Speaker 3

Speaker Key:

GD George Demetri

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00:00:12	GD	I'm Dr George Demetri from Dana-Faber and Harvard Medical School and I'd like to talk about an update on sarcomas and things from 2020 we don't want to forget from a medical oncologist point of view. Here are my disclosures.
00:00:29		Now one important thing as a medical oncologist is that not everybody has access to pathologists as expert as Paolo Dei Tos or Christopher Fletcher or a few others in the whole world. I always encourage people to question the diagnosis of any form of sarcoma simply because there are so many different types.
00:00:48		Of course, GIST is the most common type and Liposarcomas come in several types, Leiomyosarcomas can occur in many places. But you see how complicates this is and the latest book of the WHO classification for sarcomas notes more than 170, one seven zero, different subtypes of sarcomas. This is a complex field and the more we learn about this, different subtypes may require different treatments.
00:01:16		Now, let's start by talking about early stage resectable sarcomas where the surgeon is really the key person. In these cases medical oncologists must ask whether there's sufficient evidence to give systemic therapy before local therapy. In other words, when I say local therapy I mean surgery, plus or minus pre-op or post-op radiotherapy.
00:01:38		And for most sarcomas the answer still remains no, but this remains the subject of several clinical trials including a new one called STRASS 2, that we want everybody to participate in. And this emphasizes that we still need much better and more active drugs with different modes of action in different kinds of sarcomas.
00:02:00		So where do we give pre-surgery, systemic therapy, of course still the paediatric type of sarcomas like Ewing sarcoma with the standard EWS translocation, osteosarcomas,

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		rhabdomyosarcoms and of course preoperative downstaging with highly effective therapies like Imatinib for GIST. But we have new things on the block including this new drug called Avapritonib for GIST with the PGDF receptor alpha exon 18 mutations.
00:02:32		And that's based on data that Michael Heinrich and Suzanne George and others have presented Sebastian Bauer in Germany with key in this development plan where the activity of this drug in this specific type of GIST had really remarkable adjective evidence of response, in this case by central radiology review.
00:02:51		And on the basis of this, the US FDA approved it in 2020 and the EMA conditionally approved, it also in 2020. Now, recognise that these approvals were for patients in whom surgery was not possible, so that's important. But if one looks at a patient and says, well the surgery would be too big, it would be too morbid, in many ways that is not easily resectable, and that's the way we've all looked at GIST in many ways for many years with different kinase inhibitors.
00:03:22		Let me also focus on this, NTRK fusion sarcomas, including GIST, that are driven by NTRK fusion. Now as you've heard from Paolo Dei Tos in his section of this webinar, this is really important because NTRK fusions are rare but very relevant to sarcomas in both adults or children. And this is especially true in this group, I want to point this out, GIST, where they do not have mutated KIT, in other words, they have a normal KIT gene.
00:03:51		They have a normal PGDF receptor alpha gene, they have a normal BRAF gene, and they have expression of SDH subunits normally. So those are so-called quad-negative, meaning one two three four things that could be mutated or missing in GIST, are now not mutated. So, those quad-negative GIST is where we found NTRK gene fusions.
00:04:15		But they also occur in other undifferentiated sarcomas and are virtually pathognomonic in the infantile fibrosarcomas in kids. So again, 2020 brought up a lot of interesting activity just because of these beautiful drugs we have, Larotrectinib, Entrectinib, with again, fantastic waterfall plots showing that for things like infantile fibrosarcoma, in yellow, or many other, light

