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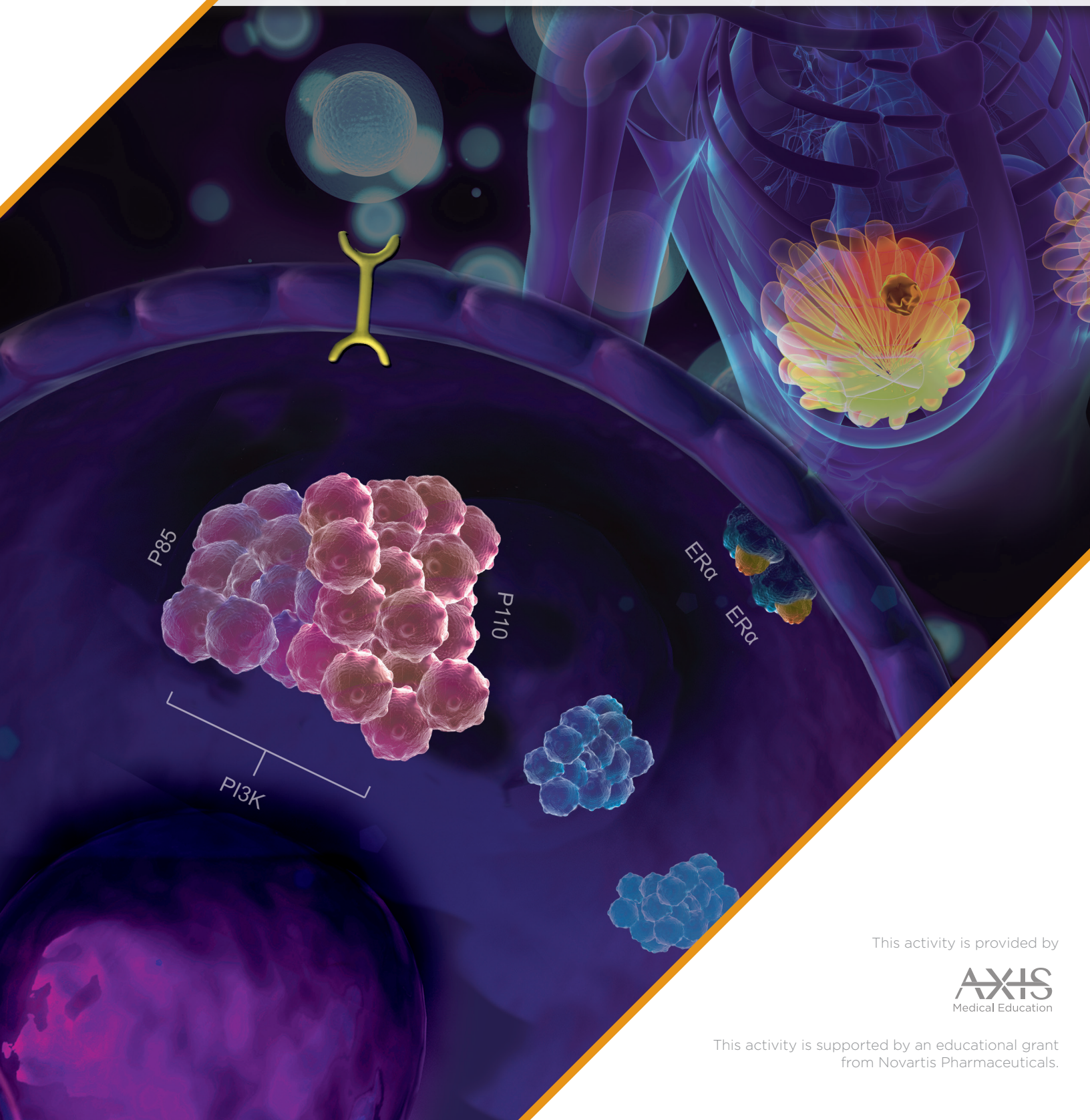
HR+/HER2-Negative Breast Cancer:

Revolutions in Precision Medicine With PI3K Inhibitors

This transcript has been edited for style and clarity and includes all slides from the presentation.



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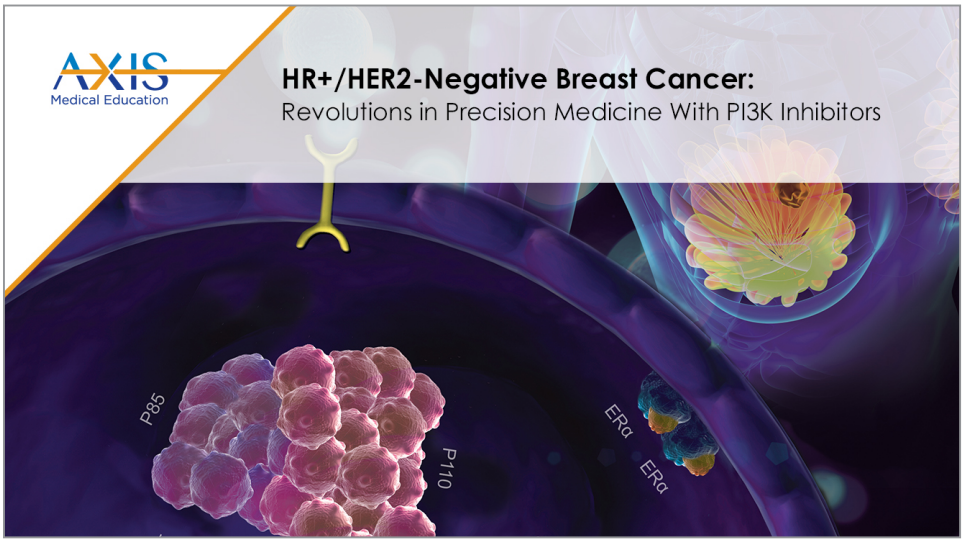
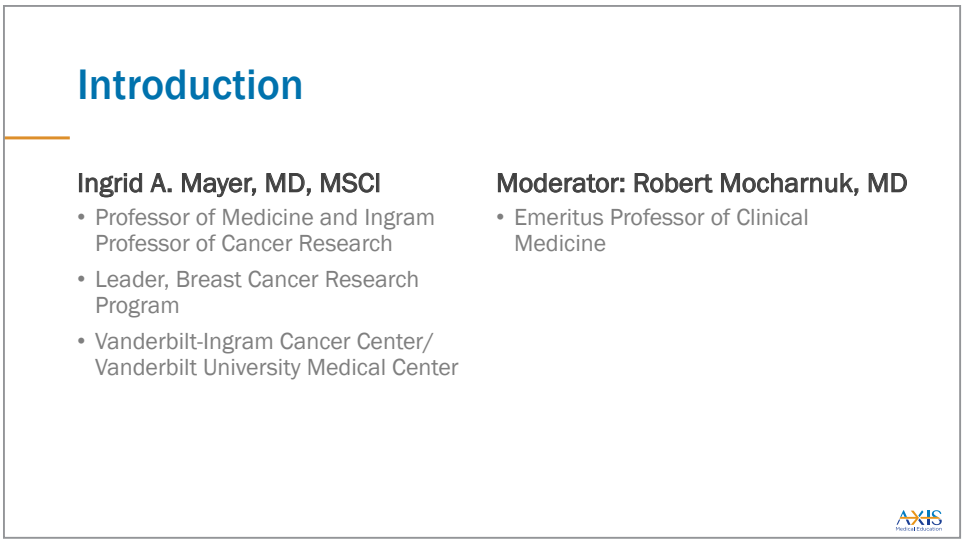
HR+/HER2-Negative Breast Cancer: Revolutions in Precision Medicine With PI3K Inhibitors

Ingrid A. Mayer, MD



Robert Mocharnuk, MD: Hello, and welcome to this educational activity, HR+/HER2-Negative Breast Cancer: Revolutions in Precision Medicine With PI3 Kinase Inhibitors.



I am Dr. Robert Mocharnuk, Emeritus Professor of Clinical Medicine. And I am joined today by Dr. Ingrid Mayer, Professor of Medicine and Ingram Professor of Cancer Research at Vanderbilt University Medical Center in Nashville, Tennessee.

DISCLAIMER

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Learning Objectives

Upon completion of this activity, participants should be better able to:

- Describe the PI3K pathway, and the significance of the *PIK3CA* mutations in HR+/HER2− breast cancer
- Analyze data supporting the use of PI3K inhibitor treatment strategies for HR+/HER2− advanced or metastatic breast cancer
- Discuss the important of precision medicine and genomic testing to identify patients with *PIK3CA* mutations who would benefit from treatment with a PI3K inhibitor

- Here are the learning objectives for this activity. Today we will review the most recent clinical data and provide expert insights on phosphoinositide-3 (PI3) kinase inhibitors for the treatment of hormone receptor–positive/human epidermal growth factor receptor 2 (HER2)–negative advanced or metastatic breast cancer.

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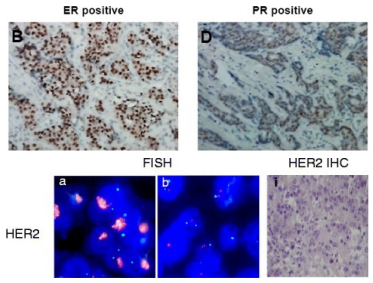
Would You Agree That We Are Finally Entering an Era of Precision Medicine for Advanced/Metastatic Breast Cancer Beyond HER2 Testing?

▶ Would you agree that we are finally entering an era of precision medicine for advanced metastatic breast cancer beyond HER2 testing?

Precision Oncology in Breast Cancer: Where Are We?

- BRACAnalysis®
- Oncotype DX®
- Breast Cancer Index
- MammaPrint®
- EndoPredict
- PAM50/Prosigna®
- FoundationOne® CDx
- Tempus
- Caris Life Sciences
- Guardant360



ER, estrogen receptor; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PR, progesterone receptor.

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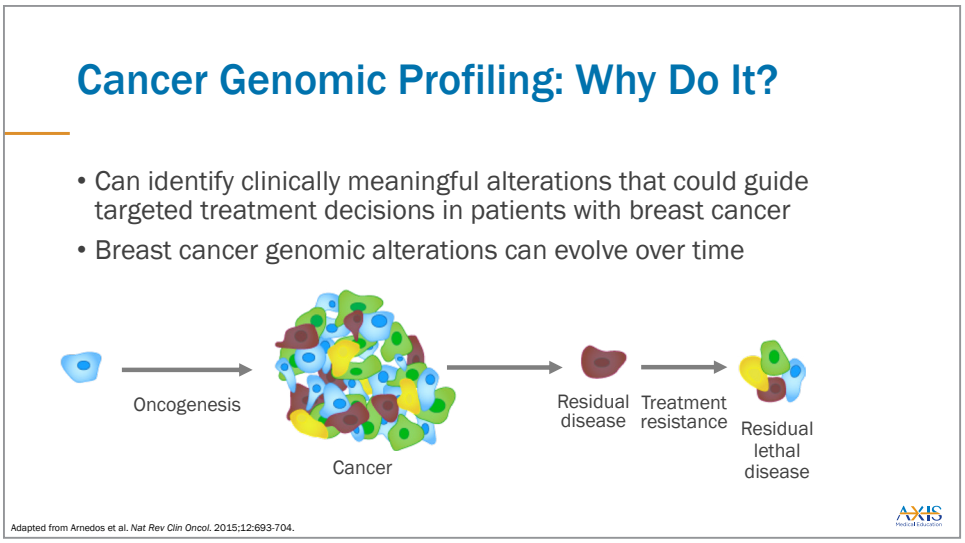
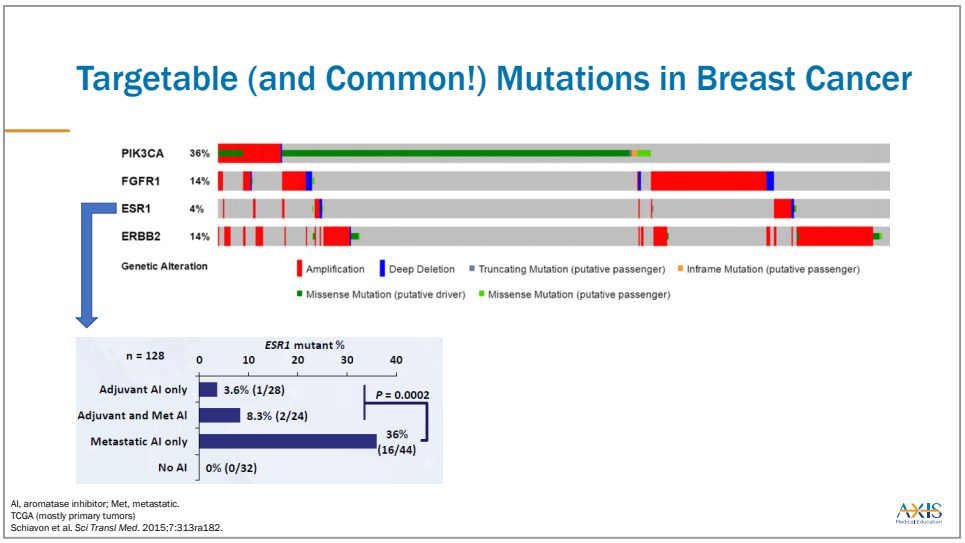
▶ **Ingrid A. Mayer, MD:** Good morning, and thank you for having me here today. I certainly agree with that. I think right now we are definitely in an era where precision oncology has permeated oncology, in general, and certainly breast cancer. We now have been using BRACAnalysis to detect cancers that have *BRCA* mutations since we have poly ADP ribose polymerase (PARP) inhibitors for direct use in metastatic disease.

