IGOR PUZANOV: [INAUDIBLE] drugs in development, I had to select some. So I was kind of looking hard, and then selected drugs from the categories which I think are promising, and these are my disclosures. And I would like to discuss, then, all the new classes of agents, enhance the immune response in patients, and also talk about precision therapy, actually. Edwin kind of made my talk a little easier, because without actually coordinating, we kind of selected similar drug, the AMG-510, which is the RAS-targeting agent.

So now, I'll go into the questions. The NKTR-214, or bempeg as it now called, is a pegylated form of which cytokine-- interleukin-15, interleukin-12, IL-2, or IL-10? And there is no winner really, so hopefully at the end, everybody will know, How do we move it forward? They might come in here and help me with that.

OK, perfect. So the second question is the AMG-510, as Edwin was discussing, showed the best activity in the patients with either melanoma with the BRAF mutation, or colorectal cancer with the BRAF mutation, or colorectal with the KRAS mutation, or the non-small cell lung cancer with a KRAS mutation. Very easy. Alright. So hopefully at the end, everybody will know the answer. Yeah, I'm kind of technically challenged, I guess.

Oh, perfect. And this one is two-fold. So the synthetic lethality concept refers to the situation where loss of either one gene which interact leaves the cell viable-- so if you hit one or the other, it's still alive. But however, if you actually hit both, the cell dies. And examples include gene pairs like ATM/ATR or BRCA and PARP and, of course, others. Is it true or false?

All right, we leading in the right direction here, so that's good. OK, perfect. So enhancing immune response in patients-- remember PD-1? You know, a lot of speakers who spoke about PD-1, and it's good. In some cancers, like melanoma, over 50% of patients are alive at five years, which is actually amazing result, and it's really amazing. But in some others, like the gynecologic cancers or the GI cancers, it is actually a distinct minority.

So what can we do? We can do a lot of different things, and there are trials for all of that. You know, targeting inhibitory signals, transferring T cells-- remember, it's Roswell, we have a pretty robust cell therapy program, actually. It's led by Dr. Odunsi, Dr. Koya, Dr. [INAUDIBLE] and we participate as the Phase 1 team as well, and these are important. We also try to enhance positive signals with either cytokines or the receptor agonists, and then of course, target microenvironment.

You know, all these cells live in the environment, and the environment affects them, including things like stroma. In the tumors like pancreatic cancer, the stroma plays an amazing role. And of course, other immune cells-- not just the T killer cells. Everybody knows about mCD8-positive, but also the T regulatory cells, suppressor cells, myeloid suppressor cells, macrophages, and we'll talk about some of these categories.

You know, there is a lot of approvals for checkpoints. The immune system is very complicated. Those slides actually are available to you, so I will not go to the detail, and believe me, this is a simplified version of how it actually works. The drug I wanted to talk about is called NKTR-214, and what it is it's actually a pegylated interleukin-2. All of us are aware of interleukin-2, which is a cytokine approved based on the NCI trials in 90's in both melanoma and kidney cancer, which actually could cure about 5 to 8% of patients who had to be highly selected. And this is one of the tries to make this interleukin-2 available to patients without having to be in an intensive care unit to get their treatment.

And the idea is to use the interleukin-2 to multiply the tumor infiltrating lymphocytes-- the ones which can kill the tumor-- and have the right phenotypes. So basically, what they do-- they pegylate the interleukin. Think about interleukin as a molecule, and the pegylation is just like a binder, where you bind a lot of these molecules together-- on average, 6. And as they kind of get into the patient's body, they start to releasing themselves, and when it's just like, two of them connected, they seem to actually stimulate these killer cells, without stimulating the suppressor cells. And the preclinical data actually suggest that.

So the study we are actually doing here at Roswell, as elsewhere, is very simple. Started with a single agent first, now with combination with nivolumab, i.e. the cytokine interleukin-2. The hypothesis is it will enhance these nivolumab activity. And we went through the dose escalation, and now we are actually studying different arms as part of what we call a basket approach, where you simply [INAUDIBLE] different arms with different tumor types, let's say melanoma, lung cancer, bladder cancer, other cancers-- and you treat them with your combination.

And as you can see, a promising activity is seen in melanoma, and based on the data, in a [INAUDIBLE] the response rate actually initially was about 70%, then it decreased a little bit. But still, the trial crossed the pre-specified boundary. We now have a Phase 3 trial in melanoma untreated patients, which will randomize patients to nivolumab versus nivolumab and the NKTR-214. Of course, it will take a long time to finish the trial, similar to the neoadjuvant IPI+NIVO. But potentially, the hope is it will be a little bit less toxic than IPI+NIVO, and have the same durability.

