

Metastatic TNBC cannot wait Optimising 1st line TROP2 ADC decisions in metastatic triple-negative breast cancer

Brought to you by;

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Dr Javier Cortés

Dear friends and colleagues.

A woman in her late 40s learns that her triple negative breast cancer has returned with symptomatic liver and lung metastasis.

She previously received neoadjuvant chemoimmunotherapy but had residual disease at surgery.

She completed adjuvant pembrolizumab and developed metastatic recurrence six months after her final dose.

She had only recently begun to feel, that life was returning to normal.

Her first questions are simple. What happens now? What of my family? Will I still be able to work? How is the future going to look like?

For the clinical team, the questions are equally urgent. Which biomarkers and prior treatment matter? Which 1st line evidence applies? How can treatment-related toxicity be anticipated from the outset?

Today with Professor Giuseppe Curigliano from Milan, Italy, we will explore how TROPION-Breast02, ASCENT-03 and ASCENT-04 are changing 1st line treatment, where BEGONIA, MORPHEUS-platform breast cancer and TROPION-Breast05 may take us next and how to select, sequence and safely deliver TROP2-directed antibody-drug conjugates.

Giuseppe, when a patient presents with newly diagnosed metastatic triple negative breast cancer, what must we establish before the 1st line decision?

Prof. Giuseppe Curigliano

Oh, thank you very much Javier.

I believe this is an important question, so we should first confirm the phenotype.

Doing a biopsy to confirm that this is a triple negative breast cancer is essential. But it is important to have tissue to evaluate the level of expression of PD-L1 and of course to perform the germline testing for BRCA1/2.

Prior chemotherapy and immunotherapy inhibitors, of course, it is also important to evaluate the time to recurrence because we know perfectly that patients with early recurrence had a poor prognosis respect to patients with late recurrence.

And then my advice is to perform a brain CT scan or a brain MRI to exclude the presence of brain metastasis.

Another thing we should evaluate is the tumour burden. If you have a huge tumour burden, the patient will be symptomatic. There will be a risk of imminent organ failure. We should evaluate the marrow reserve and the patient priorities.

So, essentially once immunotherapy suitability is established, we have one option only, that is the combination of sacituzumab plus pembrolizumab. But if you do not have expression of PD L1 and there is no eligibility to immunotherapy inhibitors, we have two options for datopotamab deruxtecan or sacituzumab govitecan.

Dr Javier Cortés

Well said, well said.

But TROPION-Breast02 improves both progression-free survival and overall survival. So, from your point of view, which patient in front of us should make us think immediately of this trial?

Prof. Giuseppe Curigliano

Okay.

Eligibility for TROPION-Breast02 included patients with untreated advanced triple negative breast cancer or PD-L1 negative or PD-L1 [positive] not eligible to an immunotherapy inhibitors*, even if very few of them were really not eligible. So, in the cohort of the TROPION-Breast02 there was also a patient population with an early relapse. I mean within six months after the end of neoadjuvant or adjuvant treatment.

As we know very well, datopotamab deruxtecan improved the median progression-free survival and improved also overall survival.

There was a better response rate respect to standard chemotherapy, and the better duration of response also respect to standard chemotherapy.

I would like to remind that the TROPION-Breast02 was not permitted the crossover. So, I mean many patients in the control arm who received chemotherapy did not receive an ADC upon progression.

So, again datopotamab deruxtecan is an excellent option and should be considered one of the two 1st line options for trial matured patients when authorised.

Dr Javier Cortés

So, Giuseppe, sometimes when we are facing patients with metastatic triple-negative breast cancer in the 1st line setting, we are like facing a dichotomic disease. PD-L1 positive – immunotherapy. PD-L1 negative – non immunotherapy. But immunotherapy is not just based on PD-L1 positivity or negativity.

So, in your opinion, even for patients with a PD-L1 positive tumour or the other way around, what does that distinction mean in practice?

Prof. Giuseppe Curigliano

Oh, this is a very good question. Here I will be very realistic.

So, I believe the only non-eligibility to a PD-L1 immunotherapy inhibitor should be the time to relapse. So, consider prior immunotherapy exposure. If you have a patient who relapses within six months after the end of an adjuvant immunotherapy inhibitor, or during an adjuvant immunotherapy inhibitor, this is the main reason not to give again an immunotherapy or an immunotherapy.

Sometimes you may have a contraindication, are very few patients, but they do exist. Let us say a scenario in which you cannot give an immunotherapy inhibitor is an active inflammatory bowel disease or a systemic lupus erythematosus, in which if you gave an immunotherapy you will exacerbate the symptoms.

Of course, some comorbidities can be a contraindication and not specifically the PD-L1 expression alone.

