Discussion to: An angiotensin system inhibitor (Losartan) potentiates anti-tumor efficacy of cisplatin in a murine model of non-small cell lung cancer

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Discussion to: An angiotensin system inhibitor (Losartan) potentiates anti-tumor efficacy of cisplatin in a murine model of non-small cell lung cancer

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Dr. Patricia Thistlethwaite (San Diego, CA):

Good morning. I'd like to thank Dr. Lanuti for a very nice presentation and for giving me the manuscript well in advance to this meeting. You talk about the association between the use of angiotensin system inhibitors. And survival in 3A lung cancer is very provocative. However, correlation does not necessarily mean causality. I have several questions. First, in the patients that you looked at where there was a survival advantage of them taking angiotensin system inhibitors, were there amplifications of the angiotensin type 1 receptor like you
showed in your genomic databases? And would you expect patients without amplifications to have a similar survival benefit?

Dr. Michael Lanuti (Boston, MA):

Yeah. A great question. And so, with regards to that analysis that we did for stage III patients, we did not harvest all those tumors or go back into the tumor bank. If you look at the expression of ATR1, we did do it on about 10 patients that had lung cancers. We didn't have the tumor beforehand, but there was increased expression of ATR1 receptor on those patients. We need to compare it to a control. And then if tumors did not have elevated expression, I wouldn't be able to tell you which direction we would go since we didn't really look at it in a steadfast way.

Dr. Thistlethwaite:

Thank you. Is there a specific drug or dosing regimen of an angiotensin system inhibitor that is needed to be clinically effective? For example, is it only needed at the time of cisplatin to potentiate the cisplatin response-- or just stopping it later, for example, abrogate the effect? And we also think of losartan as an arterial venous vasodilator. So maybe it's just delivering more drug to the tumor.

Dr. Lanuti:

Yeah. So, thank you for that question. I think that most of the-- so the patients that we looked at clinically in the exploratory phase which had stage III lung cancer, most of them were already on an ASI. And so, I couldn't tell you if they were off or on and whether the ASI contributed to the cancer-- or the ASI be part of the cancer eradication if you will with chemotherapy. So that's always the question we have is, if you're already on the drug, did it influence the tumor as it was growing, or did it help the chemotherapy more so upon multimodality therapy? And so, this notion of vasodilation as you mentioned, I do think that's part of it, although it's more than that. It's more than just vasodilation and getting drug to the tumor microenvironment. It is the capillaries and the disruptive capillaries in the tumor microenvironment somehow get normalized a little bit more so with losartan and ASIs, and perhaps that's part of the reason why there's better penetration of chemotherapy.

Dr. Thistlethwaite:

How do you reconcile your work with numerous published studies, one of them almost a million patients from Great Britain that suggest that people who were on ACE inhibitors have a higher incidence of lung cancer?
Dr. Lanuti:

Yeah. So that's definitely part of what we describe in the paper. I think there's evidence on both sides of that. That large study that you mentioned did suggest-- although the signal wasn't a huge signal, it was a small signal that perhaps the ASIs contributed to cancer. I guess we would say we're going to be careful about it. And probably it's one of those things that you're on it for a long time, so there's no real duration in that study that you mentioned. And perhaps in setting up these clinical experiments with humans it'll be a short duration.

Unidentified Speaker 1:

Maybe one more question then we're—

Dr. Thistlethwaite:

Yeah, that was my last question. Are you putting all of your 3A patients on losartan?

Dr. Lanuti:

Yeah. So, because there's been a paradigm shift in immunotherapy for 3As-- so we have to do all these experiments with immunotherapy now to be able to do that.

Dr. Thistlethwaite:

Thank you.

Unidentified Speaker 1:

Okay. A very quick question and one quick answer.

Unidentified Speaker 2:

Very nice work, Dr. Lanuti. Why do you think you see this effect in stage I and II patients? And if it's because of the EMT expression, then why not look at stage II but nodal-positive patients?

Dr. Lanuti:
So, I think it has something to do with the addition of chemotherapy. I think that traditionally the one and twos-- the twos get it on the backend. But I think that all the threes got induction therapy. And it appears to be that-- just like in the pancreatic data that showed-- it appears to be-- that has something to do with it. Neoadjuvant therapy is more potent if you will in the setting of losartan. Thanks.

Unidentified Speaker 1:

Okay. Thank you. Thank you, Mike.