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Highlights from the 13th International Congress of the Society for Melanoma Research: A Focus on Resistance

Narrator:
Welcome to CME on ReachMD. This segment, “Highlights from the 13th International Congress of the Society for Melanoma Research: : A Focus on Resistance”, is sponsored by Prova Education.
Your host is Dr. Matt Birnholz who welcomes Dr. Meenhard Herlyn, Professor at the Wistar Institute in Philadelphia, PA.
Dr. Birnholz has no relationship reported.
Dr. Herlyn has contracted research with Actelion, Ltd., Macrophage Therapeutics and Plexxikon.
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Dr. Birnholz:
This is CME on ReachMD, and I'm Dr. Matt Birnholz. With me today is Dr. Meenhard Herlyn, who joins our program to bring us updates from the 13th International Congress of the Society for Melanoma Research that took place recently in Boston, Massachusetts.

Dr. Herlyn, welcome to ReachMD.

Dr. Herlyn:
Thank you very much for inviting me.

Dr. Birnholz:
So, to start, there is increasing awareness that melanomas are among the most genetically diverse malignancies out there with up to thousands of mutations. You have obviously had a very prominent role in the founding and direction of SMR. Tell us what your perspective was on this conference this year. How do we approach therapeutic strategies that can accommodate or even take advantage of that many mutations?

Dr. Herlyn:
Yes, these many mutations really appear daunting. Melanoma is really the worst of all cancers, and sometimes there are only a few, meaning a few hundred mutations, but very often there are thousands or even ten thousands, and this appears to be a major issue when it comes to therapy. However, in recent years it is becoming clear that not all mutations are there to drive the tumor, so today we distinguish between drivers and passengers. And melanoma is not so different from other tumors that the number of driver mutations, those that push the transformation process and that push the cells from an early stage in malignancy to an advanced stage, that number is limited. It is not clear exactly, and it may differ between tumors, but it is anywhere between 3 and 5 mutations.

So, what do all those other mutations do? We don't have all the answers. However, through the immunological studies of the last year or two, it is becoming clear that melanoma has an advantage over other cancers because of these many mutations. Many of the genes, they actually code for them a mutated protein, and that gives the chance that these mutated peptides induce an immune response. And it is clear now that the more mutations there are in melanoma, the better the immune response is, and we can even now rebuild it in the laboratory, because if you irradiate melanocytes with ultraviolet light at the normal sunlight range, then we induce in those cells many, many mutations, so in melanoma it is most obvious that all the mutations came from the exposure to sunlight.

Dr. Birnholz:
Dr. Herlyn, why don't we focus for a bit on another apparent advantage of melanomas over some other cancers, and that is that melanomas seem to readily adapt to growth outside of the human host, such as in tissue culture or in these immunodeficient mice models that you mentioned. How do melanomas do this? Are there any major factors behind that?

Dr. Herlyn:
That is actually a very interesting question, and I have studied it for over 30 years. It's really, on the experimentalist's side, it's a great advantage. When you take out tumor, melanoma, from a patient and place it in culture, you have a good chance of growing them, and if you put them in an animal that has no immune system, then you even have a 95% chance of succeeding. It is really an incredible adaptation to any new environment, and we questioned ourselves. Melanomas are derived from melanocytes, and these are of neural crest origin. However, if you look closer how melanoma cells are able to adapt to a new environment, it's because they are very close to fibroblasts, to mesenchymal cells, as we say. And, actually, there's not a single marker for fibroblasts that is not expressed by melanoma cells. And at the same time, melanoma cells are so plastic in their behavior, how they move about in the tissues, what they do, how they can avoid any cell death, and if you look at... If they are in an area where there are very few blood vessels, of course you will have all the hypoxic machinery ranking up so that the blood vessels are being called in, but even if that is not happening immediately, they can form primitive blood vessels. And so it is this adaptation to normal cells of moving around through tissues that can even have many markers. More than 50% of the markers that you find on macrophages are also on melanoma cells, and even some of the checkpoints that T-cells have, you can find them on melanoma cells, so it is a quite remarkable stealthy behavior that these tumors have and that through that, in part at least, they escape the immune system, but they can also use all the tools that a normal cell has to move around in tissues. It's quite remarkable.

