Transcript Details

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Maximizing Benefit With the Expanding Options for Gastric Cancer: Patient Selection and Management

Announcer Open:
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Dr. Cleary:
So yeah, in terms of working up a gastric cancer patient, I think the oncologist taking care of this patient in the example, really showed how nicely to work up a gastric cancer patient. As always, you want to take a history, you want to get labs, but the upper endoscopy and biopsy are critical. As all of you know, when you're treating a solid tumor patient, you really need to get a histological confirmation of the tumor. So that biopsy is very, very important. And the upper endoscopy, you can visualize the tumor, then you want to do something like a CT scan of the chest, abdomen and pelvis, just to look to see if there's any evidence of metastatic disease. Because when you're thinking about caring for a gastric cancer patient, the first question I always ask is, is it metastatic, meaning that we're not really sure this but we can treat them with palliative intent to try to increase their life? Or is it localized, where we could actually do something like surgery and try to cure the patient? Again, in this fictional patient that we're discussing, this is metastatic disease to the liver, so we're not going to be able to cure this, but we can treat this patient with palliative chemotherapy.

So, molecular testing, and this is where gastric cancer has changed. The things you want to do when you get a gastric cancer patient is you want to do testing to see if the patient's MSI high. Probably the fastest way to find out if a patient's MSI high is to do mismatch repair immunohistochemistry, IHC, because that can come back in a couple of days. In addition, another very rapid IHC test is testing for HER2, and that's critical too, because if you have a patient who's HER2 amplified, has HER2 amplified gastric cancer, you can give them HER2-directed therapy. In terms of the number of patients with metastatic gastric cancer that have a HER2 amplification, it's only about 10 to 15%, but you really could help those patients by finding it. So, please check if the patient's MSI high, please check if the patient has HER2 amplification. And then the other thing that's very, very important because we're now using immunotherapy in gastric cancer is looking at PD-L1 expression. Again, that's another immunohistochemical test that can come back rapidly.

The other thing I like to do on all of my gastric cancer patients is next generation sequencing, NGS. The NGS testing does take a little while longer to come back, a few weeks. But with NGS testing, you'll get something like T and B status. You'll also - it's another way to check MSI high. The other things you'll get though, is you'll see if there's any unusual but actionable molecular alterations like NTRK translocations. Even though those are rare, it's worth looking for. So, patients with metastatic gastric cancer, only about 1% have NTRK translocation. But if you find one of those patients, you can do the world of good by treating them with an NTRK inhibitor.

So again, recommended molecular biomarker testing, you want to check if a patient has an MSI high tumor, the fastest way to do that is mismatch repair IHC. You want to check HER2 status, the fastest way to do that is HER2 IHC. You want to check PD-L1 testing, so again, doing IHC. These first three, seeing if it's MSI high, HER2, and PD-L1, those are all IHC-based tests. And you also want to do next generation sequencing to look for rare but actionable molecular alterations. And this is just emphasizing this point of how important it is to do the IHC tests and the next generation sequencing, just trying to get extra treatment options for your patients that really could expand their lives. And I'm going to turn it over to Kristen.

Ms. Madden:

Great. So, thank you. Which of the following biomarkers should be assessed in all patients with newly diagnosed advanced gastric cancer to inform initial systemic therapy recommendations? A: BRCA mutation; B: EGFR mutation; C: Mismatch repair or MSI high; D: RAS mutation. Please make a selection.

Great. The majority of folks chose the right answer in the posttest with the MMR and MSI. And again, the rationale is recommend to the patients with newly diagnosed advanced gastric cancer be tested for mismatch repair and MSI, which can inform the use of immune checkpoint inhibitors. The BRCA, the EGFR, and the RAS mutations do not generally inform treatment for advanced gastric cancer outside of a clinical trial.

So, we're going to flip back over to Rick and talk a little bit more about his case. The pathologic analysis of primary tumor specimen revealed tumor located in the gastric body. Histologic characterization of tumor is adenocarcinoma in the intestinal type, Lauren classification. CT scans reveal GC with liver metastases. Patient is not a candidate for surgical resection. The molecular characterization of Rick's tumor is MMR proficient by IHC, HER2 amplification is IHC 3+, PD-L1 expression level is CPS 2, TMB by NGS is 2.1 mutations per megabase. No NTRK or RET gene fusions, or BRAFV600 mutations by NGS. Analyses of genomic markers, microsatellite status, CDH1, APC, STK11 from NGS not suggestive of any hereditary predisposition for gastric cancer.

