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Understanding the Biological and Clinical Rationale for PARP Inhibitor Combinations as Potential Treatment for Prostate Cancer

Announcer:

Welcome to CME on ReachMD. This activity, titled “Understanding the Biological and Clinical Rationale for PARP Inhibitor Combination as Potential Treatment for Prostate Cancer,” is provided by Access Medical Education and is supported by an independent medical education grant from Janssen Biotech Incorporated, administered by Janssen Scientific Affairs, LLC. This replay of a live broadcast focuses on clinical rationale for PARP inhibitor combinations as potential treatment for prostate cancer. And now, here’s Dr. Agarwal.

Dr. Agarwal:

Hello. Welcome to the talk, and I’ll be talking about the PARP inhibitor combinations for treatment with our patients with metastatic castrate-resistant prostate cancer. Next slide.

These are the disclaimers, and these are my conflict of interest over my lifetime. I have none. No honorarium last 2 years, but I decided to include all of my consultancy fee and honorarium I have received in my lifetime. This includes the research monies to my institution. Next?

I’ll be talking about the metastatic CRPC and the role of PARP inhibitors as monotherapy briefly, and after that I’ll move towards discussing PARP inhibitor combinations, which have been a pretty shifting area, if you will, of conversation, and presentations in the meetings and publications in the last one and a half years. And we’ll discuss about some cases after that. Next slide.

So we’ll be discussing the PARP inhibitor combinations and their safety data and the efficacy data in patients with metastatic CRPC. Next slide.

So we know that multiple therapeutic targets have emerged in the last 5 years, especially, against which many of the drugs have been developed and are being tested in multiple phase 3 trials. I’m talking about phase 3, including capivasertib for P-10 deficient tumors PARP inhibitors for base tumors with homologous recombination repair mutations, and there are many more targets.

Today, we’ll be focusing on DNA repair pathways, and the mutations involving those pathways. Next?

So this is a snapshot of how PARP inhibitors work. So PARP is a poly-ADP ribose polymerase enzyme which recognizes a defect or a break in the DNA, and quickly repairs the break in the signal strength by a process known as base excision repair, following which the break is repaired and DNA multiplication continues without any problems, and it doesn’t affect cell survival. Now, let’s look at this part of the picture. Where we have inhibited PARP, and its DNA repair is not repaired – DNA break is not repaired by the PARP. However, at the next step, when the single strand break becomes double strand break with the next replication of the single strand, this portion – this double strand break is quickly repaired by homologous recombination repair. And the cell survives. However, in patients who have deficiency in homologous recombination repair, so they are deficient in multiple proteins and – or have mutation in the genes, coding for those proteins, such as BRCA1, BRCA2, and many others, if they are deficient deficiency in homologous recombination repair and we inhibit their PARP, then there is no rescue mechanism. And the cell, and the DNA tries to heal itself or repair itself, but it is ul – it ul – by a ineffective mechanism, not – known as nonhomologous enjoining, which is not really efficient and it leads to accumulation of double-strand breaks, which leads to cell death. Now in case of some other PARP inhibitors, such as talazoparib and many of some of the

PARP inhibitors as well, to varying degree the PARP can be trapped, regardless of other mechanisms, on this repair site, on this break site, which leads to replication fork instability and can lead to cell death. So this is a snapshot of how PARP works, and PARP inhibitors work. Next slide.

This was a similar publication about 10 years ago which showed 11-12% patients harbor these defects - homologous recombination repair mutations – in their germline base. Next slide.

We also reported from more than 3,000 patients that a significant number of patients also harbor DNA repair mutations in these cancer cells, known as somatic mutations, as opposed to germline mutations, I showed in the previous slide. So if you combine all these mutations, we see approximately 25% patients with MCRPC, or I would say metastatic prostate cancer, harboring these mutations. So there's a large number of patients who are harboring these mutations and are potential – potentially patients for DNA repair or PARP inhibitors, with target DNA repair. Next slide.

So let's look at the monotherapy data, also PARP inhibitors when used as monotherapy. So I'll quickly summarize the data in this regard. Next slide.

So we saw that TOPARP-A trial. It was the first trial testing a PARP inhibitor, olaparib, in – in a pro – in patients with prostate cancer, and showed that patients who had biomarker positivity, meaning they had DNA repair mutations, they had much longer out – better ou – radiographic progression-free survival compared to patients who did not have DNA repair mutations. Then a validation happened with the PROfound phase 3 trial, where we saw olaparib convincingly showing superiority over the control arm of physician choice of novel hormonal therapy in patients who were progressing on a novel hormonal therapy. And this list – this – this trial led to approval of olaparib in our patients who have DNA repair mutations and they are – they have the least progression in a nor – novel hormonal therapy. And then we saw data with rucaparib. Very similar data. Single agent, and please note that rucaparib is currently approved for patients who have BRCA1, BRCA2 alterations, and they have had disease progression or therapy on novel hormonal therapy and chemotherapy with docetaxel. TRITON-3 data showed that PARP inhibitor rucaparib was superior to docetaxel chemotherapy and novel hormonal therapy in patients with BRCA1 and BRCA2 mutations, but we have not seen the change in the label yet. And then we saw two phase 2 trials – single arm studies – showing niraparib and talazoparib, showing efficiency as far as patients with BRCA1 and BRCA2 alterations or concerns, and they also showed benefit in other mutations, but here is the data for BRCA1 and BRCA2 altered patients, 8 month and 11 month of progression-free survival with these two drugs. Next slide.