TROPION-Breast02 included both de novo metastatic disease but also recurrent and no minimum disease-free interval was established as an eligibility criteria.

So, I mean, also patients progressing on immunotherapy or with a short free interval were eligible to the trial.

So, match the patient to the actual trial criteria, of course is the best way to move when you have to define in PD-L1 negative or immunotherapy inhibitors not eligible the best patients for the two ADCs.

Dr Javier Cortés

You know Giuseppe, that the trial did not permit crossover to datopotamab deruxtecan beyond progression.

So, in your opinion, why does that matter when discussing the overall survival result?

Prof. Giuseppe Curigliano

Excellent question.

You know, in the sacituzumab govitecan trial there was the crossover and this is the only explanation in my opinion, to explain why we do not have an overall survival benefit in a very similar patient population in the frontline setting.

Of course, overall survival was less affected by protocol crossover with respect to an experimental drug.

Subsequent treatment, including other ADCs was still permitted but at the end of the story we know that the rate of crossover was higher in the sacituzumab trial respect to the datopotamab trial.

Dr Javier Cortés

Just one final question from TROPION-Breast02, if you do not mind Giuseppe. So, from your point of view again, what would make Dato-DXd a strong fit? Or the other way around, what would make you pause?

Prof. Giuseppe Curigliano

You know that datopotamab deruxtecan in my opinion can be highly considered in patients with an early aggressive recurrence.
So, a patient with high tumour burden with a clear resistance to immunocheckpoint inhibitors and to previous chemotherapy in which you need eventually a rapid response.
Or for immunocheckpoint inhibitors unsuitable, of course you may consider both of them, not specifically datopotamab alone.
Something that is good for datopotamab is that you have an every three-week administration.
So, for patients' long distance, maybe this can be more feasible in terms of access to the cancer centre.
Of course, there are some conditions in which I would personally not consider datopotamab deruxtecan.
Some of these are patients with ocular or oral disease.
I mean condition that can increase the risk of stomatitis or ocular toxicity.
I would never candidate to datopotamab a patients with a previous ILD or pneumonitis.
Datopotamab deruxtecan we know it is not the only anti-TROP2 ADC currently approved in the 1st line setting.
So, the sacituzumab govitecan evidence address two different patient population because we have two different studies, ASCENT-03 and ASCENT-04.

What is the message for patients in the 1st line?

Prof. Javier Cortés

Well, thanks Giuseppe, I think that sacituzumab govitecan improves progression-free survival, which was the primary end point of the ASCENT-03 trial, compared with physician's choice of chemotherapy.
It is true that when we compare an overall response rate between SG (sacituzumab govitecan) and chemotherapy, there were similar response rates but the duration of the response was much longer with SG compared with chemotherapy. And in my opinion from the clinical practice, this also matters. Durable control disease is important.
It is not only about shrinkage of the tumour, which of course, of course is nice to see, but also the time the tumour is controlled is very important to try to delay the progression of the disease as much as possible. So, I think that PFS is improved, duration of response is much better. That is true that the overall response rate was very similar between SG and chemotherapy.

Prof. Giuseppe Curigliano

So, Javier, in your clinical practice, which patients most closely reflect the patient population of the ASCENT-03?

Dr Javier Cortés

Well, I think that when you look at the patient characteristics of the patients included in the ASCENT-03, about 20% of these patients were treated with relapse in the first year. But it is important to remind us that patients could have received treatment in the early breast cancer if the treatment free interval was between six to 12 months.

So, I think that a great majority of patients were sensitive to chemotherapy more than a year or de novo metastatic triple negative breast cancer. So, I think that this reflects the patient population that we observed in the ASCENT-03.

Regarding the PD-L1 status, we have to remind ourselves that it is true that patients were not candidate to immune checkpoint inhibitors. And as I said before, they have a treatment free interval of at least six months.

It is important to remember that the majority of patients, they have tumours with a PD-L1 negative status.

And also, it is important to take into account the toxicity and the schedule, the schema. So, this drug is administered on day one and day eight every three weeks.

And the adverse events more classical are neutropenia and diarrhoea. It is true that these are well known adverse events, but it is important to manage this properly because in the trials we have seen very rare but also some grade 5 events.

So, very important to manage these two adverse events properly and timely.

Prof. Giuseppe Curigliano

And what is about the ASCENT-04?

Here the clinical question was, what is the activity of sacituzumab govitecan plus pembrolizumab in the patient population PD-L1 positive?

Can you provide an overview of the clinical study and about of course also the primary and secondary endpoints?