We've been using signatures, in the early setting, to detect the benefit or lack of benefit to chemotherapy in addition to endocrine therapy. So signatures such as Oncotype DX, Breast Cancer Index, MammaPrint, EndoPredict, and so forth. And in the metastatic setting, several of us have been using profiling such as FoundationOne, Tempus, Caris, Guardant, and numerous others to detect potential actionable mutations that may be able to guide therapy in and out of a clinical trial for patients.



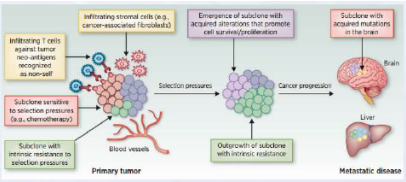
So, the reason we would want to do genomic profile is because we do want to detect meaningful alterations that could guide treatment decisions in patients with breast cancer. And these alterations can evolve over time. Some patients are born with a tumor, and some acquire them with time. However, what has become quite clear is that when you treat a cancer earlier on, some of the residual disease that may happen—either microscopic or macroscopic in the setting of neoadjuvant disease—may reflect what the metastatic disease will look like. And then we look, actually, very different at what the primary cancer was to begin with.

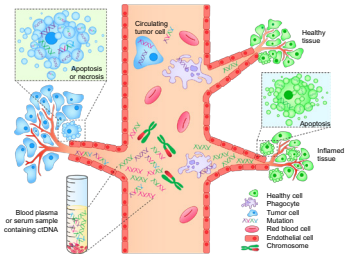


- So there are now several targetable and common mutations in breast cancer. The most common one is a mutation in the *PIK3CA* gene, which is a gene that codes for protein in the PI3 kinase signaling pathway. That is followed by HER2 amplifications, which I didn't list in there because everybody's aware of them, and they comprise about 30% of the breast cancers we see. But there are other common alterations such as *FGFR1* mutations, which can happen in up to 14% of early tumors. *ERBB2* mutations are not the same as amplifications; these are mutations that happen in the *HER2* gene, and they are quite common in estrogen receptor (ER)–positive lobular cancers.

  And then, of course, there are *ESR1* mutations, which are actionable and are very uncommon mutations early but can comprise up to 30% of the cases in the metastatic disease once patients get exposed to endocrine therapy in the adjuvant setting.

Genomic Profiling in Tumor or in the Blood?





Tumor Profiling[2]:
Requires an invasive procedure
Enough tumor material?
Issues with tumor heterogeneity

- High agreement *PIK3CA* mutations in a study of metastatic breast cancer patients between primary tissue and temporally matched ctDNA
- 72.5% agreement between unmatched archival tissue and ctDNA for *PIK3CA* mutation[1]

Blood cfDNA and ctDNA Profiling[3]:
Small fragments on nucleic acid from cells that originate from all metastatic sites
Lower sensitivity
May correlate with tumor burden

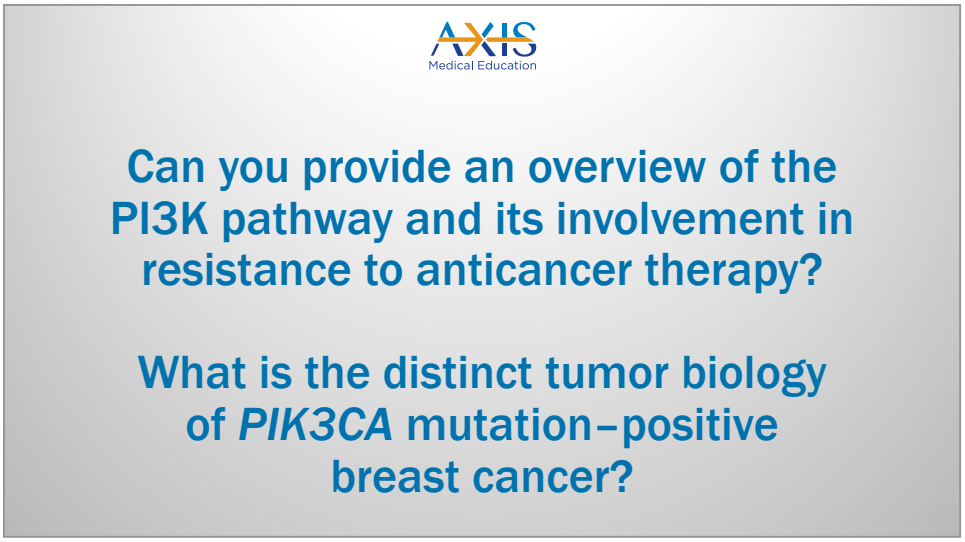
[1] Higgins et al. *Clin Cancer Res*. 2012;18:3462-3469.
[2] Jamal-Hanjani et al. *Clin Cancer Res*. 2015;21:1258-1266.
[3] Jahr et al. *Cancer Res*. 2001;61:1659-1665. Image recreated from Crowley et al. *Nat Rev Oncol*. 2013;10:472-484.

So, the big question is now that we not only have the availability to profile the tumor, but also profile the "blood" (so cell-free DNA in the blood), what should we be doing? Should we be profiling the tumor or the blood, and what are the advantages? So the big disadvantage of tumor profiling, obviously, is that it requires an invasive procedure. So, you'd have to biopsy either, unfortunately, at locations such as the lung or potentially the liver, which is a little bit easier. And if we're fortunate to get something like a skin match or a lymph node, that certainly is easier.

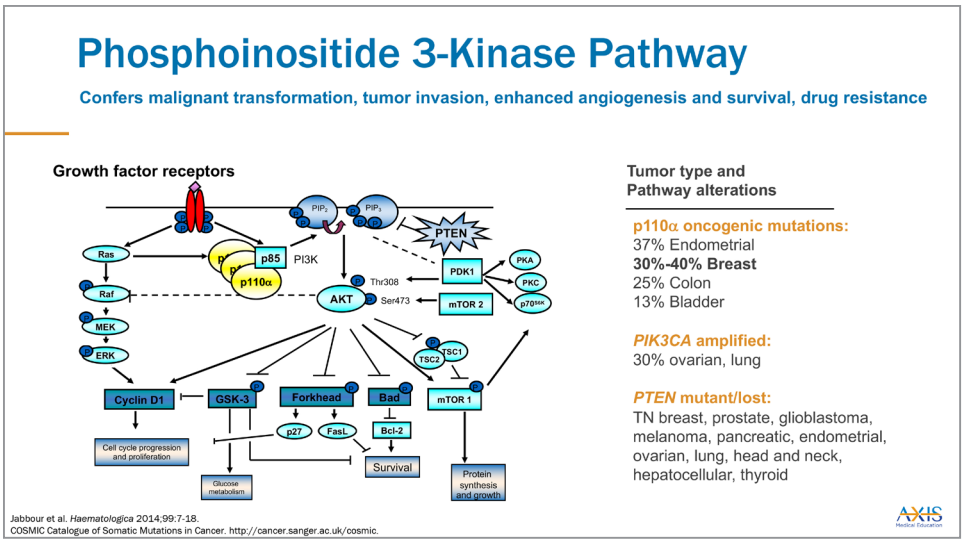
However, if we're going for a tougher site, we may not get enough material. And, obviously, we may be dealing with tumor heterogeneity because not all metastases are created equal. The newer ones may have acquired mutations that the first metastasis may not have. So that's, potentially, one advantage of performing liquid biopsies, in which we are detecting small fragments of DNA in the blood that originates from all the metastatic sites.

The advantage there is that you've got a bigger composite of what the cancer looks like and the prevalent mutations that may be common to all metastases. The problem, though, is that the sensitivity is lower, and it does, to some extent, correlate with tumor burden. Because the bigger the tumor burden, the easier it is to detect cell-free DNA. But be it as it may, both are now valid and available from a standard of care point of view. And I think you just have to choose which one would fit the patient profile a little better.

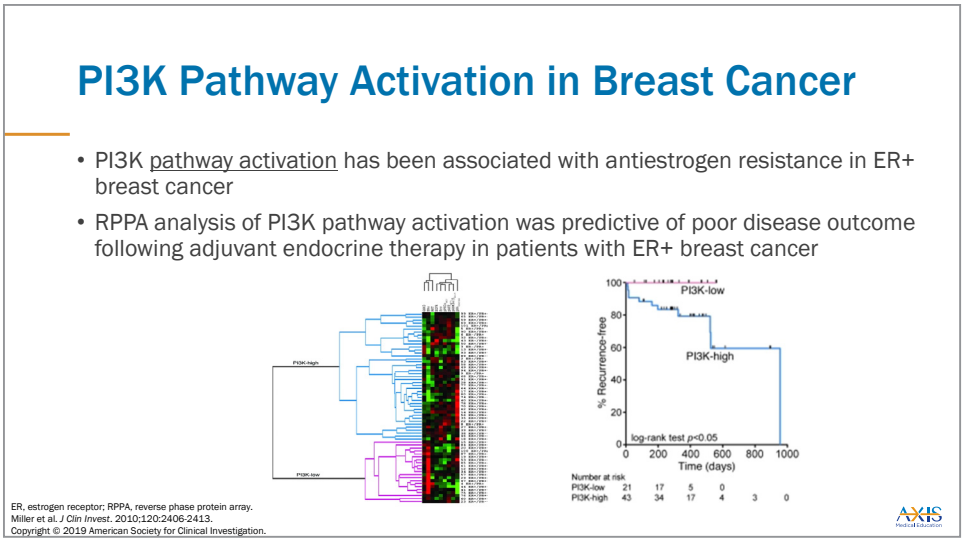
In terms of *PIK3CA* mutations, there is a high concordance between what we see in the primary tissue in the metastatic setting. So in the absence of being able to do a biopsy, you could, potentially, use the primary tissue from let's say a lumpectomy or mastectomy to detect a *PIK3CA* mutation in the cancer and potentially complement that with blood cell–free DNA. And overall, there's an approximate 72% agreement between unmatched archival tissue and cell-free DNA for the *PIK3CA* mutation.



Dr. Mocharnuk:
Dr. Mayer, can you provide an overview of the PI3 kinase pathway and its involvement in resistance to anticancer therapy? And can you tell us about the distinct tumor biology of *PIK3CA* mutation–positive breast cancer?