So what is the rationale for combining PARP inhibitor with novel hormonal therapy. So can we move this PARP inhibition to upfront setting? So first-line MCRPC setting. Next slide.

So here is the simplified version, based on the preclinical rationale – preclinical data – which suggests that there could be synergy between PARP inhibitor and novel hormonal therapy. So, to put it simply, when prostate cancer cells are targeted by novel hormonal therapy – so when we are inhibiting that AR – the PARP gets up-regulated to rescue prostate cancer cells. On the other side, when we inhibit PARP, that leads to down-regulation of androgen receptor, because it seems to be dependent on PARP for this action. So, there seem to be quite an interdependency, if you will, of cross-talk between the DNA repair pathway, or PARP, and the AR pathway. And this was based on these rationale. The trials were designed. The first trial was Study 8. Next slide.

…which was published in 2018, about 5 years ago. This was a small trial – 150 patient – progressing on docetaxel chemotherapy in MCRPC setting. No previous novel hormonal therapy exposure was allowed, and patients were randomized to olaparib plus abiraterone versus abiraterone. Next slide.

And we saw that patients benefited with the abiraterone plus olaparib combination, regardless of whether they had homologous recombination repair mutations or not. So we see benefit in both HRR mutation-positive, and HRR mutation-negative patients, although we can see here that patients who have HRR mutation-positivity, they tend to have better efficacy with the combination. And these results led to multiple phase 3 trials. Next slide.

And we can see here that these trials are the PROPEL trial, MAGNITUDE trial, TALAPRO-2 trial, which all have been published, and the CASPAR trial which is ongoing. There's a common theme among all these trials. These are all in first-line MCRPC setting. They are combining abiraterone or enzalutamide with a PARP inhibitor, in case of – versus abiraterone or talazoparib in the control arm. In case of propellant magnitude, the PARP inhibitors are olaparib and niraparib with abiraterone. For TALAPRO-2, it's the talazoparib with enzalutamide. And the ongoing CASPAR trial is using the combination of enzalutamide with rucaparib. So even though there are very similar trials, in the – as far as metastatic CRPC setting is concerned – the design, there are subtle differences in their design in this study population. So let's look at the data from these trials. Next slide.

So, this was the design of the PROPEL trial, which is randomizing patients with these two arms in front of you right now. Radiographic progression-free survival is the primary endpoint, and overall survival is a key secondary endpoint. Please note that PROPEL trial

recruited patients – all-comer patients – and did not do any, an analysis or prospective analysis for presence or absence of HRR mutations before. They went back and looked at who had mutations, or who did not. Also, the HRR status - homologous recombination repair mutation status – was not used in these as a stratification factor for randomization. So this was a major highlight of our design. Next slide.

The baseline patient characteristics show that patients were evenly balanced between the two arms, as far as median PF is concerned, or site of metastasis is concerned, or HRR status is concerned. Next slide.

And please note that PROPEL trial included patients who were tested by CTDNA as well as tumor tissue. So when we saw the results presented by Dr. Fred Saad in the GU ASCO 2022, we saw 34% reduction in risk of progression or death. So this risk of progression or death is included in the radiographic progression-free survival endpoint. But death doesn't mean overall survival here, and you can see here there was a – quite a difference in the radiographic progression-free survival with olaparib with abiraterone versus abiraterone only. There was an 8-month difference.

This is very similar to what we have seen before in the phase 2 trial. Next slide.

If we look at the subgroup efficacy, in this forest plot the combination seemed to be superior in pretty much all subgroup of patients, regardless of whether they received docetaxel chemotherapy in the castration-sensitive state, or they had HRR mutation present or not, with the caveat that patients who had HRR mutations had much higher level of benefit, with a hazard ratio of 0.50. Patients who did not have HRR mutations – the hazard ratio for benefit was 0.76. But all – all of the patients – all patients seemed to be benefiting. Next slide.

The response rates were also superior with the combination. Next.

If we look at time to progression on subsequent therapy this is a – this endpoint is considered a continuum to the overall survival, so we first see radiographic progression-free survival, then we see time to progression on next therapy, and then we see overall survival – that's the ultimate endpoint. So if you look at the continuation of these endpoints, all seem to be benefiting of favorable – favoring the combination of abiraterone plus olaparib. Next slide.

