-treated relapsed or refractory patients. It was felt that in general, the demographics reflect the characteristics of patients with sALCL.

In the trial, an objective response rate of 86% was attained ORR and 59% of the patients achieved a complete response. The latest analysis of the three-year follow-up results presented at ASH 2013, demonstrates that the median OS had not been reached at 33.4 months, and this was similar for both ALK(-) and ALK(+) patients. This is the largest study reported in patients with relapsed or refractory sALCL.

This means that with ADCETRIS, your sALCL patients have a treatment option with a high ORR if they are refractory or relapse following first line treatment.

Takeda is including as many patients as possible in the post-approval commitment trials.

ADCETRIS is an orphan drug that has been granted a licence because it fulfils an unmet medical need. It has been shown to be a real treatment option for patients with relapsed/refractory sALCL. With time, more data will become available and will be reviewed. The European regulatory agency will review new information at least once per year.

OBJECTION 9: "THERE APPEARS TO BE A CLEAR BENEFIT FROM ACHIEVING CR IN TERMS OF DURATION OF RESPONSE IN SALCL PATIENTS. HOWEVER, PATIENTS WITH PR HAD A SHORTER DURATION OF RESPONSE, SO IS THERE VALUE IN TREATING THESE PATIENTS?"

"There appears to be a clear benefit from achieving CR in terms of duration of response in sALCL patients. However, patients with PR had a shorter duration of response, so is there value in treating these patients?"

Yes, the PFS is different depending on a CR or a PR. What does that mean for your patient?

Establish the treatment goals of your customer. The following are a few questions you may ask

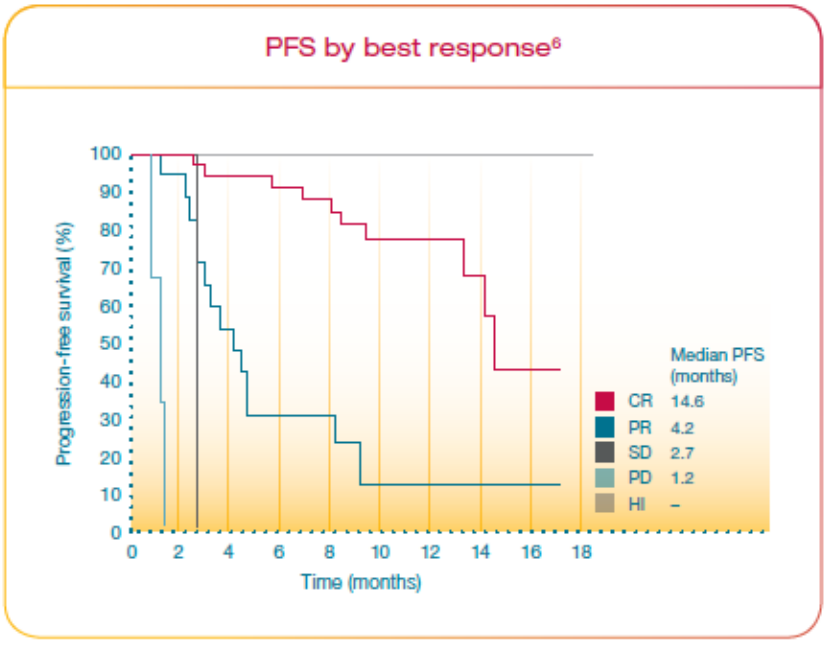
- What type of patient are you thinking of in this question?
- What are your treatment goals for your patient?
- Which sort of patient would you see as being most appropriate for this treatment?
- What value would you expect from treatment for this type of patient?

ADCETRIS is indicated for small groups of patients, who have disease that has failed to respond to previous treatments, and for whom there are limited treatments remaining.

Patients who are eligible to receive ADCETRIS may not have previously achieved PR and have a poor quality of life.

For patients such as these, ADCETRIS has been shown to give high rates of clinical response and PFS.

In the pivotal sALCL trial the estimated median PFS time was 13.3 months and the median PFS in patients who achieved PR was 4.2 months. A median PFS of 4.2 months for a patient who achieves PR may be a long time considering that it may be the first time that the patient has achieved PR.



Adapted from Pro et al. 2012.
CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease; HI: histologically ineligible.

In addition, resolution of all B-symptoms in 82% or 14 out of 17 patients who had B-symptoms at baseline, after a median time of 0.7 months from initiation of ADCETRIS was observed. Also, tumour reduction occurred in 97% patients.