So, our next pretest question: Based on these findings and current recommendations, which initial treatment option would be optimal for Rick?

Chemotherapy with CAPOX or FP; Chemotherapy plus nivolumab; Chemotherapy plus trastuzumab deruxtecan; Chemotherapy plus trastuzumab and pembrolizumab. Please make a selection.

Okay. Now, we have a pretty informed audience here, 74% chose that chemotherapy, trastuzumab, and pembrolizumab, which is the correct answer. And moving on, I'll hand the program back to Dr. Cleary.

Dr. Cleary:
Thank you. And so, this slide – this one's a very helpful slide. This slide is talking about the treatment paradigm for patients – initial treatment paradigm for patients with advanced or metastatic gastric cancer. As many of you answered correctly, in a patient with HER2-positive gastric cancer, you want to give 5-FU-based chemotherapy along with oxaliplatin or cisplatin, and trastuzumab and pembrolizumab if the CPS is greater than 1. And this is a change. We weren't doing this; we were giving it to everybody regardless of CPS about 6 months ago, but this is a new change. So really, the answer is if you have a first line, untreated patient with HER2-amplified gastric cancer, you're going to give a regiment like FOLFOX, trastuzumab, and pembrolizumab as long as the PD-L1 CPS is over 1. If the PD-L1 CPS is negative for this population, I would not give the pembrolizumab.

For patients who are HER2-negative, and this is most of the patients, we still are using immunotherapy as long as the CPS is 5 or greater. So, if you meet a metastatic gastric cancer patient who has a PD-L1 CPS score of 5 or higher, you're going to treat them with a regiment like FOLFOX and nivolumab. In addition, you could consider any MSI high patients giving pembrolizumab and dostarlimab 08:30 alone. However, the data here is still emerging and I think most patients – most oncologists would still give FOLFOX and nivolumab to that population.

Here's some of the trials that led to this. The CheckMate 649 study combined chemotherapy. And the chemotherapy was either XELOX or FOLFOX with nivolumab in patients with HER2-negative gastric cancer. And really, we saw a big effect in patients with this PD-L1 CPS over 5 compared to patients – in patients with PD-L1 CPS over 5, who got nivolumab and FOLFOX compared to patients who just got FOLFOX. There really was about a 4-month survival benefit, which was wonderful.

Similarly, with pembrolizumab, the KEYNOTE-859 trial showed very, very similar data. Basically, it showed that when you combine pembrolizumab with chemotherapy, patients with a PD-L1 CPS over 1 did better than the patients who just got chemotherapy alone. So really, what the KEYNOTE trial showed and what the CheckMate trial showed, is that by adding PD-1-directed immunotherapy to chemotherapy that you improved outcomes in patients with metastatic gastric cancer.

This is looking at some of the HER2 trials. So, a trial that was done a long time ago, it was the ToGA study. And the ToGA study was just looking to see in patients with HER2 amplified gastric cancer, whether adding a HER2 antibody, Herceptin trastuzumab to chemotherapy, was effective. And so, in the ToGA trial, they compared patients who got chemotherapy alone versus chemotherapy with trastuzumab. And they saw a survival benefit. But the survival benefit was modest, and so that was the best we had for a long time until the KEYNOTE trial, the KEYNOTE-811 trial came along. And this is the trial where we're really integrating immunotherapy to these HER2-positive patients. So, KEYNOTE-811 showed that when you have an untreated gastric cancer patient who's HER2-amplified, you are going to add pembrolizumab to the trastuzumab and chemotherapy. And as we said, the recent spin on this data is because of this subgroup analysis below, that you notice if you look down here, that's patients with CPS less than 1, really, they didn't get any benefit from getting pembrolizumab. So, really, what we're doing is we're only combining pembrolizumab with chemotherapy and trastuzumab

in patients with a CPS score of 1 or higher.