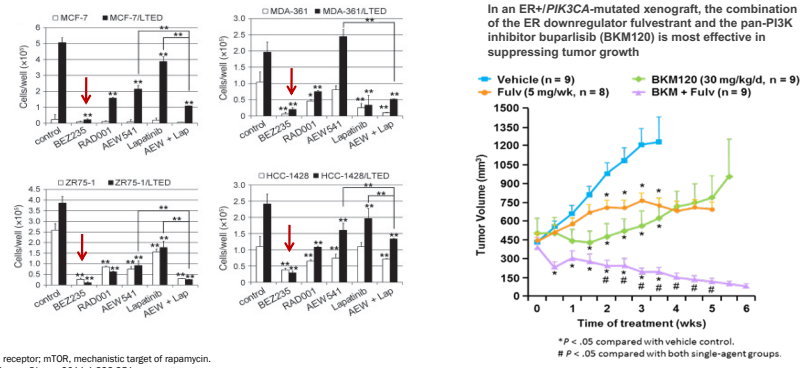


Dr. Mayer:
So the PI3 kinase pathway is quite complex, there are a lot of nodes—some of them less important than others. But, in the big scheme of things, the PI3 kinase pathway is what we call the survival pathway. This is associated with malignant transformation, tumor invasion, angiogenesis, survival, drug resistance. And alterations in this pathway are not uncommon in several different solid tumors. Particularly in breast cancer, it may be as common as having 40% of breast cancers with some genomic alteration in any node of the pathway. *PIK3CA* mutations are certainly the most common, but we also can see PTEN loss, AKT amplifications, and so forth.



So, PI3 kinase pathway activation is something that needs to be distinct of what we call a *PIK3CA* mutation. Not all *PIK3CA*-mutated tumors will have PI3 kinase pathway activation and vice versa. You could still have PI3 kinase pathway activation in the absence of a *PIK3CA* mutation. But nevertheless, the pathway activation that can be detected by RNA or reverse phase protein array analysis has been associated with antiestrogen resistance in ER-positive cancer. So if you were to profile tumors and figured out if they have a high signature for *PIK3CA* versus a low signature of *PIK3CA*, you'd see that the patients who have low PI3 kinase pathway activation usually do well; and the ones that are typically resistant to adjuvant endocrine therapy have a high risk of recurrence.

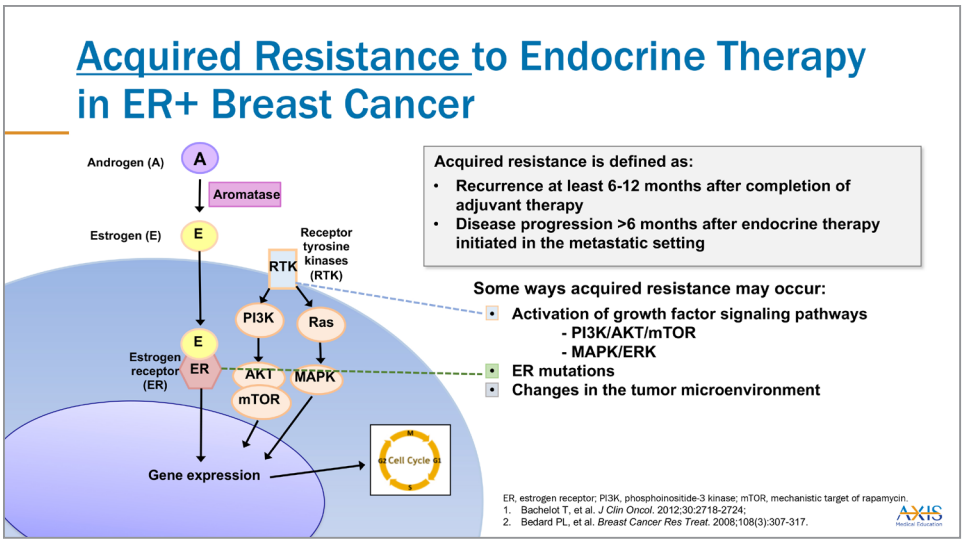
PI3K/mTOR Inhibition and Endocrine Therapy Resistance



ER, estrogen receptor; mTOR, mechanistic target of rapamycin.
Miller et al. *Cancer Discov*. 2011;1:338-351.

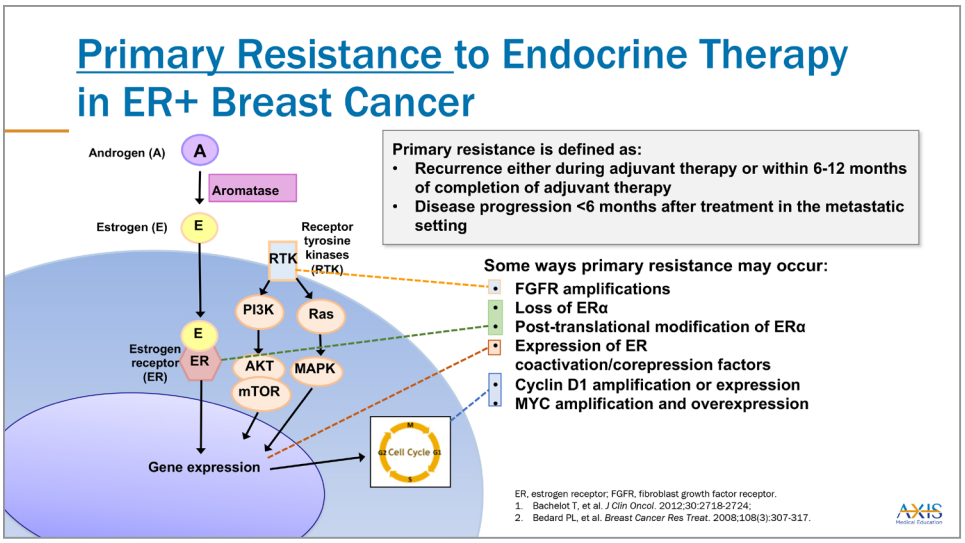
- Further work done in the preclinical setting has shown that, indeed, for tumors that become resistant to endocrine therapy, using a PI3 kinase pathway inhibitor—and many of them are tested there. The names on the screen are the ones that were initially given to these drugs when they were not yet approved. But BEZ235 was a dual PI3 kinase and mTOR inhibitor, RAD001 (most of you know today as everolimus). There are others in there that are also pan-PI3 kinase inhibitors.

  When you use a pan-PI3 kinase inhibitor, such as BEZ235, in combination with endocrine therapy, you are able to tumor suppress cancers much better than any other combination, including everolimus. And looking at xenograft models that are *PIK3CA* mutated and ER positive, certainly the combination of an ER downregulator (in this case, fulvestrant) and a pan-PI3 kinase inhibitor, BKM120 (which a lot of you may know as buparlisib), is most effective in suppressing tumor growth.



So let's talk a little bit about the relevance of this in ER-positive metastatic breast cancer. To better understand this, we have to talk about what we call acquired and primary resistance to ER-positive breast cancer. Acquired resistance is simply the type of tumor that certainly is sensitive to estrogen suppression from the get-go; so, those are patients that clinically in the adjuvant setting do well, are able to complete their 5 years of adjuvant therapy, and really may have recurrence years after the fact. If they do have recurrence, they probably will, also, have a good response to endocrine therapy in the metastatic setting for at least more than 6 months.

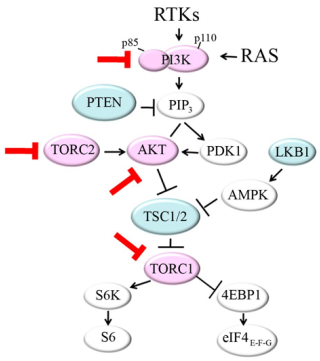
So those are cancers that, again, in simple terms, are sensitive to endocrine inhibition from the get-go but over time acquire either activation of growth pathways or other mutations that may cause them to become resistant down the road. So activation of growth factor signaling pathways, such as PI3 kinase pathway and MAP kinase pathway, is certainly responsible for some of the acquired resistant mechanisms that we often see in these cancers.



That is to be contrasted to primary resistance to endocrine therapy where that reflects the cancers that are somewhat resistant to endocrine therapy from the get-go. So, from a profiling point of view, those may be what we call the luminal B-like cancers where they have lower expression of ER/progesterone receptor, higher grades, and often are more responsive to chemotherapy and less responsive to endocrine therapy. So typically, these are patients who may have a metastatic recurrence while they're getting adjuvant therapy. Or, if they start treatment with endocrine therapy in the metastatic setting, they often progress within the first 6 months.

Some of the common pathways that are associated with that are *FGFR* amplifications, loss of ER, post-translational modifications of ER, or cyclin D amplification, which obviously becomes very relevant now in the era where we have CDK 4/6 inhibitors as a standard of care treatment for these cancers. So those are the main mechanisms for primary resistance.

PI3K Pathway Inhibitors

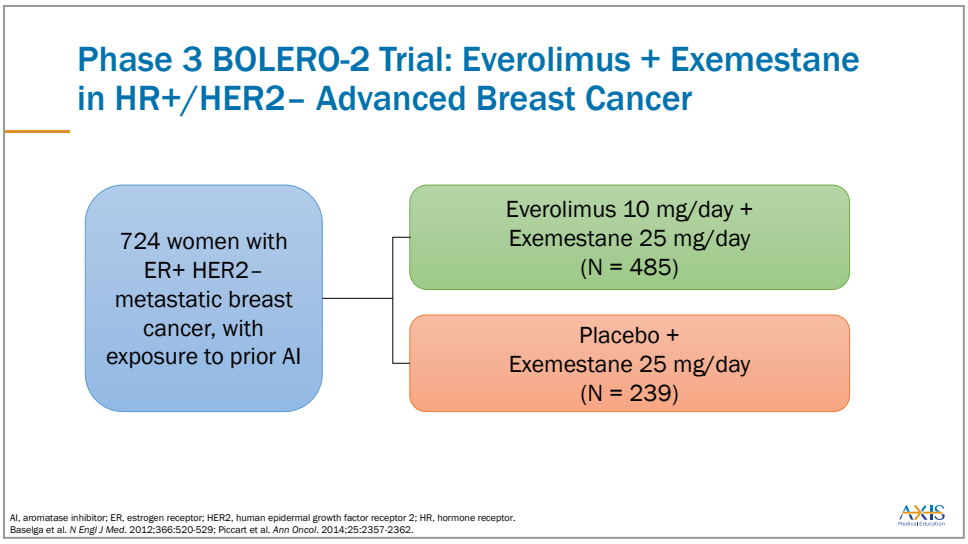


Drug	Target(s)
BYL719	PI3Kα
GDC-0032	PI3Kα
INK-1117	PI3Kα
CAL-101	PI3Kδ
XL-147	Pan-PI3K
BKM120	Pan-PI3K
GDC-0941	Pan-PI3K
PKI-587	Pan-PI3K
XL-765	PI3K/mTOR
BEZ235	PI3K/mTOR
GDC-0980	PI3K/mTOR
PF-4691502	PI3K/mTOR
INK-128	TORC1/2
OSI-027	TORC1/2
AZD8055	TORC1/2
AZD5363	AKT (catalytic)
MK-2206	AKT (allosteric)
GDC-0068	AKT (catalytic)

PI3K, phosphoinositide-3 kinase.
Akinleye et al. *J Hematol Oncol*. 2013;6:88.

- There are several PI3 kinase pathways now available, and this list, by all means, is not comprehensive. But the first on top of the list is BYL719, also known as alpelisib, which I'm going to talk about more in detail later on, as it has been recently approved for the treatment of ER-positive metastatic disease. But nevertheless, the list is quite comprehensive and includes inhibitors that we call specific inhibitors that will abrogate the alpha subunit of *PIK3CA*, which is the most relevant one in breast cancer. So the first 4 drugs on this list are perfect examples of that.