However, because we do not have any randomized data as yet, we cannot say that this will be the outcome. That's why the trial has to be done. In renal cancer, it also looks promising. It's a front line therapy.

However, based on [INAUDIBLE] George's data he presented earlier today, you now know that the axitinib and brolucizumab or axitinib avelumab really showed amazing results in the front line of patients with renal cell carcinoma. And my prediction is it would be very difficult to move the combination in front line renal cell carcinoma. So the development in some of the tumor types, you know, we used to have a hard time treating. It's now very difficult because lots of patients benefit from the drugs which already are available, but in urothelial carcinoma, this may be different.

As you know from the urothelial data presented, there is activity with PD-1, there is activity with the FGFR inhibitor. But at the same time, you know there is no clear-cut combination-- maybe with the lenvatinib combination, eventually it will show superiority. But right now, we don't have the data, so I think there is an opportunity to move this combination into the urothelial cancer, and it's actually going there.

And just to show you the drug, its benefit at this point is that, at least in the patients which were now treated, you are looking at the CD8 T cells, and you look at how they proliferate after the patient was exposed to the drug. And you can see that actually, there is like a [INAUDIBLE] tenfold amplification of those cells, especially in patients with a complete response and with a partial response. So we have to wait for the randomized data, but it is something which I think has a promise.

We, of course, are engaged in other trials using cytokines, such as other modified interleukin-2 cytokines, such as also IL-15-like cytokines and IL-10, because again, the cytokines are the proteins which are made in our bodies, and they kind of serve to augment the immune system in a targeted way. And it's possible they actually will be able to augment the response we obtained with the anti-PD-1 agents.

The other mechanism-- which, actually, in this sheet I already mentioned-- in lymphoma of the macrophage targeting approach was also tested in solid tumors. So this is that 5FD drug, anti-CD47 antibody. And remember, the CD47 is the do not eat me receptor, and the tumors like to express it to protect themselves from macrophages and being engulfed by the macrophages and destroyed. So if you block that, you potentially may see improved responses.

Unlike in liquid tumors, this approach-- as you can see from the [INAUDIBLE] plot from the Phase 1-- has not been out completely in solid tumors. You can see there are a few responses in ovarian cancer, fallopian tube cancer, there was one lymphoma patient actually involved. But this is not the same as you see in liquid tumors. So the question is, will the anti-DC47 show its affect mostly in things like lymphoma or MDS, or will there be a way to actually modify or combine it to actually harness that in solid tumors. Or is it simply that in solid tumors, the same mechanism doesn't apply, and thus this is not a very promising approach?

We are [INAUDIBLE] trial with this drug in MDS and AML. Dr. Eunice Wang will be leading the trial, so within the next three months, the drug will be available. And at least from the recent New England Journal paper, which Dr. [INAUDIBLE] cited, it looks like it's pretty active agents in the patients with hematologic malignancies. So the immunotherapy is you know for solid tumor patients a are promising new field. However, there are obstacles to be overcome-- you know, the patient selection, the biomarkers, the side effect management, and logistics are still difficult to navigate.

The cytokine-like molecules, we here at Roswell think are promising, so we tried to have a full portfolio of the drugs, including that NKTR-214 bempeg drug, which is the pegylated form of the interleukin-2, and all the multiple other immuno-oncology drugs, which all of them are going into trials. And it's really difficult to see how all these combinations will be tested. I just listed five, but there is actually over 3,000 trials of the checkpoint inhibitor plus something else.

And you can imagine with even current numbers of patients, it is virtually impossible to finish them all. So we have to be very selective, and we actually try to have a good selection system to really select the ones which may be more promising than the others. But of course, remember, out of the five drugs in Phase 1, 4.5 will fail. So it's only 1 out of 5 to 10 drugs which will actually make it all the way to approval and being useful to our patients. And the CD47-- I think it's a promising drug, but it's really interesting how it acts differently in a liquid versus the solid tumors.

You know, targeting old targets-- you know, we discussed that in multiple presentations today. I just wanted to talk about the RAS-mutant cancers, because remember, it's about 15 to 20% of all cancers have some sort of a RAS mutation or dysregulation, and it's really important target. So when we started working at Vanderbilt a long time ago, we started working on the BRAF inhibitors.

