Q&A

Speaker Key:

GD George Demetri

SB Sylvie Bonvalot

AD Angelo Paolo Dei Tos

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00:00:08	GD	So with those presentations, you see where we are from 2020. And 2021 looks like it's going to be even more promising, certainly as we get more vaccines into people, as we open up our research even more. But there are so many promising ways of approaching sarcomas. I think we're all pretty optimistic. Well, let's move to the quiz part. This is always the fun part. This is always the fun part. So what we have here are going to be some questions that my colleagues and I have pulled together for you.
00:00:39		Again, if you go out of full-screen mode, you'll be able to see the voting panels. So here we have the key concepts in a quiz. What I'll do is introduce the questions, and then you'll have 30 seconds to vote. During that time, I'll speak to my colleagues, Dr Bonvalot and Dr Dei Tos. Maybe we'll comment a bit on the questions, but they'll have 30 seconds to answer. So here we are. Now let us all teleport into the lovely City of Light of Paris, and we'll start with the first question.
00:01:15		Question 1, after STRASS 1, the preoperative versus no preoperative radiotherapy for primary retroperitoneal sarcoma, the first-line treatment per the results of this trial is preoperative radiotherapy, surgery alone with radiotherapy that might be discussed in well-differentiated liposarcoma and Grade 1 and Grade 2 dedifferentiated liposarcoma, surgery alone where radiotherapy alone may be discussed in leiomyosarcomas, or Option 4, neoadjuvant or preoperative chemotherapy.
00:01:55		So go ahead and vote. Which would you choose on the basis of the results of the STRASS trial? And while they're voting, Sylvie, do you have any other comments on that? Don't give the answer away just yet, but any other comments on this important trial that the Transatlantic Sarcoma Group did.
	SB	I'm waiting for the answers of the audience.

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	GD	That's what I was worried about, is that any comments might drive you and give it away. You're all such good test-takers, we don't want to influence that too much. So here are the answers.
00:02:37	SB	Yes, it's perfect. Clearly, leiomyosarcoma in STRASS do not benefit from this preoperative radiotherapy. And I think they shouldn't receive preoperative radiotherapy. And in the guidelines, they shouldn't receive radiotherapy.
00:03:02		And they could be included in STRASS 2 to know whether preoperative chemotherapy is beneficial or not. So the answer is clearly B. Radiotherapy is an option in low-grade liposarcoma, Grade 1, 2 dedifferentiated liposarcoma. It is an option.
00:03:29		It's because STRASS is a negative trial. So it's an option. It must be discussed in multidisciplinary board, because in some locations where you clearly know that the resection will be marginal and that resection is not possible in the case of recurrence, it may be discussed. But it is not standard of care. The standard today is surgery alone.
00:03:58		So it is an option which can be discussed when you do expect that the surgery will be marginal because of the location of the tumour. But it is really an option. It is not the standard of care.
	GD	Thank you so much. And, as always, Sylvie, you're an excellent educator, since 86% of people got that correct. So let's move to the next question relative to surgery.
00:04:30		But Question 2, according to the global, Europe, Asia, America, Consensus-Based Guideline 2020 for desmoid fibromatosis, the first-line strategy of managing a desmoid, apart from any patient with a complication is which of the following? Choose one.
00:04:59		Option 1, surgery alone. Option 2, radiotherapy alone. Option 3, active surveillance. Or Option 4, chemotherapy. What's the first-line approach? Go ahead and vote. And, again, Sylvie, we have 30 seconds to talk, but we don't want to give this one away. This is going to be interesting to see what people took away.
00:05:34		Here's how you voted. Any comments, Dr Bonvalot?
	AD	Not too bad.
	SB	So comment is that still 11% of the audience is in favour of surgery, which is normal, the standard of care. Because it is

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		very clear that nearly 75% of the patients regress spontaneously.
00:06:12		So it's a pity to operate on these patients, because they always have surgery which is a little bit mutilating, because the median size of this tumour is 5cm, so it's always a mutilating surgery. And in more than 50% of case, there is a spontaneous regression.
00:06:34		So that's the way active surveillance is standard of care now. If there is no complication, of course. Active surveillance is not... You do not see any more the patient. Active surveillance is to preform a CT scan or MRI, depending on the location, one month later and then three months.
00:06:57		And, of course, in case of progression, the patient must be discussed in the multidisciplinary tumour board to discuss between chemotherapy, surgery and sometimes radiotherapy. But, clearly, active surveillance is now the new standard of care.
	GD	Excellent. Thank you so much. We have a question we'll come back to later about desmoids. But let's move on for the moment to the rest of the quiz.
00:07:25		And we move now to Paolo Dei Tos's world of Italy, beautiful Italy. Question 3, what is the main clinical feature of BCOR rearranged sarcomas? Number 1, BCOR rearranged sarcomas are more aggressive than Ewing sarcoma. Option 2, BCOR rearranged are more aggressive than CIC or CIC-rearranged sarcomas.
00:07:52		Option 3, BCOR rearranged are less aggressive than either Ewing sarcoma or CIC-rearranged sarcomas. And Option 4, BCOR rearranged sarcomas are essentially the same aggressiveness as Ewing sarcoma and CIC-rearranged sarcomas. So choose one of these and go ahead and vote. You have 30 seconds.