Such results can help with quality of life for your patients in the time that they have.

So, in a significant number of patients, ADCETRIS offers a durable response, and not just for those that achieve CR. In addition, ADCETRIS is not associated with high levels of toxicity, treatment-related mortality or the need for use of supportive treatments. If your goal is to prolong the life of your patient with the best possible quality of life, ADCETRIS is a viable treatment option.

OBJECTION 10: "I AM CONCERNED THAT THERE ARE LIMITED DATA ON SURVIVAL WITH ADCETRIS."

"I am concerned that there are limited data on survival with ADCETRIS."

I understand your concern; however, ADCETRIS is an orphan drug and the sALCL patient group is small. The pivotal study included 58 patients and it was felt that the demographics reflect the characteristics of patients with sALCL.

Establish whether your customer is concerned that there is no OS data or about how the ORR reported in the sALCL trial, which is a surrogate endpoint translates into OS or that the survival data are not good enough to warrant treatment

You may ask the following questions to gain further clarification:

- Are you concerned that there are no overall survival data?
- What treatment goals do you have for your patient?
- Are you concerned that the trial numbers are not high enough to produce good survival data?

As you are aware, ADCETRIS is indicated for a subset of patients who have disease that has failed to respond to prior treatments, and have limited treatment options that offer substantial hope of a cure.

Data continue to emerge as this is an orphan drug that has been granted a licence to fulfil an unmet medical need.

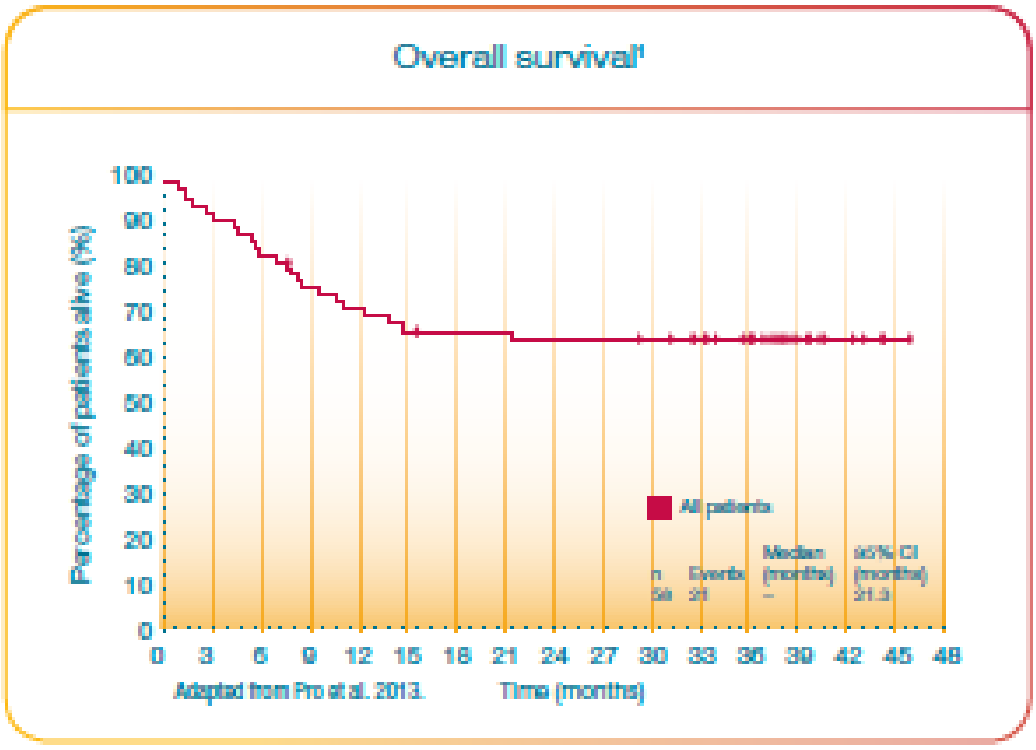
There are some overall survival data which we can review now. And with time, more data will become available and will be reviewed. The regulatory agency will review new information at least once per year.

As you know, the threshold to report median OS data is only passed when more than half of the patients have died.

At the last measure, more than half of the patients (37 of 58) were alive and the median OS had not been met at 33.4 months.

So, the data so far show that median overall survival has not been reached after 33.4 months. 3-year survival is estimated to be 63%. This survival data support ADCETRIS as a strong treatment option for patient with relapsed/refractory sALCL. In addition, we are continuing to follow patients enrolled in the ADCETRIS study.