The overall survival data were immature at the time of initial presentation, although trends were favoring the combination. Next.

If we look at the side effects, I'd like to take a minute to discuss the side effects of PARP inhibitors in general. The hematologic side effects and the gastrointestinal side effects are the class effect. Pretty much all PARP inhibitors have these side effects. And, I would like to bring your attention to the fact that this is an MCRPC population. Anemia is present in a large number of patients at baseline in this patient population. Accordingly, we see worsening of these side effects. So, patients have double upgrade, 3-4 anemia. some other PARP inhibitors are associated with thrombocytopenia. But most of these occur within the first 3-4 months. So as long as – and they don't occur in all patients. So it is very important to start the PARP inhibitor dose at the standard dose, and then follow these patients closely – say every 15 days – with laboratory data. And, to rec – to recognize which patients are going to develop grade 3 or 4 toxicities. And then only they'd use those in those patients. If we do that, most of these patients are able to tolerate PARP inhibitor quite well, after that initial 2 to 4 month period. We can also see that nausea, vomiting, diarrhea are also quite common with PARP inhibitors, but these side effects are not consistently present at the same frequency on all PARP inhibitors.

Some PARP inhibitors have more hematologic toxicity and less GI side effects, and some PARP inhibitors have some unique side effects, such as hypertension, or neuropathy – and I'll show you those data in a moment. But the bottom line is, all these side effects are easily manageable, and patients can be conservatively treated for pretty much all these side effects, and only a very small number of patients have to discontinue PARP inhibitors for these side effects. So with that discussion, I will continue to show you there are side effects of these PARP inhibitors in a more succinct fashion, with the same message. Next slide, please.

We always worry about cardiovascular events, especially when we saw those events happening in this smaller trial of Study-8, with olaparib with abiraterone in a more heavily-treated patients. And we did not see, actually, a major incidence of cardiac failure or arterial thromboembolic events. In this trial, actually, there was no higher incidence of thromboe - thromboembolic events, comprising heart rates – involving heart rates, in this trial. There were numerically higher ve – venous thromboembolic events, but we also want to remember that these patients were on the combination for longer time – 8 month longer. as far as radiographic progression-free survival is concerned, it was longer with abiraterone/olaparib arm, so this is not time-adjusted incidence. So we can see, yes, thromboembolic events are higher in the veins, and it is possibly because these patients were undergoing CT scans every 3 months so a lot of incidental thromboembolic events were likely being diagnosed in these patients. And we all know the oncologists are very well versed with thromboembolic events and how to treat them. With the novel agents, it is very much more easy to treat these patients without having to do PTI – PT-INR on a regular basis. Next slide.

So overall safety profile of olaparib was quite favorable to the combination. We can see here, as I've said before, if you look at the discontinuation of olaparib plus – versus placebo in the combination versus control arm, 13.8% patients conti – discontinued olaparib, 7.85 patients discontinued placebo, and the likely part, it was a blinded trial, so investigators were thinking it was likely because of olaparib. But if you deduct the incidence of discontinuation of – because of placebo, we are seeing improved fashion, olaparib was being discontinued in about 8% patients or less. So, most patients seem to be tolerating olaparib pretty well. Next slide.

And the quality of life – which I think is the sum of efficacy and toxicity – was maintained with the combination, so no concerns here. Next slide.

So PROPEL investigators concluded that benefit was present, regardless of HRR status, and overall survival trends were favorable, and quality of life was maintained. Next slide.

We saw the overall survival data being updated. It is for the final overall survival data, and even though there was a strong trend of about 8 month improvement in overall survival, it did not meet the prespecified criteria for statistical significance. So we did not see statistically significant improvement in overall survival, but in my experience, this was for the first time the overall survival reached the 40-month mark, in the first-line MCRPC setting. So, definitely an encouraging news for our patients. Next slide.

So, we saw that FDA approved olaparib with abiraterone for – for patients with MCRPC who harbor BRCA1 and BRCA2 mutations, regardless of which line of MCRPC it is. So first-line, second-line, third-line – didn't specify. The level doesn't say – label doesn't say first-line, actually. And why only BRCA1 and BRCA2? And I think a few issues, which I've heard, is that there was no prospective assessment of the homologous recombination repair mutations, and they were not used as a stratification factor in randomization, thus making the trial less vigorous than what you would expect, so FDA decided to – ODAC and FDA decided to approve the drug for BRCA1 and BRCA2 patients. So now we have abiraterone plus olaparib combination available for MCRPC patients who have not been – sorry, who have not had disease progression on ANHT, and who are candidate for abiraterone. So anybody who is a candidate for abiraterone and harbor these mutations – they are potentially candidate for treatment with abiraterone plus olaparib. Next slide.