Dr. Birnholz:
That does sound remarkable. Why don't we turn to those checkpoints and talk a little bit about the MAP kinase or MAPK inhibitors, such as those for BRAF, MEK or ERK. What are the common characteristics of melanomas that respond to any of these inhibitors?

Dr. Herlyn:
Yes, that is the melanoma field about now 12, 13 years ago was extremely lucky that a group in England did a sequencing approach where they suddenly found that one of the members of this MAP kinase pathway, BRAF, has a point mutation, and through this point mutation, the gene is turned on in its activity all the time, and not just 2- or 3-fold but up to 800-fold activity, so the signals that the usual cell needs to activate this growth pathway or proliferation pathway in melanoma cells, they don't need the outside activation anymore because they are turned on on their own.

So, then the other big advance came that there were some really smart, little, biotech companies who developed a structure of this mutated protein, and based on this structure, they developed their first inhibitors. And with the MEK and ERK inhibitors, they are also mutated in some cases -- and we can come back to later in the discussion on resistance -- they are more rare. So, 50% of all melanomas have the BRAF mutation, and so as the BRAF inhibitors came on the market, we have wonderful new tools to treat those. These drugs are really effective, because if you have a BRAF-positive tumor, all cells within the tumor have the BRAF mutation. If you don't have a BRAF tumor, you still have an activation of this MAP kinase pathway. In a sense the cells are addicted to signal and to basically fire through this pathway. So, the problem comes now. If you fire through this pathway and try to block it, and since they are really needing it on the long term, not on the short term but on the long term for survival, they will do everything they can. The tumor cells will do everything, literally, to make sure they reactivate this pathway. And so there are now different mechanisms, and I can explain those very briefly.

Dr. Birnholz:
I'd love to do that, but I think to help set the stage for this concept of resistance, there's a point of clarification that we should make here, and that is that even if all melanoma cells within a BRAF positive tumor harbor that mutation such as for BRAF V600E, it seems that these mutant-specific drugs generally won't kill all the cells. Is that right?

Dr. Herlyn:
Yes, that is quite remarkable, and it is, similarly, if you use some good old chemotherapeutic drugs and you treat a tumor cell, you get 80, 90% killing. The same is if you use a BRAF inhibitor on a melanoma cell. You can get up to and the patients respond --most of them if not all of them respond -- but then you don't kill all cells, and that really, that is we call this intrinsic resistance, is a remarkable achievement by the tumor cells, and they do this by, that they let one small proportion of the cells go outside of the normal cell cycle turnover. So, we find in those tumors, in patients' tumors, or in experimental studies that there is a small 2 to 3 to 5% of tumors that are basically dormant for long periods of time.

If you come now with a drug that is specific for proliferating cells like chemotherapeutic drug or like the BRAF or MEK or ERK inhibitor, you don't hit them. And as these cells are hunkering down -- they go into so-called autophagy, meaning they live on their own -- they have a relatively high intrinsic metabolic activity, the mitochondrial metabolism is very active, but they don't grow, so it's very, very hard to reach them with any of these drugs.
And as you continue to treat the patient with any of these inhibitors, the cells manage to signal around that inhibition of BRAF or MEK or ERK, and then they develop what we call acquired resistance. So, there you have already a problem that any of these drugs that inhibit members of the MAP kinase pathway, they no longer are active in these cells and they have a general resistance, so you have to revert to a second-line therapy. And in these cases… And that's why it is so important for us to combine the MAP kinase inhibitors with immunotherapeutic drugs, because immunotherapy does not care whether a cell is proliferating or not. That's the biggest advantage for immunotherapy, is that it is independent of the growth cycle of the cell.

Dr. Birnholz:
So, when we combine the intrinsic resistance with the acquired resistance of these cells, do checkpoint inhibitors have an overall response rate that is lower than 50%? Are we talking 30 to 45%, or is it a little bit more generous than that?