We will publish and share more data as results become available. The data so far show that ADCETRIS is an option in patients when previously there was none.



Adapted from Pro et al. 2013.

In a significant number of patients, complete durable clinical responses are observed with the added benefit of a reduction in disease symptoms.

OBJECTION 11: "WHY SHOULD I PRESCRIBE ADCETRIS TO MY PRE-SCT PATIENTS WHEN I ACHIEVE GOOD RESPONSE RATES WITH THE CHEAPER BENDAMUSTINE?"

"Why should I prescribe ADCETRIS to my pre-SCT patients when I achieve good response rates with the cheaper bendamustine?"

You are currently using bendamustine to treat your pre-SCT Hodgkin lymphoma patients and are getting good response rates. You have raised two issues, namely: response rates and costs.

Clarify what the main concern of your customer actually is

You may ask the following questions:

- Regarding efficacy, what are your treatment goals for your pre-SCT Hodgkin lymphoma patients? For example, do you aim to achieve the best possible response or the longest duration of response, or will your patients eventually receive allogeneic SCT? With this in mind, what is your main concern with prescribing ADCETRIS?
- Regarding costs, you note that bendamustine is less expensive than ADCETRIS. What specific concerns do you have about costs?

Regarding efficacy, limited data are available on the use of bendamustine in patients with Hodgkin lymphoma.

Only one Phase II study with bendamustine has been performed to date. It included just 36 relapsed/refractory Hodgkin lymphoma patients, 81% of whom received prior allogeneic and/or autologous SCT.

Efficacy outcomes

	Patient population	Response, %			Duration of response, months (95%CI)		Patients proceeding to SCT, %
		ORR	CR	PR	ORR	CR	
Bendamustine							
Phase II Study (n=36)[1]	r/r Hodgkin lymphoma (post-ASCT or ASCT-ineligible)	53	33	19	5	NA	20
French comp. use programme (n=36)[2]	r/r Hodgkin lymphoma (post-ASCT)	50	29	21	4.6 (1.6 to 14.6)	6.1 (2.4 to 14.6)	NA

- The ORR in the study was 53%, while CR was achieved in 33% of patients corresponding to a small absolute number of 12.
- Median response duration in patients with OR was only 5 months
- 20% of patients experienced grade ≥3 thrombocytopenia and 14% grade ≥3 anaemia
- Similar results, were reported in the French compassionate-use programme.

Efficacy outcomes

	Patient population	Response, %			Duration of response, months (95%CI)		Patients proceeding to SCT, %
		ORR	CR	PR	ORR	CR	
ADCETRIS							
Phase II Study (n=102)[3]	r/r Hodgkin lymphoma (post-ASCT)	75	34	40	6.7 (3.6 to 14.8)	20.5 (10.8 to NE)	38
Named patient programme (n=14)[4]	r/r Hodgkin lymphoma (pre-ASCT)	71	36	35	NA	NA	36
EMEA assessment[5] (n=41[b])	r/r Hodgkin lymphoma (pre-ASCT)	54	22	32	NA	NA	NA
Post-hoc analysis Phase II[6] (n=20)	r/r Hodgkin lymphoma (pre-ASCT)	30	10	20	NA	NA	75[a]
Retrospective analysis[7] (n=15)	r/r Hodgkin lymphoma (pre-ASCT)	53	46.6	6.6	NA	NA	87

NA, not available; NE, not estimable; r/r, relapsed/refractory.
[a] 4 out of 6 non-ASCT patients who achieved OR were not previously considered eligible for ASCT because of chemorefractory disease; 3 of these 4 patients were able to proceed to ASCT after receiving ADCETRIS.
[b] Patients were treated with 1.8 mg/kg every 3 weeks.

In comparison, data for ADCETRIS in this population are based on a larger Phase II study in 102 patients, all of whom underwent prior autologous SCT.

- Patients achieved a higher ORR of 75%, with a comparable CR rate of 34%
- Median response duration was longer: 6.7 months in ORR patients
- Only 8% of patients experienced grade ≥3 thrombocytopenia and 6% grade ≥3 anaemia

Regarding costs, there are currently no cost-effectiveness analyses comparing the use of bendamustine and ADCETRIS.

Adverse events caused by bendamustine have associated costs and the cost of concomitant G-CSF use must be considered. For example in the French compassionate use programme, 18% of patients received G-CSF, 11% blood transfusions, and 7% platelet transfusions.