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		blue, sarcomas you see these beautiful shrinkages of disease that are very durable over time with either Larotrectinib or Entrectinib.
00:04:50		So, I always want people to think about NTRK fusion in sarcomas, be they undifferentiated sarcomas or quad-negative GIST or other types. Now, how do we find these sarcomas driven by TRK fusions? The only way is to keep this potential differential diagnosis in mind. And many of us collaborated in a world sarcoma network effort to come up with an algorithm for testing in a collaborative way that would actually take into account different cultures and different patterns of practice across the world.
00:05:22		So, for example, if somebody with a sarcoma has a localised disease or even other types of cancers typically you don't need NTRK testing but if you have metastatic or locally advanced disease that's not amenable to surgery one could look at this in really three different ways. You have a rare cancer with high incidence of TRK fusions like infantile fibrosarcomas, those are pretty easy because there you test.
00:05:48		But the challenge is this group over here, cancers with a low incidence of TRK fusions which is virtually every other type of cancer, with a few exceptions like an unusual secretory type of breast cancer, an unusual type salivary gland cancer. But I think the world has really taken lessons from the non-small cell lung cancer world, a type of cancer with many proven molecular targets, from EGF receptor mutations to RET mutations to ELK and RUS1.
00:06:16		And so, lung cancers become much more standard to test with next generation sequencing to see if there are any actionable mutations. And I think that's exactly what we do in the rare cancers, we go right away to molecular testing, either with FISH, possibly making a pit stop with an NTRK immunohistochemistry but eventually often going to next generation sequencing.
00:06:40		But the real challenge is this group here, the cancers with a low incidence of TRK fusions, how do you find them there, and that's where this algorithm says, well if you have another driver, for example, if you have a GIST with a KIT mutation you really don't need to look for a TRK fusion, it's not going to be there.

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		But like I said before, if you don't have a clear driver in a GIST, no KIT mutation, no PGDF receptor alpha, no BRAF, you get the idea, then that's where you definitely should look for a TRK fusion..
00:07:11		And the same thing for other types of sarcomas. Typically this algorithm suggests a Pan-TRK immunohistochemical, stop, because if there's high level TRK expression, that's the type of patient where you want to look with next generation sequencing. And I think our whole world is trying to figure out how do we find these patients, not just in sarcomas, although they are enriched in sarcomas, both the quad negative GIST and other undifferentiated sarcomas. I think 2020 brought that up for us
00:07:43		Well, 2020 was not always clear and nor was it easy in many ways, in drug development as well as everything in the world. What about the CSF1 driven sarcoma known as Tenosynovial giant cell tumour? Well, here we've seen spectacular results from the CSF1 receptor inhibitor, Pexidartinib, that my colleague Andy Wagner and Bill Tap published in The Lancet in 2019.
00:08:07		This absolutely, again, beautiful shrinkage of this disease, Tenosynovial giant cell tumour with Pexidartinib and the important thing here is the durability of these responses. The median duration when this was published in 2019 was still not met 22 months after follow up. And you see, you just don't see any responses in the placebo group. So, it's not like desmoids sarcomas or desmoids fibromatosis, where occasionally even the placebos can have spontaneous shrinkage.
00:08:38		We just don't see that in Tenosynovial giant cell tumours. But what happened in 2020 was interesting. What happened is, in June 2020 the EMA refused to approve Pexidartinib, even though the American FDA did approve this drug for the treatment of this form of sarcoma.
00:08:58		And the reasons that the EMA noted was this, a small improvement in symptoms, such as pain and the ability to use the joint, and I would say that that's somewhat questionable, it depends on just how much pain and how much disability the patient was in, but they also raised the question, it was not clear how long the effect lasts.

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		Well, you saw from the durability of the responses that also could be questioned, but most importantly they had some serious concerns about potentially life threatening effects and unpredictable effects of Pexidartinib toxicity on the liver.
00:09:31		And that is true, I think for one to use Pexidartinib one has to be cognisant of that. But our group's experience in the US has been that it is actually a drug that is fairly easy to use, and can be very important for treatment of patients with this Tenosynovial giant cell tumour. So again, we see differences in practice across the world, and that's what made 2020 a little confusing for sarcoma medical oncologists.
00:09:57		Well, 2020 had much more good news for GIST patients. Besides the approval of Avapritonib specifically for the PGDF receptor alpha mutant disease of GIST, we saw another new tyrosine kinase inhibitor approved by the US FDA in 2020, this drug called Ripretinib. And so for managing metastatic or recurrent or unresectable GIST, we've become used to the idea that those patients go on lifelong kinase inhibition therapy.
00:10:27		And essentially we've waited for mutations to arise, where we start with a imatinib, when a resistance comes up we certainly think about surgery, but if it's multifocal resistance you move to Sunitinib and then more resistance you move to Regorafenib. And now we have a fourth line option in the form of Ripretinib. I also want to emphasise that at each point of progression we always assess for the potential to resect clonal or a few oligoclonal sites of limited progressive disease to continue to get time for the patient out of whatever kinase inhibitor they are on.
00:11:03		Johnny Blay presented this in Tokyo in 2019 and it was published subsequently, you see this absolutely beautiful progression-free survival benefit with Ripretinib, statistically significant. And also an overall survival difference, which you'd hopefully expect with Ripretinib due to some statistical technical details. This is was only a nominal P value, and technically it could not be formally tested.
00:11:30		But the long and the short of it is that we now have an effective fourth line drug for GIST in 2020. Now, another lesson about how 2020 was not always clear and how it's not always easy to develop new drugs, let me show you the failure of Avapritinib to