So again, just talking about the treatment paradigms for initial gastric cancer patients with metastatic disease, if it's HER2-negative and the PD-L1 CPS is over 5, you're going to give 5-FU and oxaliplatin along with nivolumab. If it's HER2-positive, you're going to give FOLFOX, trastuzumab, and pembrolizumab if the CPS score is greater than 1. And here, they're just highlighting this action item that you really, in order to make these proper treatment decisions, you need to get the molecular testing.

Now I'm going to hand it over to Kristen.

Ms. Madden:
Great, thank you. What level of PD-L1 expression is the chemotherapy plus trastuzumab plus pembrolizumab regimen indicated for in HER2-positive advanced gastric cancer? A: Regardless of any specific PD-L1 expression; B: Combined positive score CPS of less than 1; C: CPS greater than or equal to 1; or D: CPS greater than or equal to 10. Please choose.

Great, 75% with the correct answer. And again, the rationale is based on the KEYNOTE-811 trial, pembrolizumab FDA approved in combination with trastuzumab and a 5-FU-containing regimen for chemotherapy for first in line treatment of patients with locally advanced, unresectable, or metastatic HER2-positive gastric or GEJ adenocarcinoma when tumors express PD-L1 with the CPS of greater than or equal to 1.

Let's shift gears back over to Rick. You prescribe Rick chemotherapy plus trastuzumab plus pembrolizumab. He remains on treatment for 2 months and a partial response is observed. He calls to report fatigue, irritability, thyroid function tests indicate elevated TSH greater than 10 and low free T4, suggesting primary hypothyroidism. So, which of the following approaches would you recommend for

Rick? A: Continue immune checkpoint inhibitor, administer steroids; B: Continue immune checkpoint inhibitor, administer levothyroxine; C: Continue immune checkpoint inhibitor, administer steroids and levothyroxine; D: Hold immune checkpoint inhibitor, administer steroids and levothyroxine. And if everyone can make a selection on this pretest question.

Okay. Oh, we're split between B and D. B is the correct answer. Continue immune checkpoint inhibitor and administer levothyroxine. And I know Dr. Cleary is going to help clarify why B is the correct choice.

Dr. Cleary:
Yes, thank you. So, on that last question, you know, these immune-related adverse events to PD-1-directed therapy, we see them not uncommonly. For most of the immune-related adverse events, so stuff like autoimmune colitis, pneumonitis, hepatitis, those are life-threatening side effects. And when you see side effects of those nature, you really want to hospitalize the patient and get the patient on steroids. Fortunately, what we've learned with experience is that hypothyroidism is probably the most common immune-related adverse event from PD-1-directed therapy, but we really don't have to give steroids. The idea is that we could manage those patients just by giving levothyroxine. So, you are going to see a lot of hypothyroidism caused by PD-1-directed therapy. Fortunately, you can just keep giving the PD-1-directed therapy, you don't have to give steroids, but you do have to give levothyroxine. And the pattern you'll see frequently is that patients will first get hyperthyroidism, but then that hyperthyroidism will burn out and eventually the patient will get hypothyroidism. And you can just manage that with levothyroxine. If you need to partner with an endocrinologist, that's very reasonable. But again, the main teaching points for PD-1-directed toxicity-causing hypothyroidism is you don't need to stop the PD-1 inhibitor, you don't need to give steroids but you do need to give levothyroxine.

And talking about the spectrum of immune-related adverse events, they could hit anywhere. So, just like we're hoping that when we give immunotherapy that we're going to stimulate the immune system to kill off the cancer, just like the immune system would kill the bacteria, the immune system when it gets so activated, there can be collateral damage, so it can hit your normal tissue. And it can hit anywhere. It can cause a rash. It can cause autoimmune colitis, horrible diarrhea. It can cause autoimmune hepatitis, and you'll typically see that with very high AST or ALT. It can cause autoimmune pneumonitis. And those patients typically present with shortness of breath or also a persistent cough. It also can cause autoimmune myocarditis, and that's one of the trickier ones, and those patients come in very sick.

So, when we see these adverse events, that one of the most common ones we saw, we talked about the thyroid issue, we also often see a rash. Now with the rash, many times it's just a faint red rash, and that one you could treat right through as well. So, if a patient just gets this mild rash that the patient will typically say it's alittle itchy, but not a big deal, you can treat those with topical steroids and you can treat right through them though, you don't have to stop the PD-1 inhibitor. Obviously, if it becomes a very severe rash, then you have to stop treatment, but I actually have never seen that; I only have really seen the mild rashes where I can treat with just topical treatments.