So let's look at the MAGNITUDE trial. So MAGNITUDE trial was another phase 3 trial, with a different combination, as we can see here. And, there were actually 2 trials happening in 1 trial. So the MAGNITUDE investigators – Dr. Kim Chi and team – decided to have 2 distinct groups of patients. And they were homologous recombination repair mutated patients, so patients who are HRR positivity, and patients who did not have HRR positivity. And all of them had prospective tissue testing done, and these patients were randomized to the combination arm versus the control arm of abiraterone. Please note that in the HRR negative patients, the accrual was halted after 200 patients, because investigators felt, based on mostly PSA progression, that the combination is not effective. They did not necessarily halted the accrual in this cohort in the biomarker-negative cohort based on radiographic progression. So, this trial stopped here, for HRR-negative patients, and we'll not be talking about these patient population in this trial, from now onwards. Now, HRR positive patients – so radiographic progression-free survival was a primary endpoint. Next slide.

If we look at the HRR negative patients, we didn't see benefit, as I just said, so we will just not discuss about this HRR negative cohort. Next slide.

If we look at the HRR positive patients we can see here that patients were evenly distributed. Most of the mutations – because this is a randomized trial, there was an even distribution of hemoglobin patients with low hemoglobin, or if you look at other prognostic factors such as lactate dehydrogenase, presence of visceral metastasis baseline PSA – all seem to be equally distributed in these 2 arms. Next slide.

If we look at the primary endpoint of radiographic progression-free survival the primary endpoint was RPFS by central review, and it favored the combination arm. There was a 6-month improvement with abiraterone plus niraparib versus abiraterone. Next slide.

We see that all HRR positive patients, if you go beyond BRCA1 AND BRCA2, if you look at all HRR patients in this trial, there was a 4-month improvement in, um radiographic progression-free survival, with a 25% reduction in risk for progression, with the combination versus abiraterone. Next?

If we look at the subgroup analysis, this forest plot tells you that all subgroups seem to be benefiting in the HRR positive patient group. Next slide please?

If we look at overall survival data, we don't see any detriment of the overall survival with the combination. The data are immature right now, but we don't see any – any difference, so far. Next slide, please?

If we look at the adverse events, we again see the same class effect – anemia, thrombocytopenia – but, the median relative dose intensity was quite high in the combination arm. Only if we look at the discontinuation because of niraparib or placebo, we are seeing 10.8% or 4.7% discontinuation, in the niraparib or placebo – so which basically means, in my interpretation, that about 5% patients – 5-

6% patients were discontinuing niraparib because of side effects. Please note that niraparib dose was reduced by 33% because of side effects, when it was combined with abiraterone. So we already are dealing with a reduced of niraparib in this trial, and that seemed to be pretty well-tolerated, while maintaining efficacy. Next slide.

If we look at the side effects, we see anemia, thrombocytopenia, neutropenia are common side effects.

Grade 3 side effects are not as common as grade 1 or 2, but they all respond to the dose reduction in a timely fashion, and as I said, most of the dose reduction happened in first 3, 4 months. And as long as we can reduce the dose in a timely fashion, patients seem to be tolerating well, as we saw that only 5% patients had to discontinue niraparib because of dose – because of toxicities. Hypertension and cardiovascular side effects seem to be a unique aspect of niraparib, especially grade 3 hypertension, but we all know – I know the viewer here is an experienced group of oncology providers, so hypertension can be easily managed in the clinic but this seems to be a somewhat more unique side effect – or more exclusive side effect of niraparib. Next slide.

So, to conclude, MAGNITUDE trial showed benefit of the combination in HRR positive patients, and BRCA1 and BRCA2 patients tend to have more benefit over other HRR positive patients. Next slide.

So if we look at the comparison of these 2 st – trials, and of course, across-the-trial comparisons are not ideal but we all are doctors, providers. We see our patients, and we are trying to see which combination to use. I think whenever we are using abiraterone, and patient is harboring one of those mutations, we definitely have to keep in mind that now, the olaparib plus abiraterone and nirapa – plus – niraparib plus abiraterone combinations are available now for these patients, and they can be used. although, PROPEL base combinations seem to have an edge over the MAGNITUDE a – MAGNITUDE-based combination. But as I said, none of these patients were allowed to be exposed to abiraterone in the metastatic castration-sensitive prostate cancer setting. In the MAGNITUDE trial, a brief duration of exposure to abiraterone was allowed – up to 4 months of exposure to abiraterone was allowed. So I'm not sure that the difference in patient population could have resulted in slightly diminished efficacy with the combination of abiraterone plus niraparib, but as I said, I'm just showing it for the sake of discussion, and not for use in the clinic. next slide. Let's look at the TALAPRO-2 data.