But initially, we were trying to target the mutated BRAF. In a melanoma, it's like 45%, 8% mutations in other tumor types. We have seen some interesting data from crystals in gallbladder cancer. But the idea of this pan-RAF inhibitor is to not just block the BRAF mutation, but also block the other components of the BRAF gene, as well as potentially the KRAS and NRAS mutants, so kind of be more useful in a sense that it will hit broader tumor portfolio.

And so the Phase 1 study was done. It was reasonably well tolerated. You can see the grade 3 toxicities were only in about 5% of patients, so that actually is pretty good. And it was mostly rash or skin changes, which is not surprising to anybody who has ever worked with a BRAF targeted drug, such as being vemorafenib or cobimetinib or encorafenib that you can get some rash. That's why we actually use them with the MEK inhibitor as the combination.

And you can see there were actually responses, and when you look on the right side of the table, you'll see there were responses not just in the G12C, but there were responses in the NRAS, in the NRAS Q61K, in the Q61R, in the G12V. So this drug potentially can actually go broader than some other drugs in development, and may actually increase our portfolio for these hard-to-treat cancers where we are running out of options, and they do not respond to immunotherapy, and they actually have a whole host of these mutations.

And like I said, across all solid tumor types, these mutations are approximately 20%, so this is not actually a small group. And you can imagine one can design a basket approach, where you go in for the approval across histologies-- you know, histologically agnostic-- similar to the approach with the NKTR fusions with larotrectinib or entrectinib. And also, those responses were actually reasonably durable. You can see responses going on up to two years, close to one year, and that, actually, for targeted therapy, is a reasonably good durability for these responses. So of course, more work needs to be required, but this is one of the drugs which I think will be moving forward and the serve us well in these mutated cancers.

The combination is going to be developed with a MEK inhibitor because this is, after all, a BRAF inhibitor, as well as in the NRAS melanoma in combination with atezolizumab, trying to target the 17 to 20% of melanomas which have no such mutation. The AMG-510 510-- actually Edwin mentioned-- this is the first in the class KRAS inhibitor specific for that one mutation G12C.

Why is that? Because the molecule is difficult to target, so they have to be very specific and use something which will actually [INAUDIBLE] that molecule in a non-excited state. And the study was done with multiple dose escalations. The toxicity was actually well tolerated. As you can see, none of the 35 patients reported dose limiting toxicities, severe toxicities, or grade 4 life-threatening toxicities. So this is an interesting drug currently in clinical trials, including here, in patients with lung cancer.

We do have that cohort open. You heard from [INAUDIBLE] that actually the colorectal was just closed for analysis, but it may reopen soon, because that's what happens in early phase trials-- there is a lot of changes at all times. And you can see that over 50% of patients had a partial response-- out of 10, so small numbers. They seem to be holding with more updates coming out.

And in colorectal patients, it's mostly stable disease, so colorectals do not respond as well, and it's possible that there is, despite having the same mutation, that there will be a similar scenario to the BRAF mutations, where in melanoma or lung cancers, if you target BRAF, it will be better the same way lung will be better with the RAS mutation, and colorectal may actually need a partner to fully see the benefit from the targeting.

The duration actually is good. You can see that the responses are actually going on for over a half year, and that the PRs are mostly seen in the non-small cell lung cancer. So it's a novel, first in class, irreversible inhibitor, has a good PK profile, and has the activity in KRAS G12C in non-small cell lung cancer. So we are moving forward in that cohort, and enrollment is ongoing.

Last [INAUDIBLE] concept, some synthetic lethality. Going back to olaparib, and a PARP inhibitor, it is very similar to what was being discussed here before. Remember, if you use PARP inhibitor, the better responses in the gynecological cancers or in GI cancers were seen in tumors, which actually harbor a mutation or defect in DNA repair, and that's the BRCA mutated patients and others. So the idea is, if you have two genes and they are all fine, the cell is well-- if you have one mutation but the other one is actually fine, you still actually can go on and be alive as a cell.

The other way, as well-- but if you get a mutation or hits in both of these genes, the cell will die quickly. And you don't have to target both of these genes with a drug. You can simply select types of tumors which already harbor one of the mutations, or one of the defects, and then simply come with one drug, and they will actually potentiate each other and the inhibitors you have here, BRCA and PARP, and ATM/ATR, and that's what it's called, synthetic lethal.