The adverse events I worry about the most, because these are the serious ones that are most common, autoimmune colitis. And these patients with autoimmune colitis, they're having diarrhea at least 5 times a day, not uncommonly, 10 or 15 times a day. So, for those

patients with this horrible diarrhea from a PD-1 inhibitor, do you want to hospitalize them, you want to get them on steroids, you want to consult GI, and most typically you do not restart the PD-1 inhibitor.

Same thing with pneumonitis. So, if you get a patient with grade 2 or 3 pneumonitis, the way you can diagnosis it is with a chest CT scan, but you want to get them in a hospital, you want to get them on high doses of steroids. And it's uncommon that you'll rechallenge them but if you do rechallenge them, you need to do that in collaboration with a pulmonologist because it's very risky to rechallenge the patient.

So, really what this slide is trying to get across is when you have a serious immune-related adverse event that you want to put them in a hospital, something like autoimmune colitis, hepatitis, or pneumonitis, or myocarditis, you want to put them in the hospital, you want to get them on high doses of steroids. So, prednisone 1 mg/kg per day, which can be very, very high doses.

And you want to also partner with the specialist of that disease. So, if you have a patient who has autoimmune pneumonitis, you want to partner with a pulmonologist. If you have a patient with autoimmune hepatitis, you want to partner with a hepatologist who can help you. So, really, hospitalize the patient, steroids, and get help by getting the appropriate services involved.

Immune-related endocrinopathies, we talked about thyroid dysfunction. Fortunately, here you can continue the PD-1 inhibitor, you don't need steroids, but you do need to start levothyroxine. It's very reasonable to consult the endocrinologist. Adrenal insufficiency, it's uncommon but it does happen. So, if this happens, you can treat through but it's more - because this is a very difficult thing, adrenal insufficiency, I would recommend consulting an endocrinologist. Hypophysitis, this doesn't happen with PD-1-directed therapy, but it does happen when you're using CTLA4-directed therapies like ipilimumab. Here, these patients can be very sick, so you really need to get an endocrinologist involved.

So, really, what this slide is trying to get across is when you're giving immune therapy, it's not like chemotherapy, when we just saw a lot of nausea and vomiting and low cell counts, these side effects can be all over. So, you really have to have a high degree of suspicion. You really should be monitoring TSH every 6 to 8 weeks because you don't want it to sneak up on you. It's awful when you forget to check the TSH and then 4 months later you find out it’s 50, you’re going to feel very badly. So, please try to regularly check the TSH. And then if you do get suspicious that the person is having an immune-related adverse event, please get them into the hospital and please have a low threshold to start steroids. And this is really just trying to emphasize, be suspicious for these immune-related adverse events.

Ms. Madden:
All really excellent points of monitoring for the endocrinopathies.

So, jumping back to Rick and his case, his hypothyroidism does respond to levothyroxine. He has a good response to chemotherapy, trastuzumab, and pembrolizumab, completing 14 cycles of treatment. At his recent follow-up visit, imaging revealed disease progression and new metastases. Based on his molecular profile, MMR, MSS, HER2-amplified, PD-L1 CPS 2, NTRK fusion negative, TMB low, which of the following second-line options would be optimal for Rick? A: Docetaxel; B: Ramucirumab plus paclitaxel; C: Trastuzumab plus ramucirumab plus paclitaxel; D: Trastuzumab deruxtecan. Please choose.

Okay. So, our correct answer is D: Trastuzumab deruxtecan; 23% chose that, and 52% chose C, so I could kind of see where that came in. But we'll get a little bit more clarity as we continue on. So, just a little bit more about Rick. So, he starts the trastuzumab deruxtecan. This is generally well tolerated. At 6 months, CT/PET shows a continued partial response but reveals hazy infiltrates in the upper lobes of both lungs. Rick was diagnosed with a grade 2 shortness of breath and a grade 2 interstitial lung disease.

So, I'll hand it back over to Dr. Cleary to talk a little bit more about the treatment option selection and the complications.