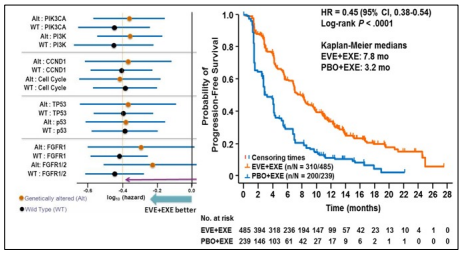
  There are pan-PI3 kinase inhibitors—two of them are BKM120 or buparlisib or GDC-0941 or pictilisib—that have been tested in phase 2 and 3 clinical trials; and unfortunately, due to a poor toxicity profile and not that active clinical activity, were actually taken off market. But now we are seeing a lot of dual PI3 kinase mTOR inhibitors, and there may be a lot of advantage of exploring that. But as you can imagine, those compounds are potentially more toxic.



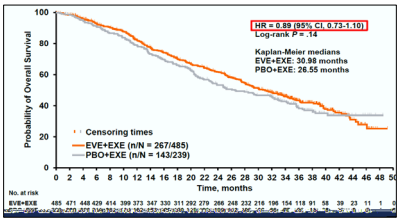
- So the first drug within the PI3 kinase pathway that ended up being FDA approved for use in ER-positive metastatic disease was an mTOR inhibitor called everolimus. This has been tested in a lot of phase 1 and phase 2 clinical trials. But I'm going to fast forward to the phase 3 BOLERO-2 trial that compared the performance of everolimus plus exemestane, a steroidal aromatase inhibitor, versus placebo and exemestane in patients who have had been exposed to aromatase inhibitors. So these are patients who have been treated with second- or third-line endocrine therapy and were randomized to one of those two arms.

Phase 3 BOLERO-2 Trial: Everolimus + Exemestane in HR+/HER2– Advanced Breast Cancer

Progression-free Survival



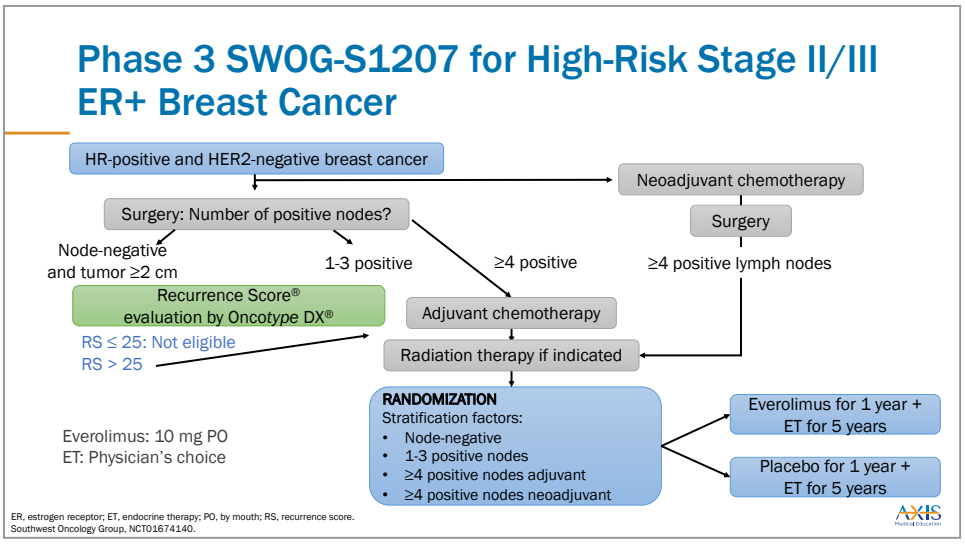
Overall Survival



AI, aromatase inhibitor; ER, estrogen receptor; EVE, everolimus; EXE, exemestane; HER2, human epidermal growth factor receptor 2; PBO, placebo.
Baselga et al. *N Engl J Med*. 2012;366:520-529; Piccart et al. *Ann Oncol*. 2014;25:2357-2362.

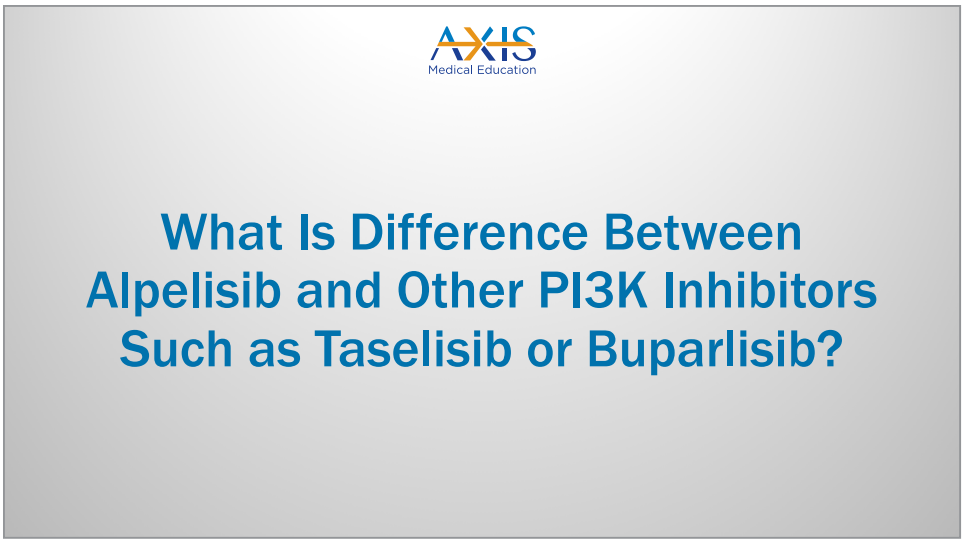
- And as you can see on the screen, there was actual substantial and statistically significant progression-free survival advantage to the addition of everolimus with almost 8-month progression-free survival versus 3 months seen with exemestane alone. On the graph on the left, you can see that there was no particular genomic alteration that really could tell you that one subgroup behaved better than the other.

  Unfortunately, once the data matured and after about 40 months of follow-up, we did not really see an improvement in overall survival with the addition of everolimus. However, patients did have, to some extent, obviously, not much in terms of side effects, especially once we've learned to deal with one of the very annoying side effects that this drug can cause, which is mucositis, by using steroid mouthwashes. And, after that, one potential gain that patients have were in quality of life where they were able to delay the initiation of chemotherapy and still have good control of their disease by using an endocrine therapy combination strategy.

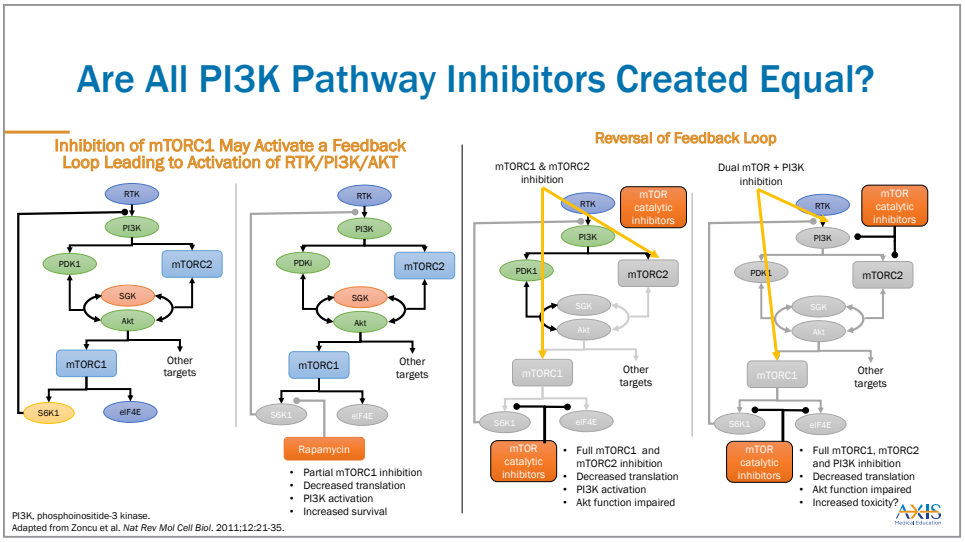


- So now, everolimus is being explored in the early setting for high-risk patients with stage II or III ER-positive breast cancer. In this phase 3 trial done through SWOG called S1207, in which patients with high-risk disease of recurrence, most of them node positive and high recurrence score by Oncotype DX, were randomized to receive everolimus for 1 year or placebo in addition to their standard endocrine therapy looking for disease-free survival and overall survival as a primary endpoint.

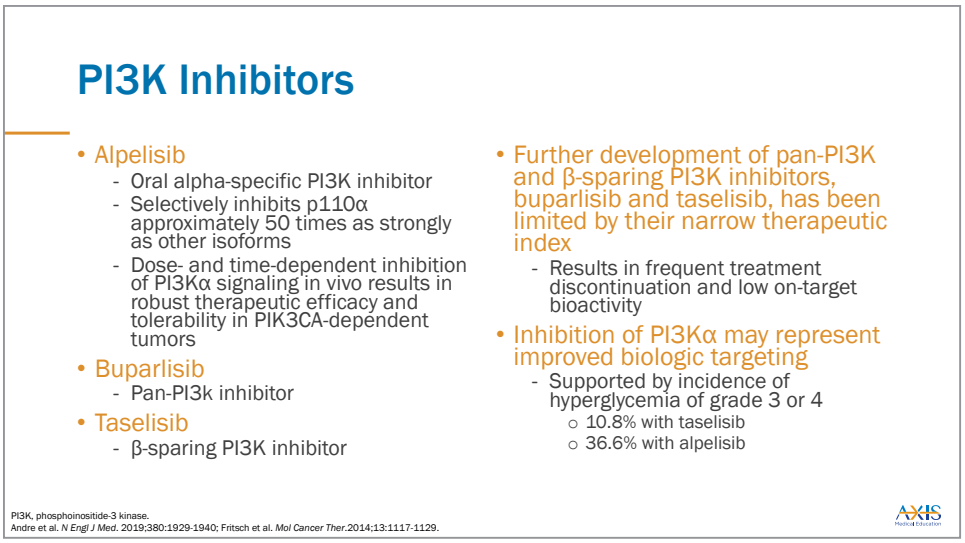
  This study recently completed accrual and, obviously, will probably a few more years before we can see a result. But this is potentially an interesting strategy for these patients at high risk, although the bigger question is since acquired resistance to endocrine therapy is really what you see, where the PI3 kinase pathway inhibition really shines, it's not that clear if this trial is actually going to be helpful for this patient population because a lot of them will probably have more of a primary endocrine resistance rather than acquired.



Dr. Mocharnuk:
So, Dr. Mayer, can you tell us the difference between alpelisib and other PI3 kinase inhibitors such as taselisib or buparlisib?



Dr. Mayer:
Certainly. So not all PI3 kinase inhibitors are created equal. As I told you, there are multiple drugs out there, some that block PI3K, some that block AKT, some that block mTOR. And mTOR has 2 subunits, TORC1 and TORC2. Everolimus or any rapamycin derivative usually blocks TORC1. And what that ends up causing is potentially this feedback loop that could then go back and activate AKT. So while you're blocking the PI3 kinase pathway downstream, you may actually, at the same time, be stimulating other nodes in the pathway higher up that could interface with other signaling pathways such as MAP kinase. So ideally, using things like dual mTOR inhibition or PI3 kinase inhibition or AKT inhibition that are upstream of mTOR may be advantageous to take that feedback loop activation.



So alpelisib is an oral alpha-specific PI3 kinase inhibitor that selectively inhibits p110α, which is really the most common kinase to be mutated in patients with ER-positive disease. And it has a very, very strong affinity than other isoforms for this particular subunit of PI3K. And obviously, this is dose dependent. Buparlisib, on the other hand, is a pan-PI3 kinase inhibitor, which again, unfortunately, had a lot of clinical toxicities and really its development was arrested.