So this new agent, the BAY1895344, is a selective and potent ATR inhibitor. And what is ATR? You have it actually there. The ATR/ATM-- these are key regulators in response to DNA damage and the replication stress, promoting repair and survival. So the cells are being damaged all the time, but if that machinery is intact, it's going to be fixed, and the cell will go on. However, if that machinery is not intact, the cell is supposed to die. And the ATR inhibition in cancer cells, which already have defect in the DNA repair machinery, actually should induce rapid cell death, and that's what we call the synthetic lethality.

And you can see that in preclinical studies, the nice, flat curve-- that's actually the inhibitor, the BAY drug, in the cells which actually harbored the appropriate mutation. So preclinically the drug looks really promising. And that gamma-H2AX, you know, it's a test where you are actually looking at the cells, and you look at the breaks, how many breaks the cell has in its DNA. And you are simply counting them, and the more breaks you have, the more gamma-H2AX foci you see, the more damaged the cell is. So you can see, with the new drug, the gamma-H2AX is much higher than with the placebo-- i.e. you damaged the cell real well.

And of course, now you have to go to the Phase 1, and the Phase 1 was being done. And most adverse events were anemia, neutropenia, and fatigue. And the one thing this table tells you is it was not an easy development, because they actually went from 5 to 10 to 20 to 40 patients, and then they go to 80, and they develop like, two dose limiting toxicities out of the three patients, which is actually a lot. So they tried some intermittent schedule at 60 but they failed, so they went to 40. So the one thing I would actually caution-- you know, how really tolerable this drug will be when it goes to wider testing, and hopefully to usage.

The pharmacodynamics-- you know, the damage was there, so it actually is doing what it's supposed to do, and you can see responses. So that's all you can see at this point with the responses with this drug. And you can see, with appropriate schedule, they see partial responses, which is typical for targeted agents. There are not that many complete responses, typically, with targeted agents.

But they are durable, again, going over one year, as you can see. So this is something of promise, and again, you can see that the hard-to-target patients in those tumors-- urothelial [INAUDIBLE], clear cell endometrial, ovarian-- you know, these are all typical cancers which do not have good immunotherapy options, and they did have actually damage to their DNA machinery, and they did have ongoing responses.

So you know, the interaction will require a complementary genomic protein-level and functional assays of pathway proficiency, because the real issue is, like we have discussed, how you select the right patient with the right mutation, especially in an environment where sometimes the insurance will not necessarily pay for the test you actually need to find that patient for which the drug is appropriate. So we really have to work together, not just on the research side, but the practice side and the management side, to actually be able to really get that done. Because if you do not put the dots together, all that science will actually come in vain, because that science will not be applicable to patients, because the patients will not get tested. And if they don't get tested, you will not find them, and that would be a real shame.

So in conclusion, these novel targeted agents are promising. They target new, previously non-druggable targets like the KRAS. You know, people didn't think it can be targeted, and now with the AMG-510 510, we actually are able to target it. And we are now able to tease out some of the synthetic lethality and some of these defects, and select them to actually develop drugs across different tumor types, which hopefully will then be used, and we will be treating cancer not based just on the tissue of origin, but based on the molecular changes in that particular cancer.

And with that, I would like to thank the patients' families who actually devote their lives to clinical trials, and they suffer from cancer. And of course, I'm proud to lead our investigators and a group of dedicated nurses, pharmacists here at Roswell in the Phase 1 drug development, early phase program. Thank you very much, and now I will give you the post-test.

So now the question is, the NKTR-214, the first drug I mentioned, is a pegylated form of which cytokine? You have four choices. It's 15, 12, 2, or 10. And it's 2, yes. Thank you. I mastered it actually at the end.

So the question number 2, you know, that was my test, and I'm doing the test in a different way. So the AMG-510, the drug showed the best activity in either melanoma with BRAF, colorectal with BRAF, colorectal with KRAS, or non-small cell lung cancer with the KRAS G12C mutation. You have over 50%. And it's the non-small cell lung cancer with the KRAS. That's the right answer.

And the last one is, what is the concept of the synthetic lethality? Does it refer to the situation where the loss of either one gene which interact leaves the cell viable-- however, if both are lost, the cell dies. Examples include genes pairs ATM/ATR or BRCA/PARP. Is it true or is it false?

And it's true. Thank you very much. That's all I had, and I thank everyone for coming and making this a great Post-ASCO Review again.