Dr. Cleary:
Thank you, Kristen. So, second-line therapy in gastric cancer, the mainstay of second-line therapy in gastric cancer is ramucirumab and paclitaxel. We also occasionally will use FOLFIRI. However, with the emergence of HER2-directed therapies, what we're excited about is the one exception to that is patients with HER2-amplified gastric cancer, we could use the antibody drug conjugate, trastuzumab deruxtecan, in patients with HER2-positive gastric cancers. And this has been wonderful because it's really - the response rate for this agent is 40% and it just gives these patients another way of treating the disease. So, when I have a patient with HER2-positive gastric cancer who progresses on first-line therapy, first thing I'll do is I want to make sure they're still HER2-positive, so oftentimes, I'll do something like a cell free DNA test, just to make sure they're still HER2-positive because one of the ways that you can become resistant to HER2-directed therapy is you can lose that HER2 positivity. So first, when a patient progresses on a first-line regimen such as FOLFOX, pembrolizumab, and trastuzumab, I first confirm they still express HER2. Once I've confirmed they still express HER2, then I really want to try the trastuzumab deruxtecan, because I get more mileage out of the HER2-directed therapy. And then in third line, when they progress on this, I could put them on ramucirumab and paclitaxel. So, it really just gives them more treatment options.

Again, though, just to say for the patients who are not HER2-amplified, because that's basically most of the gastric cancer patients, typically I'm using a regiment like ramucirumab and paclitaxel. Occasionally when I feel like they, for whatever reason, they didn't tolerate the first-line chemotherapy well, and I feel like they'd benefit from getting more chemotherapy, I will have the FOLFIRI. But most of the time, I do give him ramucirumab and paclitaxel. And then in third line after the ramucirumab and paclitaxel, then I'll use a regiment like trifluridine tipiracil, and that's also called Lonsurf or TAS-102. And that's the regimen I use in third line.

So, second-line therapy, there's other things you could think about is if you find a patient – so, this is why next generation sequencing is so important; occasionally with next generation sequencing, you'll find an actionable alteration. So, if on next generation sequencing you were to find something like an NTRK translocation, you'd absolutely want to target this. So, if you found an NTRK translocation, you want to try entrectinib or larotrectinib, two very good NTRK inhibitors in the second line. And also, if on next generation sequencing, you were to find a RET fusion, again, it's rare, but it happens and it's worth looking for, you really want to try a RET inhibitor in this population.

So, we'll talk about the trials that led to these recommendations. This trial is known as the RAINBOW study and it combined paclitaxel, Taxol, with ramucirumab, and these are for patients with non-HER2 amplified gastric cancer. And this was an advance. So, basically the patients who got ramucirumab, and ramucirumab is an anti-angiogenic agent, it targets VEGF by combining paclitaxel with the anti-angiogenic ramucirumab, you improved median overall survival from 7.4 months to 9.6 months. So, it's very worthwhile trying with your patients. And the ramucirumab is well tolerated. So, ramucirumab, like all anti-angiogenic agents can cause hypertension. In rare cases, it can cause bleeding. So, if you have a patient who you're worried about bleeding, this isn't a great regimen for but in general, it's very, very well tolerated.

And this is the DESTINY-Gastric01 trial. And this was the trial for HER2-amplified patients that showed that we could use the antibody drug conjugate, trastuzumab deruxtecan, in patients with HER2-amplified metastatic gastric cancer after first line. And really what made a big, big impression on me was when I looked at the response rate. The response rate for trastuzumab deruxtecan in this population was 51%; whereas with chemotherapy alone, it only was 14%. So, a huge increase in response rate. And also, if you look at overall survival, it increased it by over 4 months. So, this is really a homerun. And so, it's something I highly encourage you to do; that if you have a HER2-amplified patient, treat them in first line with FOLFOX, pembrolizumab, and trastuzumab. But if they still express HER2 in second line, please use trastuzumab deruxtecan.

And this is just showing similar data, just showing that this response rate is 42%, so it to me, it's a very, very active agent, and it's something you really want to think about giving to HER2-positive patients.