Dr. Herlyn:
It is higher than that. The checkpoint inhibitors are really a godsend to the field because they give us the long-term responses that we didn't have with the MAP kinase inhibitors, so they are -- particularly, if you take the CTLA-4 inhibitors, those are giving you really new responses after often several months of treatment. PD-1 is much better as a target because we get a quicker response, but together, if we can harness both the signaling therapy together with the immunotherapy -- we know exactly how to do that -- then we can again make great additional strides to the current success rate in melanoma therapy.

Dr. Birnholz:
Now, Dr. Herlyn, the last area that I'd like to cover with you for this discussion today is the subject of tumor heterogeneity, which is a huge concern in melanoma therapy, but why is this such a pressing issue, and what therapeutic strategies aim to help address that?

Dr. Herlyn:
You know, melanoma is famous for its heterogeneity, and if you remove a tumor from a patient, you can see white areas and black areas, and so just from looking at tumors, you have always known that there was considerable heterogeneity. Then what is now coming with both immunotherapy as well as signaling therapies like the kinase inhibitors, that suddenly a single nodule will continue to grow, whereas all the other metastases may decline in their size, so some respond, and then individuals are totally resistant. And we don't know all the mechanisms, but it is clear that we first have to deal with the intrinsic resistance -- and I explained it before -- that these slow-cycling cells, these dormant cells that we have in every tumor are a challenge for signaling therapy.

In immunotherapy we have a not so dissimilar challenge, because those tumors that are expanding despite all the other tumors within one patient responding to the therapy, if you then look closer -- and this came out also very interestingly by some talks in the meeting -- the resistance to human tumors we find both in signaling therapies and in immunotherapies. In signaling therapies we talked about the existence of small subpopulations that then are escaping the initial therapy but can grow up and can come up and can form again a heterogeneous tumor later on as the tumor develops a so-called acquired resistance. In immunotherapy we find similar phenomenon in that the T-cells that are supposed to kill the tumor cells, and in the same patient also do it with some of the metastases but not with individual metastases, selected metastases, in those cases the T-cells are unable to infiltrate into the tumor. We don't know exactly all the mechanisms, why and how the tumor manages. Usually T-cells can go through any tissue. It's not the physical barriers. It is more a chemical barrier that the tumor is able to establish. For example, it produces growth factors and cytokines that the T-cells simply cannot tolerate, and so they do not move into this area. That is still a big problem. There are certainly, also, populations of T-cells and, in general, of lymphocytes that are not able to kill, so we have bad T-cells or we have no T-cells, and these two phenomenon together may lead to a heterogenous response to therapy.

Dr. Birnholz:
Before we wrap up, Dr. Herlyn, is there anything else you'd like to point out or reiterate that we didn't address here in this conversation?

Dr. Herlyn:
Melanoma, indeed, is a very heterogenous disease, not only within one tumor but also between tumors. What is coming now is that there are small subgroups of patients that have very unique mutations outside of the MAP kinase pathway that we discussed that can be targeted with drugs, and these drugs come from other tumors. For example, there are drugs that are used in ovarian cancer or in colon cancer, and suddenly in this specific 3%, 5% of melanoma patients, they may be very, very active if you use them appropriately, so we

have to now not just look for BRAF mutations if a patient's tumor is tested, but we have to broaden the spectrum so that we get a better picture of all the important genetic drivers of a disease.

And the second final point I want to make and I think that is most important, we have to find more routine ways to combine immunotherapy with targeted therapy, to take the strengths of each approach, and then I think we can again double the response rates of what we have now in melanoma. It's quite an exciting time, and it's really… Every year you go to these meetings; you see tremendous progress being made.

Dr. Birnholz:
Well, with that takeaway point, I very much want to thank my guest, Dr. Meenhard Herlyn, for joining us today to share insights on immunotherapy from the 13th International Congress of the Society for Melanoma Research.

Dr. Herlyn, it was great to have you with us today.

Dr. Herlyn:
Thank you very much.

Dr. Birnholz:
I'm Dr. Matt Birnholz inviting our audience to access this and other CME expert interviews on ReachMD where you can be part of the knowledge. Thank you for listening.

Narrator:
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