Taselisib is somewhat similar to alpelisib, which even though it is not a pure alpha inhibitor, it's what we call a beta-sparing inhibitor. But it has both an alpha inhibition as well. However, because it is not pure, it also suffers from a lot of other side effects that you end up not seeing as much with alpelisib. So, a lot of the clinic toxicity, unfortunately, has limited the development of some of these drugs, and very few of them actually moved on to become FDA approved.

However, they have class effect side effects such as hyperglycemia, which is a big hallmark of all PI3 kinase inhibitors, including mTOR and AKT inhibitors and either alpha-specific or pan-PI3 kinase inhibitors; fatigue; GI toxicity such as nausea, diarrhea, and to some extent mucositis. So all those are common on-target effects of all of these drugs.

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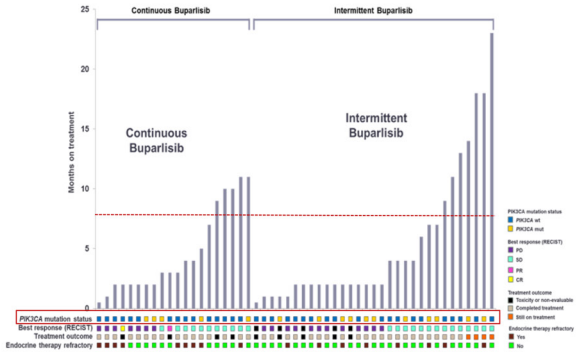
What Have We Learned From Trials Concerning Pictilisib (FERGI), Taselisib (SANDPIPER), and Buparlisib (BELLE-2 and BELLE-3)?

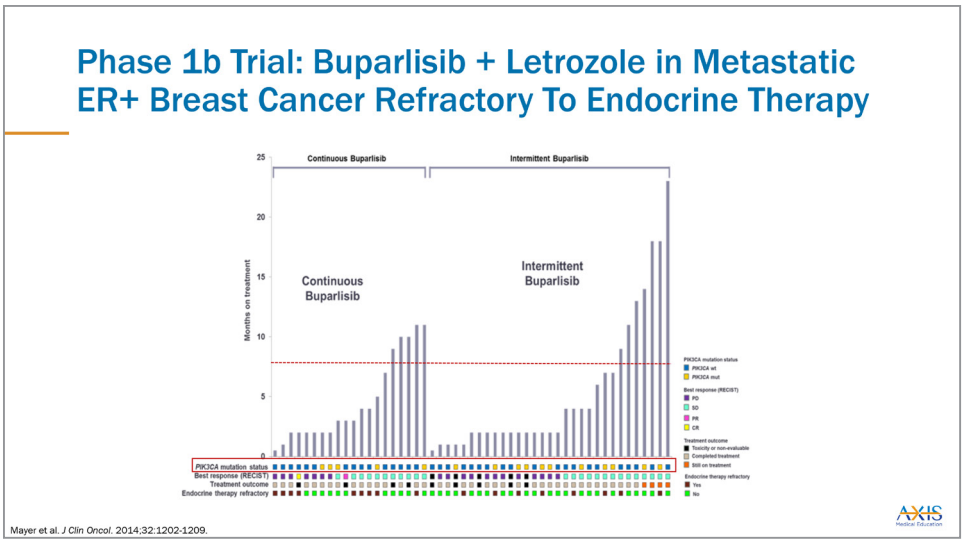
Dr. Mocharnuk:
What have we learned from trials concerning pictilisib, taselisib, and buparlisib?

Phase 1b Trial: Buparlisib + Letrozole in Metastatic ER+ Breast Cancer Refractory To Endocrine Therapy



Mayer et al. *J Clin Oncol*. 2014;32:1202-1209.

Dr. Mayer:
So I think, unfortunately, not as much as we hoped. However, I think these trials were important to show a proof of concept where when you target a specific mutation that may or may not be a driver of the disease, you may potentially have a differential effect on genotypically selective patient population. So the very first trial that was published addressing a combination of endocrine therapy with a pan-PI3 kinase inhibitor was this particular trial published a while back now in which buparlisib, a pan-PI3 kinase inhibitor, was combined with letrozole in metastatic ER-positive breast cancer that was refractory to endocrine therapy.

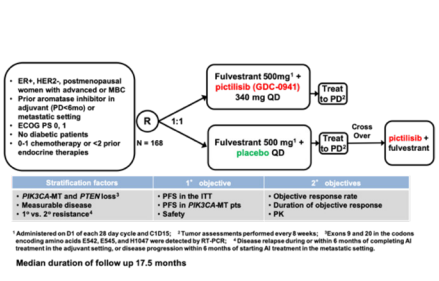


So all patients participating in the trial had either 1 or 2 lines of treatment in the metastatic setting that may have included medications such as tamoxifen, fulvestrant, or any of the aromatase inhibitors, including letrozole. And at that point, at open enrollment, they were exposed to 2 different schedules of buparlisib, and that was done to minimize toxicity. So initially the trial started with continuous buparlisib and subsequently was switched to a 5 out of 7 days of buparlisib administration, and letrozole was given sequentially.

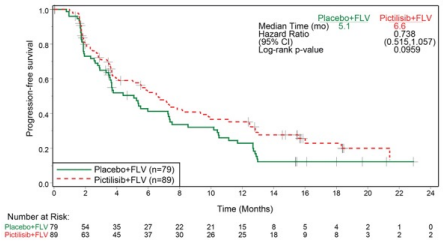
As you can see on that graph (it may show up a little small on the screen), clearly the patients that are above that dotted red bar were patients that had a more durable response—mostly a clinical benefit, stable disease. Yet, it's pretty clear that, especially for the ones that were already on letrozole, adding buparlisib made a difference in controlling their tumors. So that was the first evidence that these drugs were active in combination with endocrine therapy to rescue some of the endocrine therapy resistance, especially acquired ones that these cancers may have developed.

However, what we didn't see in this trial was a specific predilection for *PIK3CA*-mutated tumors. It looked like the *PIK3CA* mutation status did not matter in the clinical benefit rate seen with pan-PI3 kinase inhibitor added to letrozole.

Phase 2 FERGI Trial: Pictilisib + Fulvestrant in ER+ Endocrine-resistant Breast Cancer



PFS in the ITT Population

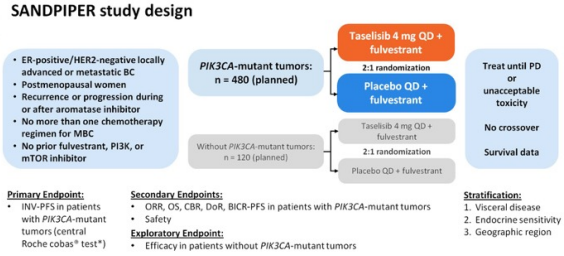


ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; FLV, fulvestrant; HER2, human epidermal growth factor receptor 2; ITT, intention to treat; MT, mutation; PD, progressive disease; PFS, progression-free survival; PK pharmacokinetics.
Krop et al. *Lancet Oncol*. 2016;17:811-821.

- Then came this phase 2 trial called FERGI, which combined pictilisib, which is a pan-PI3 kinase inhibitor, this time in combination with fulvestrant, which now in this day and age we know it's potentially a little bit stronger than an aromatase inhibitor in this setting, also for patients who had metastatic ER-positive cancer that was endocrine resistant. So all these patients had at least 1 or 2 treatments in the metastatic setting. And they had been randomized to receive either fulvestrant with placebo or fulvestrant and pictilisib. And what we saw was that there was a very, very minor advantage in progression-free survival in the intention-to-treat population but not statistically or clinically meaningful to cause a lot of enthusiasm to move the drug forward.

Phase 3 SANDPIPER Trial: Taselisib + Fulvestrant in Postmenopausal Women with Locally Advanced or Metastatic ER+/HER2– *PIK3CA*-mutated Breast Cancer and Disease Recurrence or Progression During or After an AI

SANDPIPER study design



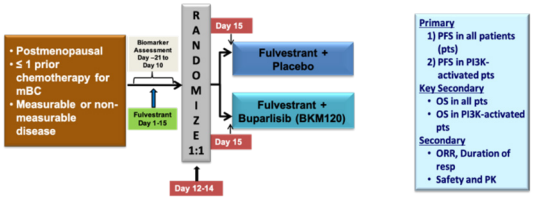
Parameter	Fulvestrant + Taselisib (N = 340)	Fulvestrant + Placebo (N = 176)
Median PFS, mo	7.4	5.4
HR	0.70	
P	.0037	
ORR	28.0%	11.9%
P	.0002	

AI, aromatase inhibitor; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; ORR, objective response rate; PFS, progression-free survival.
Baselga et al. *J Clin Oncol*. 2018;36:LBA1006.

- Nevertheless, there have been phase 3 trials done with this very same drug focusing on *PIK3CA*-mutant tumors because FERGI was in a non-selected patient population. And unfortunately, again, even though numerically superior, the combination didn't really provide a meaningful improvement in progression-free survival that really justified approval of this drug, particularly in the setting of a severe toxicity such as colitis, pneumonitis, severe hyperglycemia, and so forth.

Phase 3 BELLE-2 and BELLE-3 Trials: Buparlisib + Fulvestrant in Postmenopausal HR+/HER2– Advanced Breast Cancer

- BELLE-2: patients had progressive disease on or after aromatase inhibitor treatment and had received up to one previous line of chemotherapy for advanced disease
- BELLE-3: relapsed on or after endocrine therapy and mTOR inhibitors



HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mBC, metastatic breast cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI3K, phosphoinositide-3 kinase.
Baselga et al. *Lancet Oncol.* 2017;18:904-916; Di Leo et al. *Lancet Oncol.* 2018;19:87-100.

Then came phase 3 trials called BELLE-2 and BELLE-3, and those explored the use of buparlisib, which is another pan-PI3 kinase inhibitor, in combination with fulvestrant in patients who were postmenopausal with ER-positive metastatic breast cancer. Patients were randomized—just like in the SANDPIPER trial—to receive either fulvestrant with placebo or fulvestrant with buparlisib.

Phase 3 BELLE-2 and BELLE-3 Trials: Buparlisib + Fulvestrant in Postmenopausal HR+/HER2– Advanced Breast Cancer

BELLE-2

Full Population (N = 1,047)	Buparlisib + Fulvestrant n = 576	Placebo + Fulvestrant n = 571	ctDNA *PIK3CA* Mutant n = 200	Buparlisib + Fulvestrant n = 87	Placebo + Fulvestrant n = 113	ctDNA *PIK3CA* Non-mutant n = 387	Buparlisib + Fulvestrant n = 199	Placebo + Fulvestrant n = 188
Median PFS, mo (95% CI)	6.9 (6.8-7.8)	5.0 (4.0-5.2)	Median PFS, mo (95% CI)	7.0 (5.0-10.0)	3.2 (2.0-5.1)	Median PFS, mo (95% CI)	6.8 (4.7-8.5)	6.8 (4.7-8.6)
HR (95% CI)	0.78 (0.67-0.89)		HR (95% CI)	0.56 (0.39-0.80)		HR (95% CI)	1.05 (0.82-1.34)	
One-sided *P*	<.001		One-sided nominal *P*	<.001		One-sided nominal *P*	.642	

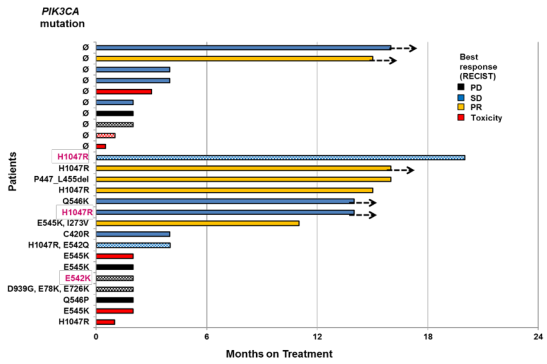
BELLE-3

Full Population (N = 432)	Buparlisib + Fulvestrant n = 289	Placebo + Fulvestrant n = 143	ctDNA *PIK3CA* Mutant	Buparlisib + Fulvestrant	Placebo + Fulvestrant	ctDNA *PIK3CA* Non-mutant	Buparlisib + Fulvestrant	Placebo + Fulvestrant
Median PFS, mo (95% CI)	3.9 (2.8-4.2)	1.8 (1.5-2.8)	Median PFS, mo (95% CI)	4.2 (2.8-6.7)	1.6 (1.4-2.8)	Median PFS, mo (95% CI)	3.9 (2.8-4.3)	2.7 (1.5-3.6)
HR (95% CI)	0.67 (0.53-0.84)		HR (95% CI)	0.46 (0.29-0.73)		HR (95% CI)	0.73 (0.53-1.00)	
One-sided *P*	<.001		One-sided nominal *P*	<.001		One-sided nominal *P*	.026	

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PFS, progression-free survival.
Baselga et al. *Lancet Oncol.* 2017;18:904-916; Di Leo et al. *Lancet Oncol.* 2018;19:87-100.