So TALAPRO-2 trial was a third trial – was a third trial in this setting, using the novel combination of enzalutamide plus talazoparib versus enzalutamide. Primary endpoint was radiographic progression-free survival by independent radiology assessment, and there were 2 components of TALAPRO-2 trial. The first component – 800 patients – were all-come-aboard patients. So, they did not have to have HRR mutations, with a big difference from the PROPEL trial. All these patients had to have prospective tissue testing done, before they enrolled in the trial. In fact, 100% patients had prospective tissue testing done. And second, HRR status was a stratification factor in the randomization.

And stratification factor basically makes sure that the given variable is evenly distributed in both arms, and there is no over-representation of one of these factors in one arm, just by chance. Then, there was a second component of TALAPRO-2 trial, which include – which focused on HRR positive patients, and that included 169 patients from the first cohort, and 230 patients – so total 400 patients, 399 patients to be precise – who had HRR mutations. So I'll first discuss the results of the all-comer patient population. Next slide.

As we can see, the baseline disease characteristics and demographics were similar. It was a randomized trial. This is what we expect. Next slide.

100% patients had tumor tissue testing done, and in addition, about – a small number of patients also had circulating tumor DNA testing. But 100% patients had tumor tissue testing done before they enrolled in the trial. And not surprisingly, we saw the most common mutations are the ones we always knew from our previous studies – BRCA2, CDK12, ATM, CHEK2, BRCA1, and some other co – uncommon – relatively uncommon mutations. Next slide.

So let's look at the primary endpoints. First, there was a 40 – 37% reduction in risk of progression or death with accommodation in all-comer population. Next slide.

It seems – the accommodations seem to be benefiting regardless of Gleason score, denovo disease, HRR status, prior docetaxel or abiraterone, given in castration-sensitive setting. In fact, with the small – that we had a small sample size, patients who received these drugs seem to be benefiting quite well with the combination arm. patients with HRR mutations seem to be benefiting, but who do not have mutation also seem to be benefiting, as I will show you in a more elaborate fashion in a second. Next slide.

If we look at the radiographic progression-free survival in patients who were HRR deficient, so any homologous recombination permutations, there was a 55% reduction in risk of progression on that. It's quite remarkable to see this kind of benefit with a combination.

Now on next slide, I will show you the HRR negative patient by prospective tumor tissue testing. So these patients were – did not have

any HRR deficiency, by prospective tumor tissue testing, which is considered gold standard for testing. And even in those patients, we see 34% reduction in risk of progression or death, with the combination arm. Next.

Overall survivor data are immature right now, with only 31% maturity, so we cannot say much about the overall survival. But at least we don't see any downward trend, and it's seen to be favorable to the combination arm. Next slide.

If we look at time to PSA progression, there was a 10-month improvement in PSA progression with the combination, versus enzalutamide. Next slide.

If we look at the time to chemotherapy, which is a very meaningful endpoint to our patients, or time to progression on next subsequent therapy, they all seem to be favoring the combination. Next.

If we look at response rates, complete response was present in 37% patients with the combination, and only 18% patients in the – with the enzalutamide. And please note that BRCA2 patients were only 5%, or 5.6%, so complete responses are happening in patients way beyond BRCA2, or BRCA1 mutations. Next slide.

If we look at the side effects, as I said, anemia is a hallmark of MCRPC. So 49% patients had grade 1 or 2 anemia at baseline. Now grade 2 anemia 9 gram percent percent. And this trial allowed, actually, patients who could have up to grade 2 anemia at a hemoglobin of 9 gram percent, to enroll on the trial. So almost half of the patients had grade 1 or 2 anemia. Once they started the treatment, after a median duration of 3.3 months, 46% patients developed grade 3 or 4 anemia. And grade 3 – hemoglobin of 8 gram percent. So, many of these patients required a 1 point drop in hemoglobin to reach the grade 3 level. However, protocol mandated dose reduction or transfusion, once hemoglobin reached grade 3, so these patients underwent protocol – protocol-mandated dose reduction, and after that they seem to be tolerating talazoparib quite well, because only 8.3% patients decreased or discontinued talazoparib due to anemia. And, the median relative dose intensity of talazoparib remained more than 80% in this trial. So what does data tell me? That hematologic side effects seem to be more common with tala – talazoparib. They mostly occur in first 3-4 months, and recognition of those grade 3-4 side effects is important because they do pretty well after dose reduction. And first, looks like most of them only had to decrease – decrease the dose by one level, because the median relative dose intensity is quite high. We all – also see one more unique, or different aspect of talazoparib, that gastrointes – intestines, or GI side effects, don't seem to be as common with talazoparib. And in my view, nausea, vomiting and diarrhea and other GI side effects seem to be more associated with quality of life issues, versus these hematologic side effects, which can be easily managed by dose reduction.

Regardless, the common message here is, recognition of side effects is important early on, and they – most patients can be managed very conservatively, symptomatically, without discontinuing the PARP inhibitor in vast majority of patients. Next slide.