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		demonstrate superiority and progression-free survival compared head-to-head to Regorafenib in third or fourth line GIST.
00:11:54		Remember, what you just saw with Ripretinib is Ripretinib compared to placebo, but Avapritinib had a higher bar to meet, it was compared to Regorafenib. We see no difference in progression-free survival. And interestingly, no difference in duration of responses. In fact Regorafenib had a slightly longer duration of response in previously treated GIST. And that's because by the time multiple mutations come up in GIST, you probably need a more broad spectrum coverage of kinase mutations.
00:12:26		Avapritinib is a very selective exon 17 KIT mutant drug, it is specific for exon 17, but these are polyclonal resistance mechanisms, and that's probably why it did not work, even at this dose in third or fourth line GIST. But that really raises the issue of whether we're simply playing this game called whack a mole, where you just have to wait for another mole to come up, and the model here is that those moles represents mutant subclones.
00:12:57		And in 2020, we all had to think about how cancer teaches us lessons about one other thing, think of how this relates to the evolution of SARS-CoV-2 or the COVID-19 virus across the world in different ways. So, we learn a lot from cancer about virology and virology has taught a lot about how cancer mutants come up.
00:13:17		2020 brought new hope, at least in the United States, with epithelioid sarcomas. We know that loss off INI1 in epithelioid sarcomas creates this dependency on the enzyme EZH2, and so a drug known as Tazemetostat can orally be available to selectively inhibit that. And Silvia Stacchiotti and her colleague Mrinal Gounder at Memorial Sloan-Kettering and many others participated in a study that led to the accelerated approval for epithelioid sarcomas of Tazemetostat.
00:13:49		I want to point out only a few patients have disease regression, but many patients have durable disease control. So, it's an interesting issue that needs more work so we can figure who are these patients who are lucky to get regression and who are the ones who get the long-term disease control. Still not

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		approved in Europe, but we'll see what happens as more research goes into this field.
00:14:13		And then finally, the immune system, 2020 brought new information about how immunotherapy can benefit sarcomas. Anti-PD-1 immune checkpoint inhibitors certainly work in a subset of these sarcoma subsets, undifferentiated pleomorphic, dedifferentiated liposarcomas, alveolar soft part and angiosarcomas of the scalp with extensive DNA signatures of solar damage.
00:14:37		But they don't work as well as they do in many other cancers, for other sarcomas, so we're seeing other research go on with combinations of DNA damaging chemotherapy in combination with radiation therapy to test whether this might improve the incidents of responses or the duration of benefit.
00:14:55		And then finally, 2020 continued to build on gene transfer technology to target synovial sarcomas and high grade myxoid liposarcomas with things like these adoptively transferred T cells that target NY-ESO-1, with beautiful work published by colleagues Sandra D'Angelo and Crystal Mackall and others. Up to 50% response rate, some of them very durable, moving into international trials with the cell therapy, and then others with a different type of cell therapy now targeting MAGE-A4 with SPEAR cells from Adaptimmune.
00:15:29		Brian van Tine presented this at ESMO 2019 again some durable responses with this technology as well. We're going to see a lot more about that in 2021. So, in summary, we see that sarcomas offer insights and hope for the precision therapy development that we so much need for our patients and sarcomas. We have to understand the key biochemical genetic and epigenetic drivers of different sarcomas to target them effectively.
00:15:56		And I cannot emphasise the importance of molecular diagnosis being key to optimally managing our patients. I would also say it's very difficult for practicing clinicians to stay current, there are so many new approaches and so many are so complicated that education is more important than ever. So, with that, I'd just like to say thank you for joining us for this webinar today and we'd be happy to help you with any of our expert centres in the European status, in the Asian status or

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		anywhere in the United States as well. So, thanks for you attention. Bye-bye.