Dr Javier Cortés

Well, you know Giuseppe, the KEYNOTE-355 demonstrated that chemotherapy plus pembrolizumab was superior to chemotherapy in triple negative breast cancer in the 1st line setting when the tumours express PD-L1 with a CPS score 10 or higher.

So, when these patients are candidates to immunotherapy.

We know today that sacituzumab govitecan plus pembrolizumab is superior to chemo plus pembrolizumab in terms of progression-free survival and time of disease control. So, I think that this is very important because we have established a good option to treat these patients. But with two important comments here. The first one, patients should be candidates to immune checkpoint inhibitors. You said before very nicely that there are some diseases or

some situations that patients could not receive immune checkpoint inhibitors. And second, the tumour should express PD-L1 with a CPS score of 10 or more. In this patient population I think that today SG plus pembrolizumab should be the preferred option.

So, taking into account all these things, I think that we have to move forward.

So, I would like to discuss with you new and ongoing clinical trials. I would like to discuss the BEGONIA, the MORPHEUS, the TROPION-Breast05. So Giuseppe, does BEGONIA suggest a role of datopotamab deruxtecan beyond the currently defined immune checkpoint inhibitor ineligible population?

Prof. Giuseppe Curigliano

Oh yes, of course.

The BEGONIA trial addressed for the first time the combination of datopotamab deruxtecan plus durvalumab*.

I really believe a combination of ADC with immunocheckpoint is the future because for PD-L1 positive disease we have already the evidence that sacituzumab govitecan plus pembrolizumab is better than chemotherapy plus pembrolizumab.

We know also that there is ongoing a prospective randomised trial that is the TROPION-Breast05 in which the combination of datopotamab deruxtecan and durvalumab is compared to the combination of chemotherapy plus pembrolizumab.

We know there is an encouraging activity including across PD-L1 subgroups and these support the enrolment in this prospective randomised trial.

Just to mention another trial that I believe is also important is the MORPHEUS.

The MORPHEUS trial is an umbrella trial, finally, in which you have a combination in several subgroups of breast cancer, including HR-positive, triple-negative and also HER2-positive and HER2-low. In this case we have a combination again with immunocheckpoint inhibitors like atezolizumab. I mean, combining an ADC (sacituzumab govitecan) plus immunocheckpoint inhibitors can increase immunogenic cell death and once you combine the immunocheckpoint inhibitor, you enhance the immune response.

So, personally I do not know what MORPHEUS-panBC is going to add, but maybe this is a question for you.

What do you think exploring the activity across subtypes may add eventually in terms of activity, Javier?

Dr Javier Cortés

Well, I think it is reassuring to see that the data in triple-negative breast cancer with MORPHEUS and with BEGONIA is so 'similar'.

I think that looking at the PD-L1 negative population also with an overall response rate near to 80%, 70 to 80%, and the median PFS exceeding one year, I think is absolutely extraordinary.

Prof. Giuseppe Curigliano

So, I have a question for you Javier.

With ASCENT-04 already positive, what would make TROPION-Breast05 clinically persuasive?

It is, of course, a provocative question.

Dr Javier Cortés

Well, we will see if the benefit is superior compared with the standard treatment it's not just looking at the higher response rate it's looking at the end.

What about progression-free survival and potentially overall survival?

It is also about safety. It is about quality of life.

So, I think that we sometimes are talking just about what drug is superior to the one in terms of efficacy. But it is much more than that. How do patients behave with this new strategy, whatever the strategy is.

I think the TROPION-Breast05 will be beautiful to answer also the safety issue and the quality of life.

You know we have to remind ourselves that Dato-DXd plus durvalumab remains investigational at this time.

We have to wait and see the results.

The data we have seen from BEGONIA is really promising but the TROPION-Breast05 will definitely answer if this is something that we will establish a new standard of care or a new good option to treat our patients in the clinical practice. Great feeling, but we have to wait and see.

Prof. Giuseppe Curigliano

Thank you, Javier.

So, since we have now two ADCs approved at least in PD-L1 negative, when do you believe we should consider sacituzumab govitecan?

Which patient factors matters the most?

Dr Javier Cortés

Well, I think that one big comment here Giuseppe, if you do not mind, is that we have to think about anti-TROP2 ADCs from the very beginning.

I would have Dato-DXd, I would have SG.

We have both great drugs. I think that related to SG, it has been basically included in many guidelines.

I think that ESMO/ASCO recognise that the antibody-drug conjugates in general are here to stay, are here to improve outcomes. And that is something that we have to think about. But it is true that afterwards we have the patient in front of us and we have to think about the prior therapy and the disease-free interval.

So, if we have a very short disease-free interval, lower than six months, we do not have enough data to suggest that SG is the best drug to be used.