I'll go to the and these were again summary of adverse events. pulmonary embolism, as we have discussed in the past, were reported in 2.5% patients versus 0.7% patients, and please remember, these patients were on the combination for longer time, and they were getting CT scans every 3 months, so a lot of incidental pulmonary embolisms were likely diagnosed with – in these trials, be – just because they were – patients were getting CT scans. I think this was good for the patients, because they could promptly start treatment with anticoagulants without those pulmonary embolism become – becoming severe. Next slide.

Uh, you can see quality of life data favored the combination arm. There was a significant delay in deterioration of quality of life as reported by the patients in the combination therapy, versus enzalutamide alone. Next slide. (Pause) Next slide.

Now let's look at those 399 patients who had DNA repair defects. So, this was a second part of the TALAPRO-2 trial, which we just presented in ASCO meeting. Dr. Karim Fizazi was the presenter on the podium, and he showed that. Next slide.

The demographics were evenly balanced between the two arms. Next slide.

There was a remarkable improvement in radiographic progression-free survival, with a 55% reduction in risk of progression or death with the combination arm. Next slide.

All subset of multiple other gene subsets seem to be benefiting. Fortunately to me, this was a pleasant surprise. The CDK12 patients – and CDK12 is a common mutation – it is, I think among the top 3 most common mutations in this category, in our patients. So BRCA2, ATM and, CDK12. In this trial, CDK12 seemed to be more common that the ATM mutation, and we can see here that hazard ratio seemed to be quite favorable. There was a 50% reduction in risk of progression or death in the CDK12-mutated patients with the combination arm. We also see PALB2 mutation patients to be benefiting, and please note that these are very small subgroups, and they were not powered for independent analysis. So – but it's good to see that transfer favoring the combination arm.

Next slide.

If we look at the overall survival data, I think this is a pretty strong trend favoring the combination arm. there was a – with this immature

data, we already see a – quite a strong trend with a 31% reduction in risk of progression or death, although confidence interval has dropped 1, so it's not significant yet. But I have no doubt, looking at these trends, that we will see significant overall survival benefit, hopefully in the near future, with the combination. Next slide.

We can see, time to PSF progression was 27 – 17 months delayed. So, it was 28.6 months with the combination arm, 11 months in the control arm. And this tells us another – gives us another message. If you look at 11 months PSF progression-free survival with enzalutamide, that tells us how aggressively the disease is behaving in patients with HRR positivity. Just for your quick recollection, the PREVAIL trial, which led to approval of enzalutamide in first-line MCRPC setting, the PFS was 21 months with enzalutamide alone. So this tells us how aggressive disease is in this patient population. Next slide.

Time to cytotoxic chemotherapy, time to disease progression, other subsequent therapies – all favored the combination arm. Next slide.

These are the summary of adverse events. There were no cases of MDS or AML. Pulmonary embolism was reported in 2% patients in the combination arm and 1% patients in the enzalutamide arm. And we know that patients who are on the combination arm, they were on treatment for much longer than the enzalutamide arm. Next slide.

So in this slide, we can see that 55.6% patients had grade 1 or 2 anemia at baseline. This again tells us how aggressive the disease is, in MCRPC setting when these patients have HRR mutations. 55.6% have – patients have grade 1 or 2 anemia, but again, the median duration of onset of anemia was 3 months, so as long as we can recognize anemia and decrease the dose promptly, only 4% patients discontinued talazoparib due to anemia. So I think prompt recognition, frequent follow-up early on is important in these patients. Next slide.

Again, quality of life strongly favored in the combination arm in this patient population. Next slide.

So, please go back to the previous slide. So, based on these data, only yesterday FDA has approved the combination of enzalutamide plus talazoparib for patients with MCRPC with any HRR alterations. So that's a new happening, which happened just less than 24 hours ago. And now, our patients have one more combination available, as long as they have MCRPC with any HRR mutations. And they did not specify label dosing, specify line of therapy, so my – my interpretation is any time I'm using enzalutamide in our patients, and they have HRR mutations, we ought to be thinking about the enzalutamide plus talazoparib combination. Next slide.

So, this story is not going to end here. These combinations are moving to hormone-sensitive setting. Next slide.

Uh, as we can see, several new combinations are being tested in combination with lutetium, radium 223, immunotherapy, VEGF-targeted therapy. So I'm sure we'll see ma – more data coming up, in combination with PARP inhibitors. Next slide.

So we'll be asking multiple questions in the future. I'll probably defer these questions to our question-answer session. Next slide.