And what we saw is that numerically, again, there was a little superiority for the addition of buparlisib to endocrine therapy more so in the patients where *PIK3CA* mutations were detected by cell-free DNA, and that happened in both BELLE-2 and BELLE-3 trials. The difference between those trials is that BELLE-3 allowed patients to have had prior exposure to everolimus, which at that point had already been FDA approved. So again, considering all the side effects of this drug, which also included CNS toxicity where patients could have changes in personality, severe depression, there was actually even one case of suicide. Unfortunately, based on the lack of substantial clinical benefit, this drug, again, was not further developed for use in breast cancer.

Phase 1b Trial: Alpelisib + Letrozole in ER+/HER2– Metastatic Breast Cancer Refractory to Endocrine Therapy

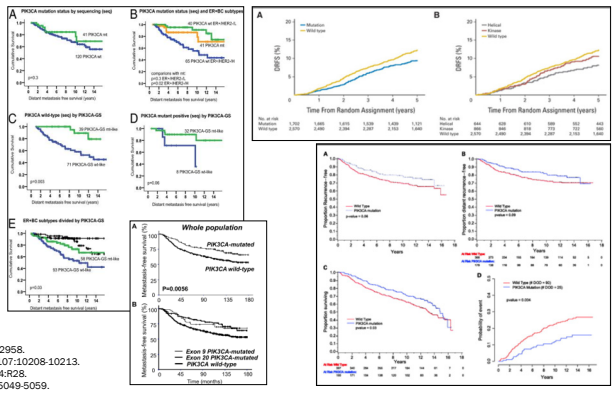


ER, estrogen receptor; HER2, human epidermal growth factor receptor; PD, progressive disease; PR, partial response; SD, stable disease.
Mayer et al. *Clin Cancer Res*. 2017;23:26-34.

- But then came PI3 kinase inhibitors that, again, were more specific, particularly blocking the Ð110 subunit of PI3K. One prototype of this drug is alpelisib, which was initially combined with letrozole. So similar to the very first clinical trial that I showed you where buparlisib had been combined with letrozole with patients for ER-positive/HER2-negative metastatic breast cancer refractory to endocrine therapy. But here, the results were a little different.

  Not only the responses were a little superior and more durable than what's seen with buparlisib, but also there's a big difference between the responses and durability of responses seen in patients with *PIK3CA* mutations. So the upper part of the graph clearly shows that some patients benefited despite not having a mutation, but the brunt of patients that benefited from the combination certainly have mutations mostly on the hotspots of *PIK3CA*.

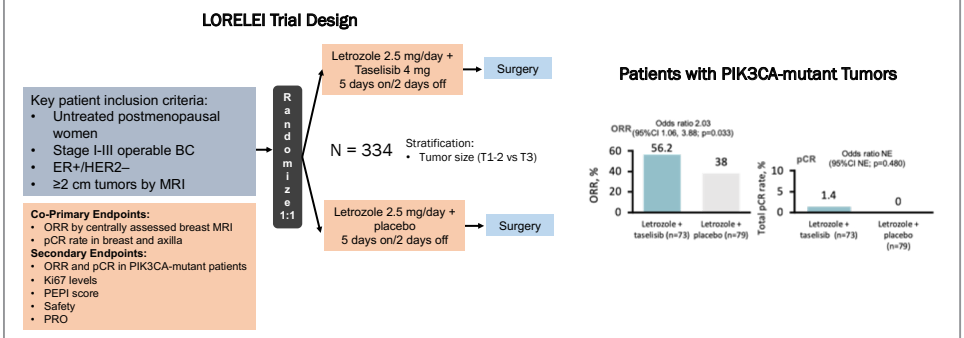
PIK3CA Mutations Confer a Good Prognosis in Early ER+ Breast Cancer



ER, estrogen receptor.
Sabine et al. *J Clin Oncol*. 2014;32:2951-2958.
Loi et al. *Proc Natl Acad Sci U S A*. 2010;107:10208-10213.
Cizkova et al. *Breast Cancer Res*. 2012;14:R28.
Kalinsky et al. *Clin Cancer Res*. 2009;15:5049-5059.

- Now, *PIK3CA* mutations, as I said, do not necessarily correlate with activation of the pathway. And, in the early setting—so when you profile patients early—the presence of the mutation, honestly, is very often associated with luminal A cancers, which are actually quite endocrine sensitive. So, when you look at the outcome of patients in the absence of endocrine therapy, some of them actually do even better than the ones who don't have a *PIK3CA* mutation. But very likely, that is not necessarily reflective of the activation or not; it's just reflective of the fact that luminal A-like cancers are actually more likely to have *PIK3CA* mutations.

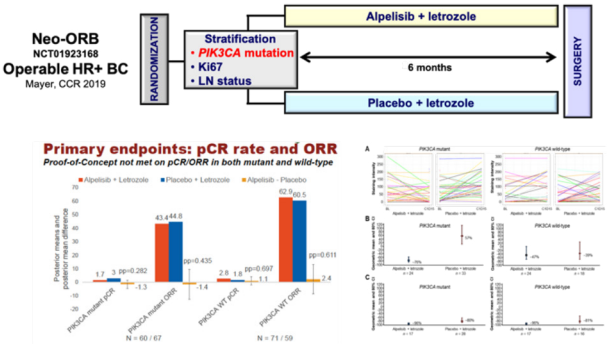
PI3K Inhibition in Early ER+ BC



BC, breast cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; MRI, magnetic resonance imaging; ORR, objective response rate; pCR, pathologic complete response; PI3K, phosphoinositide-3 kinase.
Saura et al. *Ann Oncol*. 2017;28:LBA10_PR.

- So it's potentially not a surprise that PI3 kinase inhibitors were tested in early estrogen-positive cancers in the neoadjuvant fashion. One example here is a trial called LORELEI, which explored the addition of taselisib, a beta-sparing PI3 kinase inhibitor, to letrozole. Even though a little bit higher clinical response rates were seen, there was definitely no advantage in terms of pathologic complete responses between one drug or the other. And most importantly, no substantial differences in Ki-67 as well, which is, to some extent, somewhat of a surrogate marker of long-term outcome benefit.

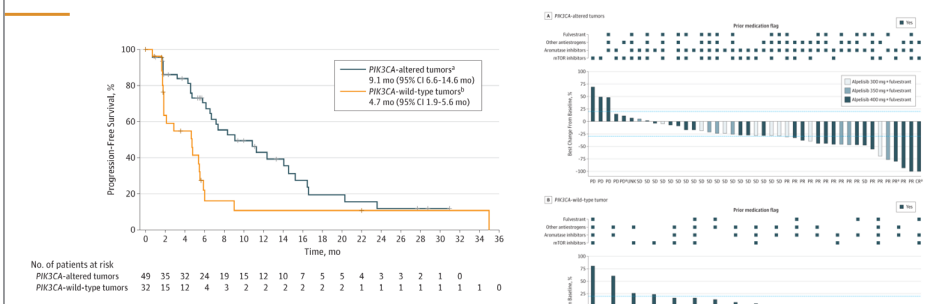
PI3K Inhibition in Early ER+ BC



BC, breast cancer; ER, estrogen receptor; HR, hormone receptor; LN, lymph node; ORR, overall response rate; pCR, pathologic complete response; PI3K, phosphoinositide-3 kinase.
Mayer et al. *Clin Cancer Res*. 2017;23:26-34.

- Another trial that was just as big, also mostly focusing on *PIK3CA* mutations, showed that the addition of alpelisib this time to letrozole really did not have any impact on Ki-67 suppression or clinical benefit whatsoever neither in terms of decreasing the size of the tumor any further than letrozole did nor causing more pathologic complete responses compared to letrozole alone. So, in the early setting, this is probably not a strategy that we want to bring it on potentially because what I had mentioned before. The PI3 kinase pathway inhibition is probably something that will be much more relevant in acquired resistance to endocrine therapy, which may not happen until later on.

Phase 1b Trial: Alpelisib + Fulvestrant in *PIK3CA*-Mutated and *PIK3CA* Wild-Type ER+ Advanced Breast Cancer With Progression During or After Antiestrogen Therapy



ER, estrogen receptor; mTOR, mechanistic target of rapamycin.
Juric et al. *JAMA Oncol.* 2018 Dec 13:e184475. doi: 10.1001/jamaoncol.2018.4475. [Epub ahead of print].

- So, subsequent to that first phase 1 trial with letrozole and alpelisib, a bigger trial with alpelisib and fulvestrant was undertaken looking at both *PIK3CA* altered and *PIK3CA* wild-type ER-positive metastatic breast cancer progressing during or after antiestrogen therapy. And here, again, the signal that this is very active and more potent almost exclusively in *PIK3CA* altered cancers was, again, substantiated. And it was numerically and slightly statistically significant benefit in terms of progression-free survival for patients receiving alpelisib with fulvestrant, especially in the setting of a *PIK3CA* mutation.

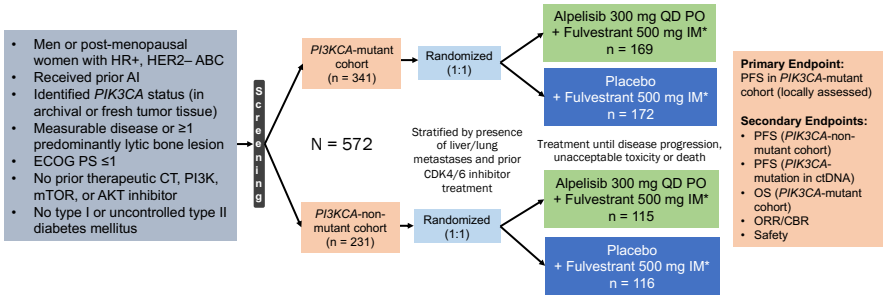
AXIS Medical Education

In the SOLAR-1 trial, alpelisib nearly doubled progression-free survival. Can you elaborate on this trial's design and results?

What do these results mean for current or future clinical practice?

- **Dr. Mocharnuk:**
  In the SOLAR-1 trial, alpelisib nearly doubled progression-free survival. Can you elaborate on this trial's design and results? And what do these results mean for current or future clinical practice?

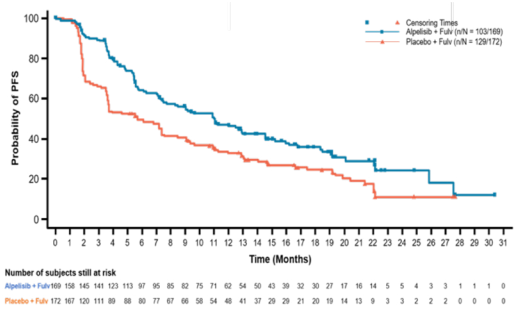
Phase 3 SOLAR-1 Trial: Alpelisib + Fulvestrant in HR+/HER2– Advanced Breast Cancer Previously Treated with Endocrine Therapy



ABC, advanced breast cancer; AI, aromatase inhibitor; CBR, clinical best response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor; HR, hormone receptor; IM, intramuscularly; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, orally; QD, once daily.
Adapted from Andre et al. *N Engl J Med*. 2019;380:1929-1940.