Maybe datopotamab deruxtecan could be used in this setting. But also, we have to take into account other aspects. We have to take into account the disease tempo. We have to take into account the required speed of response if we need that response. That is something that we have to take into account with these two great drugs into the system.

We have to take into account also the toxicity. So, we know that the most important adverse events are basically neutropenia and diarrhoea, so which is the bone marrow reserve?

What about the febrile neutropenia risks? What about the gastrointestinal history? I have also discussed with our patients the schedule, day one and day eight. It has pros and cons. But that is something that we have to discuss with our patients.

What is very clear is that diarrhoea, nausea and alopecia could decrease the quality of life and that is something that we have to discuss with our patients. I am not saying yes, I am not saying no. What I am saying is that we have to take all these aspects into account to decide at the end when and how to use these drugs. That is true, is very effective and clearly superior with chemotherapy.

So, let me ask you the other way around.

Giuseppe, if you are thinking about Dato-DXd, which factors matter the most?

Prof. Giuseppe Curigliano

Okay, first of all we have two ADCs and TROP2 approved in the 1st line, and we should follow the ESMO and the ASCO guidelines.

So, the standard of care in a metastatic triple negative breast cancer, PD-L1 negative or immunocheckpoint inhibitors ineligible should be also datopotamab deruxtecan.

So, of course we need to consider that in the TROPION-Breast02 there was also the opportunity to include patients with a disease-free interval of less than six months.

So, if you have a patient, high tumour burden with early relapse, for sure, datopotamab deruxtecan is an excellent option.

Do a baseline assessment of this patient. Ocular health should be assessed because there is a risk of ocular toxicity.

Oral health should be assessed because we have a risk of stomatitis.

Of course, exclude from exposure to datopotamab deruxtecan patients with the previous ILD or at risk of pneumonitis.

And the most important thing is the ability to follow prophylaxis monitoring.

So, steroid mouthwash to prevent stomatitis, ocular drops to prevent ocular toxicity management and monitoring of the risk of ILD.

An opportunity, I believe for datopotamab deruxtecan is the schedule. An administration every three weeks, of course will not give the patient the stress to come back after eight days. And as for sacituzumab, evaluate every time the impact on work, family life and patient preference. They are both excellent drugs with a different schedule administration and different eligibility criteria in the clinical trials.

Dr Javier Cortés

Giuseppe, I think that we are, we do not have many more time, but I have maybe one or two questions that I would like to ask you.

After progression on an anti-TROP2 antibody-drug conjugate, should the next treatment be another anti-TROP2 antibody-drug conjugate?

Prof. Giuseppe Curigliano

You know perfectly that there is no established TROP2 after TROP2 sequence.

I personally believe that we have some clinical trials actually ongoing that are studying the sequence of an ADC following an ADC and the concept is finally to consider a strategy

rather than a drug versus another drug. Strategy means having as primary endpoint of median progression-free survival.

Two, is having a lot of biopsies to better understand the biology behind the mechanism of resistance.

So, I would like to invite you, Javier now to give to our clinicians the take back to practice of all this discussion we need.

Dr Javier Cortés

So, Giuseppe, we have been talking all the time about metastatic triple negative breast cancer.

Metastatic triple negative breast cancer is an incurable disease with a very poor prognosis. It is true that unfortunately many patients will be unable to receive a 2nd line treatment. So, we have to offer our patients the best drugs we have and the anti-TROP2 antibody-drug conjugates are probably the best drugs we have in this setting. That is why we have to think about Tropion-Breast02 and ASCENT-03 to support the 1st line treatment for patients who are not candidates for immune checkpoint inhibitors. And maybe think about ASCENT-04 to support SG + pembrolizumab in those patients who are candidates for immune checkpoint inhibitors.

It is true that we have to individualise our selection.

We have to take into account the disease characteristics, the prior treatment and the treatment-free interval, the schedule, adverse events and we should always avoid to make comparisons between dato-DXd and SG because we do not have a face-to-face randomised phase 2 or randomised phase 3 trials.

And last but not least, we have to translate the Dato-DXd and SG safety evidence into treatment-specific prevention. We have to monitor the adverse events, and we will have to escalate the plans before dose one.

Prof. Giuseppe Curigliano

So, my message for all the audience is to review your 1st line triple negative breast cancer pathway now.

So, first identify the patients that are PD-L1 positive and PD-L1 negative or ineligible and finally identify which patients reflect the TROPION-Breast02 population or the ASCENT-03 or the ASCENT-04 population and put the appropriate ADC specific adverse events plan in place before treatment begins.

Thank you for listening and thank you very much indeed also to Javier Cortés.

Dr Javier Cortés

Thank you, Giuseppe. Likewise.

Tonke

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