So I want to show you this slide in next one minute, and I'll go to question-answer session. Many people ask me that most patients have received or have progressed on a novel hormonal therapy by the time they reach MCRPC setting – first-line MCRPC setting. And, I'd like to dis – respectfully – disagree with that, because most common way for prostate cancer to present in not de novo metastatic CSPC. Most common way to present is localized prostate cancer. And, vast majority of patients are treated with surgery or radiation or both, and then if they are unfortunate to have recurrence of disease, which happens in 30-40% patients, they are not treated with NHT. They are treated with intermittent androgen deprivation therapy, which transitions to continuous androgen deprivation therapy, and the time comes when PSS stops rising on continuous androgen deprivation therapy and at that point of time, if you do a conventional scan – a PSM or PET scan – you'll find metastatic disease in vast majority of these patients. When they are progressing on – PSS progressing on continuous Lupron or continuous androgen deprivation therapy. So MVO CRPC state has literally been ex – replaced by the MCRPC state, as identified by PSM or PET scan or conventional scan. And these are the majority of patients, leading to MCRPC. We also know that a significant number of patients do not receive NHT in the metastatic CSPC setting. We just showed the data in ASCO meetings. 35-40% patients did not – never – had never received any intensified therapy. 10-15% patients had received only docetaxel chemotherapy in last 6 years, and 35-40% patients had received ARPI in last 2 or 3 years, and before.

So based on this, even in this setting you see a significant – we expect significant number of patients developing MCRPC without disease progression on a NHT. I have several patients who are exceptional responders to ADT plus a NHT, and they are doing well. PS is undetectable, and they decide to take a break from NHT after being on NHT for 3-4 years. So when they have disease progression, they remain candidate for treatment with NHT. And anytime they remain candidate for treatment with NHT, they are candidate for treatment with these combinations if we have HRR deficiency.

And last group is the locally advanced prostate cancer. The STAMPEDE trial recently showed that they will benefit with radiation plus ADT plus abiraterone for 2 years. And most of these patients who receive this intensified ADT for 2 years for locally advanced prostate cancer, in association with radiation therapy, they're rarely PSA, and when they develop PSA recurrence, or PSA rise, most of them will

have suppressed testosterone, and we do the scan, we'll see metastatic disease. So in my – I would argue that many of the patients will still see – at least for next 5-7 years, maybe longer alot of patients who are developing MCRPC without disease progression on a NHT. Next slide.

We also need to remember that many patients – we lose half of the patients for disease progression, when they have disease progression for any line. This was available data from Dan George and team, published 3 years ago. And next slide.

We updated the data with higher number of patients – like 10,000 patients in first-line setting. Only 5,000 patients received second line therapy. Only 2,400 patients received third line therapy. So if we have therapy available up front, we should be using it. So intensification helps, whether it is metastatic hormone sensitive setting, or it is metastatic CRPC setting, intensification of ADT helps. Because if we do not intensify, and leave it for a particular drug to second or third line setting, we lose our patients to disease. With that, I will open the forum to question and answer. Thank you very much. Next slide, please.

So, and first question is, should we offer PARP inhibitor to those patients that MRCPC with BRCA1 and BRCA2 alterations only? Answer is likely not, because only yesterday, FDA has approved enzalutamide plus talazoparib for patients with MCRPC with multiple other HRR mutations. So, we have that option available. So, answer is no. Yes, we should be offering BRCA1 and BRCA2 to patients. These are combinations, but now we saw that many of the patients could be eligible.

Next question is: Should PARP, in combination with novel hormonal therapy, be offered in men with first-line MCRPC setting, regardless of HRR mutations? We don't have the approval for HRR-negative patients, so if we have approval down the line, we'll discuss that, but for now we don't have the approval.

Uh, third question. Should PARP inhibitor, in combination with NHT, be offered in first-line MCRPC setting regardless of prior receipt of NHT in the first line, or in the MCSPC setting? This is a brilliant question. When you say receipt, what do you mean by receipt? If patients ha – unless patients have not progressed on a NHT, what do we do in our practice? So if I see MCRPC patient who is progressing – PSA is rising – after having received abiraterone for 2 years, in the context of radiation therapy and ADT for locally advanced prostate cancer, and 3 years after, patient is progressing – PSA is rising – should I, should we be offering them abiraterone or enzalutamide? Answer is we should be, because they are not really progressed on a NHT. So answer is yes as long as they have not progressed on a NHT, we can offer the combination. We – we can even argue that many patients discontinue first NHT for side effects. one NHT can be discontinued because of hypertension, or hyperkalemia without disease progression. Will I now be using enzalutamide for those patients? Yes, I'll be using enzalutamide. If my patient, who enrolled on TITAN trial – we conducted TITAN trial and reported the results for – 4 years ago now – and many patients – please remember, 67% patients will achieve a PSA of 0.2, and the median survival is close to 6-7 years. Many patients don't wan – may not want to continue the NHT for entire duration of 5-6 years. Many will take a break after 3 years, or 4 years. Although we don't have data, but that's happening in real world. So, when they have disease progression, wouldn't you offer another NHT? Answer is yes, I will. So my take is very simple on this – when you should offer this combination. As long as patients have BRCA1 and BRCA2 mutations for the abiraterone-based combination, or as long as they have any HRR mutation in first-line MCRPC, and you are contemplating using enzalutamide, you can use talazoparib in those patients who have HRR mutations. So similarly, if I'm using abiraterone in the first-line MCRPC setting, and the patient has BRCA1 and BRCA2 mutations, I should be strongly considering adding olaparib to abiraterone combination – abiraterone backbone. So I'll keep it simple – if you are going to use enzalutamide in MCRPC setting, in a patient who have homologous recombination repair deficiency, I'll strongly consider adding talazoparib. Next slide. sorry, next question.