Dr. Mayer:
So SOLAR-1 was then a follow-up for that fulvestrant/alpelisib phase 1b trial that now has been in a phase 3 fashion where about close to 600 patients were randomized to receive either alpelisib or fulvestrant. The trial pretty much had as its primary endpoint the benefit of alpelisib added to fulvestrant in the *PIK3CA*-mutant cohort. So the trial was powered as such that there was an enrichment of *PIK3CA*-mutated patients enrolled in the trial.

Phase 3 SOLAR-1 Trial: Median PFS in *PIK3CA*-mutated HR+/HER2– Advanced Breast Cancer



Data cut-off: June 12, 2018	Alpelisib + fulvestrant (N=169)	Placebo + fulvestrant (N=172)
Number of PFS events, n (%)	103 (60.9)	129 (75.0)
Progression	99 (58.6)	120 (69.8)
Death	4 (2.4)	9 (5.2)
Censored	66 (39.1)	43 (25.0)
Median PFS (95% CI)	11.0 (7.5-14.5)	5.7 (3.7-7.4)
HR (95% CI)	0.65 (0.50-0.85)	
p-value	0.00065	

First PI3K inhibitor to demonstrate clinically meaningful, statistically significant results in breast cancer

Fulv, fulvestrant; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PFS, progression-free survival; PI3K, phosphoinositide-3 kinase.
Andre et al. *N Engl J Med*. 2019;380:1929-1940.

And, essentially what was seen, as you mentioned before, is that was, indeed, almost a doubling in the progression-free survival on the trial where patients who received alpelisib and had *PIK3CA* mutations had a median progression-free survival of 11.0 months opposed to 5.7 months with fulvestrant alone. Now one thing to note on this trial, though, is that this it completed accrual prior to approval of CDK 4/6 inhibitors. Therefore, we don't know now in the real world that this drug is FDA approved if the benefit that we're going to see is going to be as profound as that seen on the SOLAR-1 trial.

However, there are trials now looking at this combination not in a randomized fashion but in the CDK 4/6 era, in which patients are going to be exposed to CDK 4/6 inhibitors in first- or second-line treatment. So we will see with the current landscape of treatment whether the addition of alpelisib is going to be at least proportionally just as effective as it was in the SOLAR-1 like population.

SOLAR-1 Adverse Events

Most Frequent Grade 3 or 4 Adverse Events (occurring in at least 5%)		
Adverse Event	**Alpelisib + Fulvestrant**	**Placebo + Fulvestrant**
Hyperglycemia	36.6%	0.7%
Rash	9.9%	0.3%
Maculopapular rash	8.8%	0.3%
Diarrhea	6.7%	0.3%

Hyperglycemia led to the permanent discontinuation of alpelisib in 6.3% of patients

Andre et al. *N Engl J Med*. 2019;380:1929-1940.

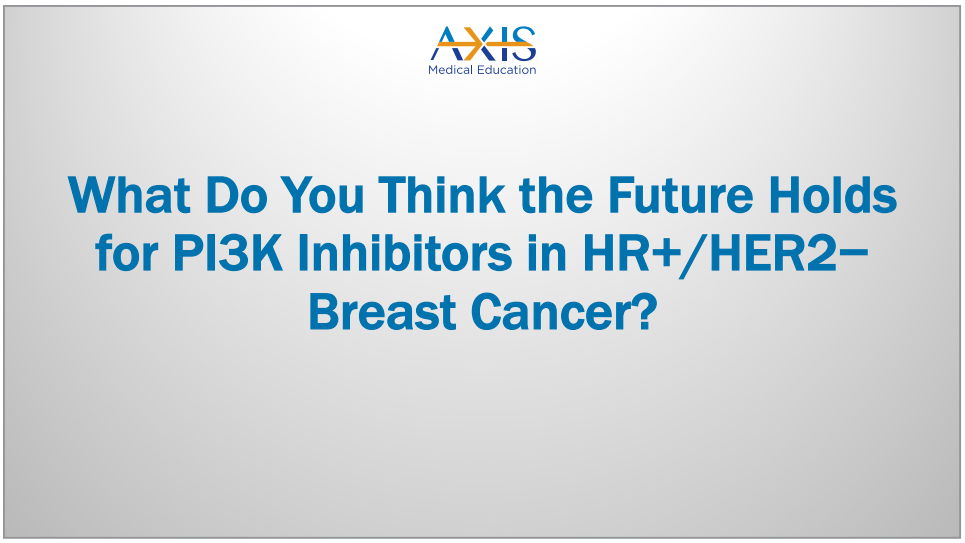
- The adverse events were as expected; there were no new signals. The most common side effects were hyperglycemia, some rash, and diarrhea. The diarrhea and the rash are actually manageable. The rash particularly seems to be quite responsive to antihistamines and topical steroids. Some patients have to use oral steroids to deal with the rash but that certainly can be manageable. The hyperglycemia, in a similar fashion, most of the time was asymptomatic and easily manageable by metformin, diet intervention, and whatnot. And now there's a big effort to come up with consensus of how to best treat and manage these side effects because they're fairly new to the oncology world, but certainly very manageable and really not as effective from a quality-of-life point of view.

Alpelisib FDA Approval and Testing for *PIK3CA* Mutation

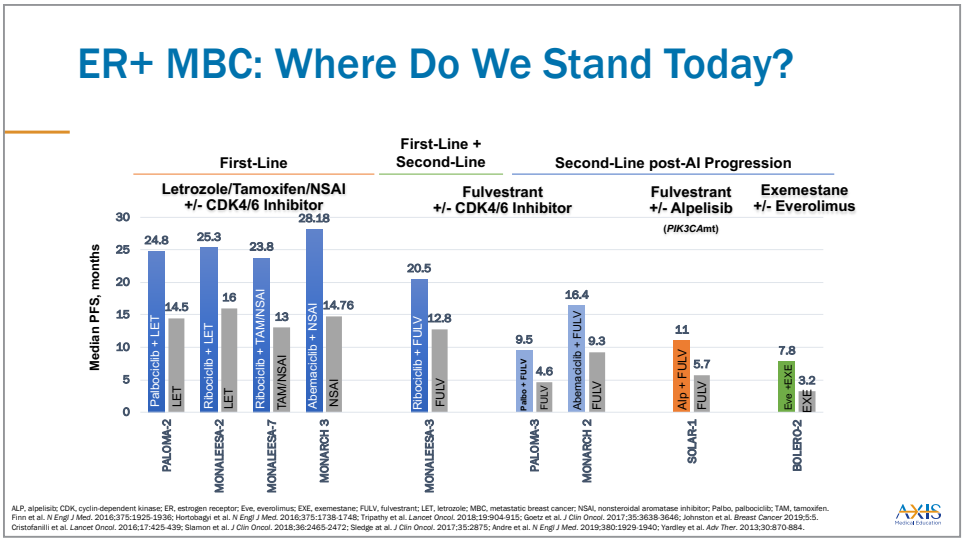
- May 2019: FDA approval of alpelisib + fulvestrant for postmenopausal women or men with HR+, HER2–, *PIK3CA*-mutated, advanced or metastatic breast cancer following progression on or after an endocrine-based regimen
- Companion diagnostic test, *therascreen*® PIK3CA RGQ PCR Kit, to select patients who have PIK3CA mutations in tumor tissue specimens and/or in ctDNA isolated from plasma specimens
  - If negative for *PIK3CA* mutations in plasma, patients should undergo testing for *PIK3CA* mutations in tumor tissue

ctDNA , circulating tumor DNA; HER2, human epidermal growth factor receptor 2; HR, hormone receptor.
FDA News Release, 2019.

- So in May of this year, the FDA approved alpelisib in combination with fulvestrant for patients that are postmenopausal with estrogen-positive, HER2-negative, and *PIK3CA*-mutated tumors with either advanced or metastatic breast cancer following progression on or after an endocrine-based regimen. There's a companion diagnostic test that has been approved with it called therascreen PIK3CA, a PCR kit, which is actually pretty simple and fast to do to select for patients with these mutations. However, I suspect that most people will not have issues getting the drug approved if they already know that a patient had a *PIK3CA* mutation on a test such as FoundationOne or Guardant360, which are commonly done for other indications nowadays.

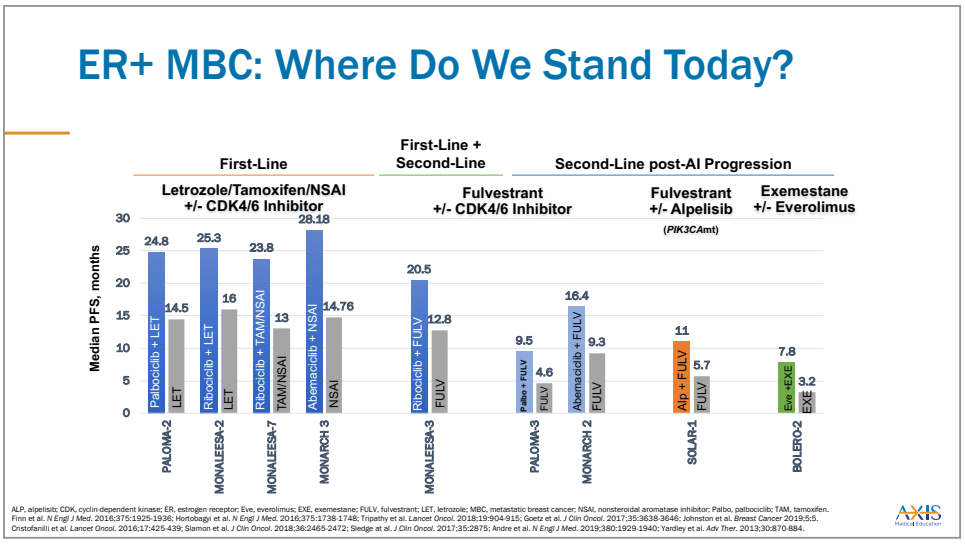


Dr. Mocharnuk:
What do you think the future holds for PI3 kinase inhibitors in hormone receptor–positive/HER2-negative breast cancer?



Dr. Mayer:
That's an excellent question. And I think to better answer that question, I would like to have you focus a little bit on this graph on the screen that gives you a bird's-eye view of what we have available today. And it seems daunting and confusing because it actually is. But now, we have first-line established data with combinations of CDK 4/6 inhibitors with letrozole or tamoxifen or any other nonsteroidal aromatase inhibitor.

And even with fulvestrant, based on this clinical trial called MONALEESA-3 where fulvestrant was actually given in first line, really interestingly because of the FALCON data that has shown that fulvestrant was a little superior to aromatase inhibitors in first-line setting. But what is actually striking is because of the very consistent hazard ratios of benefit seen with these combinations, now these drugs have become FDA approved, as well, in first line.



ALP, alpelisib; CDK, cyclin-dependent kinase; ER, estrogen receptor; Eve, everolimus; EXE, exemestane; FULV, fulvestrant; LET, letrozole; MBC, metastatic breast cancer; NSAI, nonsteroidal aromatase inhibitor; Palbo, palbociclib; TAM, tamoxifen.
Finn et al. *N Engl J Med*. 2016;375:1925-1936; Hortobagyi et al. *N Engl J Med*. 2016;375:1738-1748; Tripathy et al. *Lancet Oncol*. 2018;19:904-915; Goetz et al. *J Clin Oncol*. 2017;35:3638-3646; Johnston et al. *Breast Cancer* 2019;5:5.
Cristofanilli et al. *Lancet Oncol*. 2016;17:425-439; Slamon et al. *J Clin Oncol*. 2018;36:2465-2472; Sledge at al. *J Clin Oncol*. 2017;35:2875; Andre et al. *N Engl J Med*. 2019;380:1929-1940; Yardley et al. *Adv Ther*. 2013;30:870-884.