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	GD	Here's what everybody says. What do you think, Paolo?
	AD	I think this is crazy, in a way. There is a caveat, of course. The number of cases that's been collected, it is in the range of couple of hundreds until now.
00:08:54		And, of course, George, this is a question that gets back to many medical oncologists. Because we know it does better, we know that the response to the conventional Ewing chemo is not perfect. So maybe, maybe there is room for thinking in the future of something different from this type of patients. The numbers, of course, makes it difficult to think of randomised trials or whatever. Maybe we need to think Bayesian and try to find a way to find what is the best way to treat these unfortunate people.
00:09:33	GD	I agree. I love the way you framed the question as well, because they're not BCOR rearranged Ewing-like sarcomas. That's an unfortunate phrase, and the sooner we get rid of that the better. So thank you for phrasing it that way. The next question from, again, Italy again. What of the following statements is correct? Choose the one that is correct.
00:09:59		Option 1, current WHO classification is based exclusively on molecular genetics. Option 2, the current WHO classification is based exclusively on morphologic findings. Number 3, the current WHO classification is based on morphology, immunohistochemistry and, when relevant, molecular genetics. And Number 4, the current WHO classification is based exclusively on methylation profile. Go ahead and vote.
00:10:33	AD	I admit it's a bit provocative questions, but then, in a way, it's also nice to underline what's going on in terms of evolution or classification schemes and what is the role of each techniques we are currently using to make more accurate diagnoses and to get more relevant predictive biomarkers also. Let's see what people think.
00:11:09		Well, we admit the question was quite busy, but this is important to say that of course WHO's changed significantly over the last 20 years. Now genetics is much far relevant than it was 20 years ago, and it is a good thing.
00:11:30		And just sharing some of the discussion we had while putting together a new classification, there is a concern because WHO

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		is valid for anywhere, any place in the world, but there are places in which, for example, fusion gene NGS testing is not available.
00:11:54		Still, I believe that we should try to make any effort in order to provide the patient, for example, a diagnosis with a specific level that includes specific genetic alterations. In those cases, we should need to prove the presence of the genetic alteration. And to make this, of course, this can be done in networks, can be done within cooperative groups.
00:12:24		So it's not necessary that any remote place gets access to a personal NGS platform, but they can easily share these cases with bigger centres, and they will get back the correct answer.
	DG	That's great, Paolo. Thank you so much. So now we move across the pond, and I think there's a very nice picture of Boston here. We need more meetings in Boston.
00:12:55		Avapritinib was approved in 2020 for what type of sarcoma? Number 1, rhabdomyosarcomas with MIC overexpression. Option 2, just with KIT mutations. Option 3, just with mutations of either KIT SDHB or PDGF receptor alpha. Or Option 4, just with certain PDGF receptor alpha mutations. Go ahead and vote on this.
00:13:32		And, by the way, if you have any other questions, feel free to put them through the other question box. I've got a couple of other questions here already, so feel free to have those come through. After we've done this quiz, we'll address your questions. Avapritinib.
00:13:53		So the correct answer is, indeed, D, just with certain PDGF receptor alpha mutations, the ones down in Exon 18, which is analogous to the KIT Exon 17 mutations. But it is not approved for anything else, certainly not approved for rhabdos. It didn't work formally enough compared to an active control with regorafenib and the GIST with the KIT mutations, although it does show up on some guidelines still, because it had some activity, just not enough to be better than regorafenib, because it's much more selective.
00:14:27		And it didn't get tested, really, in SDHB deficient GISTs. So good job for the 86%. And now we go to the next one. Last question of this quiz. Here we have, now, which of the following is false? This is one of those, one of these is false, the rest are true. Which of the following is false about NTRK fusions?

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00:14:56		Number 1, NTRK gene fusions are found in most infantile fibrosarcoma cases. Number 2, point mutations in NTRK genes do not predict for effectiveness of larotrectinib or entrectinib, but NTRK gene fusions do predict the effectiveness of those agents. Number 3, NTRK fusions should be sought in GIST without any mutations in the KIT, PDGFRA/BRAF or SDH subunit genes.
00:15:26		And Option 4, NTRK fusions are found in at least 50% of all sarcomas if you use the optimal technology to sequence the tumours. Which one of these four is false? Go ahead and vote.
00:16:11		And here's what you say. The correct answer is, indeed, D, NTRK fusions are not found in 50% of all sarcomas even if you use the optimal technology to sequence tumours or look at them. Paolo, what's your latest estimate, and what percent of sarcomas have an NTRK fusion?
	AD	Well, we are in the range of less than 1%. I would say 0.5%, something like that.
00:16:38	GD	Yes, that's what I would think as well. So for every hundred sarcomas you see, you probably will find one. So they're still rare even in sarcomas. But for many carcinomas, it's one-in-10,000. So they are somewhat enriched in sarcomas.
	AD	Sure.
	GD	About 20%, almost 20%, of patients, of people, sorry, folks, we're all pre-patients... But B intrigues me, because B is actually correct. Point mutations in NTRK genes do not predict for effectiveness. NTRK gene fusions do. It's only the fusions.
00:17:13		Now, with that having been said, perhaps those 20% were focused on the issue that Paolo Dei Tos mentioned, that a lot of gene fusions are not drivers. And, Paolo, I don't know if you want to comment on that. How do you really know if a gene fusion in NTRK is a driver or a passenger? Because you mentioned that paper about how most gene fusions are not drivers.
00:17:36	AD	Yes. Definitely, NTRK is a driver. You can look at what happens when, in a way, you try to target fusion, which is... The data you have generated is really amazing, so definitely I believe NTRK is a driver. As you mentioned, it's so much enriched in

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		sarcomas, but the big question is also how to get after those rare cancers.
00:18:04		Among the big killers, you may have had some NTRK fusion, which is in the range of 0.2. But, ethically, it would be wrong to leave those patients behind. So, in a way, as you also mentioned, there is a way to create the algorithm and try to go using immunohistochemistry as a screening, which, for example, for epithelial cancers it works pretty well, and then moving into molecular genetics, whenever we found a signal. Because it is a driver, and the drug seems to be really working great.
00:18:43	GD	Terrific.