This is the problem, as you probably can tell I'm very, very enthusiastic about this drug. But just like anything else, it has an Achilles heel. And the Achilles heel of this drug is interstitial lung disease. So, I really want you all to hear that if you have a patient on trastuzumab deruxtecan and they get short of breath, you really need to get them in the hospital. And there's been several deaths with this drug. So, it really is a significant drawback. So, please be aware. It's a great drug. We talked about it's very, very high response rate, it improves survival by 4 months. But there have been deaths. And the reason there's been deaths is it can cause interstitial lung disease. So, if you get a patient with unusual cough or dyspnea on exertion, usually the dyspnea on exertion is subtle, it's like the patient will say to you, 'You know, I'm just getting short of breath walking from my living room to the bathroom.' If you're hearing that, please get them in the hospital, please get them a chest CT. And if it is interstitial lung disease, get them on steroids ASAP and partner with a pulmonologist.

And this is just talking about the management of interstitial lung disease. As soon as you hear about it, you stop the trastuzumab deruxtecan and you won't rechallenge them. So again, just because there's been deaths, if you if this patient has interstitial lung disease, you stop it permanently. So, stop the drug, get them in the hospital, get a chest CT. If it's interstitial lung disease, get them on high doses of steroids, typically 1 mg/kg of prednisone ASAP and partner with a pulmonologist.

So, this slide is really just again driving home in second line, and this is why molecular testing is important. If you have a HER2-amplified patient, you want to get them on trastuzumab deruxtecan, because the response rate is so much higher, there's a 4-month survival benefit. However, please, please, please be watching for interstitial lung disease. And if you see signs of interstitial lung disease, get them in the hospital, get them on steroids, and stop the drug. Again, just really trying to emphasize this point, because people have died. And that's why they're really just trying to get the word out that it's a great drug, but you just have to worry about interstitial lung disease. I'll hand it over to Kristen.

Ms. Madden:
Great. So, thank you, Dr. Cleary.

Let's move on to one of our posttest questions: What is the most appropriate next step with trastuzumab deruxtecan if grade 2 interstitial

lung disease is suspected? I hope that this kind of hit home with this previous talk, so – or this previous segment. So, choices are: A: Continue drug and start empiric antibiotics; B: Reduce drug by one dose level and monitor symptoms; C: Pull drug, treat with ibuprofen, obtain pulmonary consult; D: Permanently discontinue drug, start steroids, obtain pulmonary consult. Please make a selection.

Okay. So, our correct answer is D: Permanently discontinue drug and start steroids. Just trying to open up my poll there. The majority of you did answer the correct answer. You chose the correct choice. And that was per the prescribing information of trastuzumab deruxtecan, patients who develop grade 2 to 4 interstitial lung disease while receiving this agent should permanently discontinue treatment and promptly initiate systemic high-dose corticosteroid treatment.

And I'm going to hand this back to Dr. Cleary quickly to go over the next PC action plan.

Dr. Cleary:
Thank you. So, we just wanted to review some of the points we've made in today's talk. First thing is there's an increasing awareness that there are some genetic causes to gastric cancer CDH1 mutations but also things like DNA repair mutations. So, if a patient has a family history of gastric cancer, if they're getting it at a young age, please send them for germline testing. Big, big point for management of advanced gastric cancer patients is you want to get molecular testing. The test you need is, you need IHC tests. The IHC tests are going to look for PD-L1, HER2, and mismatch repair deficiency. And you also want to get next generation sequencing to look for unusual but actionable alterations such as NTRK and RET fusions. The reason this molecular testing is so important is we change therapy based on the molecular test. So, we talked about the exciting advances that have happened in HER2-amplified gastric cancer; that in a patient with HER2-amplified gastric cancer in first line, you want to give them a regiment like FOLFOX, trastuzumab, and pembrolizumab if their PD-L1 score is 1 or greater. And then in second line, if they still express HER2, you want to give them trastuzumab deruxtecan.

Similarly, in patients who aren't HER2-amplified, you still need that PD-L1 testing, because in first line, if their PD-L1 score is 5 or greater, you want to be giving them a regimen such as FOLFOX and nivolumab.

We also spoke about the exciting developments of trastuzumab deruxtecan, the antibody drug conjugate, but we also wanted to get the word out that patients can get fatal interstitial lung disease, so please, please watch out for that.

And then finally, since we're using immunotherapy more and more in gastric cancer, just know that if you're giving a patient a drug like nivolumab or pembrolizumab, that the immunotherapies can hit anywhere in terms of side effects. So, be suspicious if you get a patient with horrible diarrhea, very high AST or ALT, or shortness of breath. Thank you.

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