Given the potential of metal toxicity, should the – should there be a fixed duration of treatment with PARP inhibitor, who continue to respond to PARP inhibitor? And for this, we don't have the data to limit the duration of PARP inhibitor. Like we don't have the data to limit the duration of immune checkpoint inhibitors yet. But we all use our medical judgment, we discuss with the patient, we go with patient's wishes.

So I think on an ad hoc basis, we can consider that, but we shouldn't be doing this on a regular basis because the disease is quite aggressive in these patients, and they should be treated aggressively. Next question. Do we have any more questions? I think with that, I think we still have 5 minutes. Oh, there are 2 more questions. Sorry.

Based on the current imaging evidence supporting a combined approach with PARP inhibitor, can you provide a stop line summary of the most impactful clinical activity takeaway and defining factors among these combination trials? This is a great question, and I will summarize this in the following manner: So first of all, as I said, anyone in the first-line MCRPC setting where we are contemplating using abiraterone or talaz – or enzalutamide, and the patients have HRR mutations for the talazoparib combination, or BRCA1-BRCA2 for the abiraterone-based combination, we should strongly consider these combinations. Now, what is my experience? My experience is these patients will require frequent monitoring for the laboratory data. They can do the labs locally. They don't have to come to the cancer center. And if – not all patients will develop grade 3-4 anemia or hematologic toxicity. So if they develop grade 3-4 anemia,

reduce the dose by one dose, and they will do fine. The – dose discontinuation because of hematologic toxicity is extremely uncommon. Less than 10% patients have to discontinue. The dose intensity is very common with PARP inhibitors. So we should never decrease the dose up front, until there are contraindications to full dosing, and I cannot think of many. We have to beg – start the patient with full dose, monitor them closely, and reduce the dose. I send every patient with antinausea medicines when I prescribe them PARP inhibitors. Nausea and vomiting are best prevented than controlled and treated. Once nausea cycle starts, patient have – patient cannot take the pill. If they take the pill, they have vomiting, that I cannot keep down the pills, so I think the best place to prevent nausea – even with grade 1 nausea, we should be very aggressive with antinausea medications. Other than that, I will refrain from comparing these trials head-to-head, because they are different patient populations. What I think I was – I hope I was able to show you, how convincing the data is – data are, favoring the combination in HRR positive patients. When we saw in the TALAPRO-2 trial, there was a 17-month delay in PSF progression on a – based on a 11-month with enzalutamide alone. That's quite meaningful to our patients. What we saw with the abiraterone/niraparib combination in BRCA2-BRCA1 patients – the data are very compelling. So I think we should be keeping in mind that whether we are starting abiraterone or enzalutamide, in those patients – in MCRPC setting – where they have these mutations, we should strongly consider the combination arm. Please do not leave it to next line or third line setting, because we lose half of the patients when they have disease progression.

And when – next question. Are you all concerned about potential for cumulative toxicities when looking at combined modality treatment.

Every drug has toxicity. Every combination has toxicity. Surgery and radiation have toxicities. But we are dealing with a lethal disease. We are dealing with a disease which has a median overall survival – in the enzalutamide arm is still hovering around 35, 36 months, despite all the recent developments. And a progressive disease has more side effects than all medicines combined together, so enzalutamide-talazoparib combination together cannot – cannot match the toxicity of a progressive prostate cancer. So when we are talking about life and death, I would say, yes I'm worried about toxicity, but I will be aggressive in managing those toxicity, and not – and will try my best, and my most emphasis or focus is on controlling the disease

What message would you give the community oncologists about the treatment of MCRPC with PARP inhibitor combination strategies? I would say, again, the same message. Anyone, really any patient, where you are contemplating using abiraterone or enzalutamide in a metastatic CRPC setting, I think we should be strongly considering the PARP inhibitor combinations, if they have underlying mutations for which those PARP inhibitors are approved. Please do not leave it to second or third line setting, or in my view – that is my practice – I won't let – if I have a drug available, intensification regimen available up front, I will use intensification regimen. I will not leave it to third or fourth line settings, because we know intensification works for metastatic hormone-sensitive setting. We know now that intensification works with metastatic CRPC setting, and we lose half of the patients every time disease progress. So let's not worry about leaving the drug to the third or fourth line setting. And that's my message for you today. Thank you so much for your kind attention.

Announcer:

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