Importantly, only ADCETRIS is currently approved by the European Medicines Agency (EMA) for the treatment of patients with relapsed/refractory Hodgkin lymphoma.

In contrast, bendamustine is EMA-approved for use in patients with rituximab-refractory NHL, fludarabinein eligible CLL, and elderly SCT-ineligible MM, but not Hodgkin lymphoma.

Both bendamustine and ADCETRIS appear to achieve good CRs in patients with relapsed/refractory Hodgkin lymphoma; however, studies with ADCETRIS consistently report higher ORRs in a much larger patient population.

In addition, safety data indicate that ADCETRIS may be more tolerable in patients with Hodgkin lymphoma.

Although bendamustine itself may be less expensive than ADCETRIS, there are additional factors to consider such as duration of treatment, cost of managing adverse events, and availability of reimbursement.

OBJECTION 12: "I HAVE GOOD EXPERIENCES PRESCRIBING GEMCITABINE-BASED REGIMENS TO RELAPSED/REFRACTORY HODGKIN LYMPHOMA AND SALCL PATIENTS; THEREFORE, I SEE NO REASON WHY I SHOULD TRY ADCETRIS?"

"I have good experiences prescribing gemcitabine-based regimens to relapsed/refractory Hodgkin lymphoma and sALCL patients; therefore, I see no reason why I should try ADCETRIS?"

You are currently prescribing gemcitabine-based regimens for your relapsed/refractory Hodgkin lymphoma and sALCL patients and getting good results. You are not convinced that you will get better results with ADCETRIS.

It is important to clarify how your customer defines "good experiences" and also to clarify which gemcitabine-based regimens he/she is using.

You may ask the following questions:

- You indicated that you have good experiences with gemcitabine-based regimens. What do you mean by "good experiences"? Are you looking at response rates, duration of response, survival, stem cell mobilisation, tolerability, other?
- Not all gemcitabine-based regimens achieve the same results. Which gemcitabine-based regimens are you using?
- With this in mind, what is your main concern with prescribing ADCETRIS?

Present evidence that supports the preferential use of ADCETRIS over gemcitabine in the treatment of relapsed/refractory Hodgkin lymphoma and sALCL patients.

Let's look at the response rates first.

Studies evaluating gemcitabine as a single agent or in combination with one additional agent reported ORR in the range 20–48%, with CR in the range 0–15%.

In contrast, the pivotal study evaluating ADCETRIS as a single agent reported ORR of 75% and CR of 34% in relapsed or refractory HL .

Only gemcitabine-containing regimens with three or more agents have reported response rates (ORR: 70–81%; CR: 17–78%) comparable to those of single-agent ADCETRIS.

Available data indicate that patients treated with either ADCETRIS or gemcitabine-based regimens are able to collect sufficient stem cells and proceed to transplantation, if warranted.

Let's now look at the safety data.

Safety data from different studies indicate that ADCETRIS may be more tolerable in patients with relapsed/refractory Hodgkin lymphoma than gemcitabine-based regimens containing three or more agents.

Grade 3/4 haematological adverse events were more common with most gemcitabine-based regimens than with ADCETRIS (e.g. neutropenia, thrombocytopenia, anemia).

The most common non-haematological adverse events were also more common with gemcitabine-based regimens than with ADCETRIS (e.g. fatigue, nausea, vomiting).

Importantly, only ADCETRIS is EMA-approved for the treatment of patients with relapsed/refractory Hodgkin lymphoma.

In contrast, gemcitabine (GEMZAR®, Eli Lilly) is EMA-approved in patients with bladder cancer, pancreatic cancer, non-small-cell lung carcinoma (NSCLC), ovarian cancer, and breast cancer, but not Hodgkin lymphoma.

Only gemcitabine-containing regimens with three or more agents have reported response rates comparable to those of single-agent ADCETRIS in patients with relapsed/refractory Hodgkin lymphoma.

Although the gemcitabine regimens are better tolerated than comparable chemotherapy regimens, available data suggest that patients will tolerate single-agent ADCETRIS better than any of these 3- or 4-drug combinations.

With the exception of PVAG study in elderly patients with relapsed/refractory Hodgkin lymphoma, available data indicate that single-agent ADCETRIS achieves comparable or better response rates, including CR, and has a better tolerability profile than multi-agent gemcitabine-based regimens.

Therefore, in most relapsed/refractory Hodgkin lymphoma patients, ADCETRIS is the best choice.