And with the recent reports of overall survival data from the MONALEESA-7 trial, which was done exclusively in premenopausal patients, it's hard to argue that these therapies should be first-line choice for patients with ER-positive metastatic disease. However, in second-line post–aromatase inhibitor progression, now it's a little hard to determine what to do.

There are certainly phase 3 data suggesting that a CDK 4/6 inhibitor, when added to fulvestrant, is also quite effective in prolonging progression-free survival with similar hazard ratios seen in first line, also 0.5, but obviously with a much smaller magnitude of month benefit because these patients had already been exposed to endocrine treatment. However, I suspect that this situation will become rarer because more and more patients will be exposed to CDK 4/6 inhibitors in first line.

So, an obvious choice for second line would be to either use fulvestrant by itself, which I suspect a lot of people are not going to be very enthusiastic about, or combine it with another targeted treatment. Everolimus was the one that has been approved now for quite some time, and it does not require patients to have any mutation in their tumor. But now, with the approval of alpelisib for *PIK3CA*-mutated cancers, certainly this is very solid and important options for patients that progress on CDK 4/6 inhibitors and endocrine therapy and have a *PIK3CA* mutation in their cancer.

How Will PI3K Inhibition Work After CDK 4/6 Inhibition?

BYLieve (NCT03056755): Phase 2 trial of alpelisib + endocrine therapy in patients with *PIK3CA*-mutated HR+/HER2– ABC post-CDK 4/6 inhibitor

Status (as of May 1, 2019): recruiting

- Men and women (pre- and post-menopausal; ≥18 years) with *PIK3CA*-mutant, HR+, HER2– locally advanced or metastatic breast cancer
- Progressed on/after prior CDK 4/6 inhibitor combination therapy
- ≥1 measurable lesion (RECIST v1.1) or predominantly lytic bone lesion
- ECOG PS ≤2
- ≤1 line of prior chemotherapy in the advanced setting
- No prior PI3K inhibitor therapy

Patients received prior CDK 4/6 inhibitor + AI
Alpelisib 300 mg QD
+ Fulvestrant 500 mg
(n = 80)

Patients received prior CDK 4/6 inhibitor + fulvestrant
Alpelisib 300 mg QD
+ Letrozole 2.5 mg QD
(n = 80)

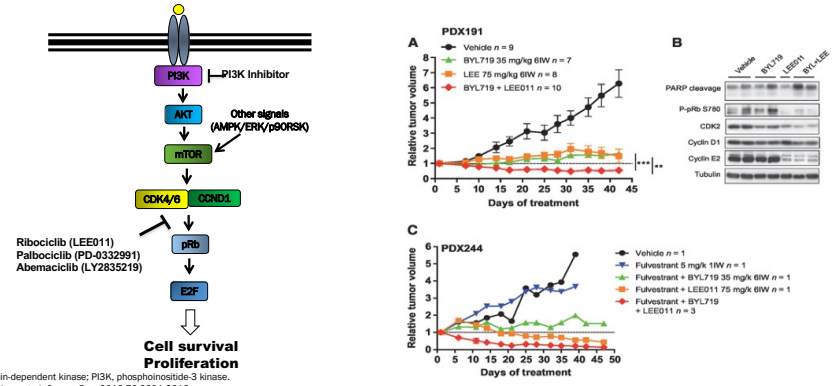
Primary endpoint:
Proportion of patients who are alive without disease progression at 6 months (RECIST v1.1; local assessment)

ABC, advanced breast cancer; AI, aromatase inhibitor; CDK, cyclin-dependent kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PFS, progression-free survival; PI3K, phosphoinositide-3 kinase; QD, once daily.
Rugo et al. *J Clin Oncol*. 2018;36: abstract TPS1107.

So, one trial that is now addressing how this PI3 kinase inhibition will work post–CDK 4/6 inhibition is this trial called BYLieve, which is not a randomized trial, but it's a very smart and pragmatic design where patients who have had prior CDK 4/6 inhibitions with aromatase inhibitors. We see fulvestrant with alpelisib. And patients who have received prior CDK 4/6 inhibitors with fulvestrant receive alpelisib with letrozole.

And the primary endpoint is the number of patients who are alive without disease progression at 6 months, the local assessment. So, this is really to prove that this potential strategy will be at least proportionally just as active as it was seen in the pivotal phase 3 trial leading to the approval of alpelisib for *PIK3CA*-mutated cancers.

CDK 4/6 Inhibition + α-PI3K Inhibition Combinations Could Reverse Resistance to Endocrine Therapy as well as CDK 4/6 Therapy

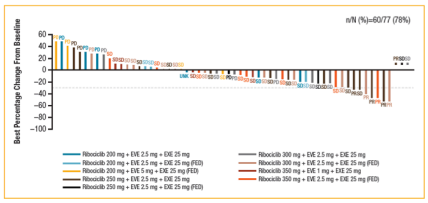


CDK, cyclin-dependent kinase; PI3K, phosphoinositide-3 kinase.
Herrera-Abreu et al. *Cancer Res*. 2018;76:2301-2313.

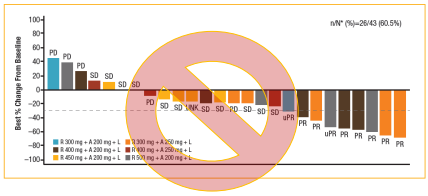
But obviously, we need to do more homework because with CDK 4/6 inhibitors now being in phase 3 clinical trials in the early setting for high-risk patients—and all these trials now have completed accrual—it is going to be hard to figure out what to do post–CDK 4/6 inhibition when patients then still have a recurrence in the metastatic setting. And there are a lot of preclinical data to suggest that the one pathway that could potentially reverse resistance to endocrine therapy, as well as CDK 4/6 therapy, is to potentially engage in the PI3 kinase pathway as the escape mechanism and blocking that may be substantially important to prevent or reverse the resistance to both endocrine therapy and CDK 4/6 inhibition.

Combination of Endocrine Therapy with a CDK4/6 Inhibitor and a PI3K Pathway Inhibitor

Exemestane + Everolimus + Ribociclib
Phase 1b/2 study of postmenopausal women with AI-resistant ER+ MBC



Letrozole + Alpelisib + Ribociclib
Phase 1b study of postmenopausal women with ER+ MBC



AI, aromatase inhibitor; ER, estrogen receptor; MBC, metastatic breast cancer.
Bardia et al. *Cancer Res.* 2016;76:P6-13-01; Juric et al. *Cancer Res.* 2016;76:P3-14-01.

So, there have been 2 trials attempting to do that. One of them was a combination with exemestane, everolimus, and ribociclib—everolimus being an mTOR inhibitor and ribociclib a CDK 4/6 inhibitor—where certainly responses and durable responses were seen. All these patients have had aromatase inhibitor–resistant disease, and a lot of them have had prior exposure to CDK 4/6 inhibition.

A similar trial has been done with alpelisib, which is the alpha-specific PI3 kinase inhibitor, but that did not move forward due to severe liver toxicity, so that was not compatible with patient safety. And therefore this trial was aborted.

Phase 2 Trials Combining CDK 4/6 and mTOR Inhibition

Trial	Strategy
TRINITI-1 NCT02732119	mTOR inhibitor Everolimus/ribociclib/exemestane
PASTOR NCT02599714	mTORC 1/2 inhibitor Vistusertib
NCT02871791	mTOR inhibitor Everolimus/palbociclib/exemestane

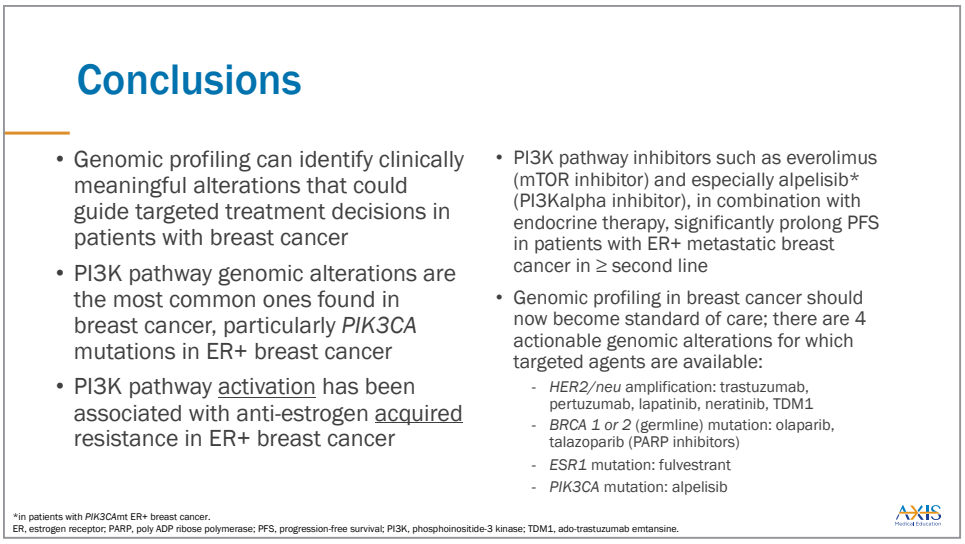
Progression on CDK 4/6 inhibitor and AI after ≥4 months as last therapy
- Ribociclib 300 mg/day
- Everolimus 2.5 mg/day
- Exemestane 25 mg/day

Endpoint	Response (n = 43)
Clinical Benefit	39.5%
Partial Response	7%

52% ribociclib dose reduction; 86% temporary interruption

AI, aromatase inhibitor; CDK, cyclin-dependent kinase; mTOR, mechanistic target of rapamycin.

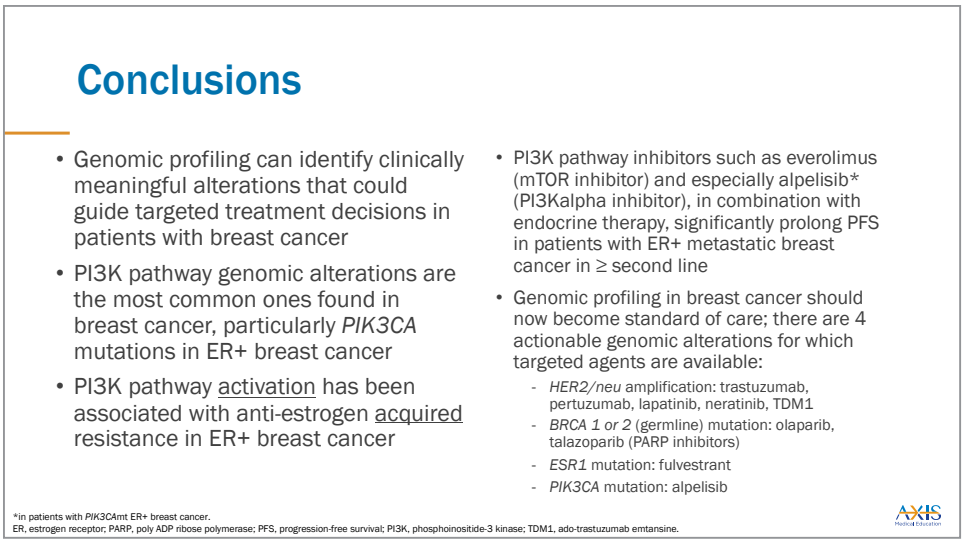
Now there are several clinical trials combining CDK 4/6 inhibitor and mTOR inhibition. One of them was recently reported called TRINITI-1 that did show a clinical benefit and partial responses in a substantial number of patients definitely showing that from a proof of concept point of view, this is not a crazy strategy to go after. So obviously, there are some toxicities, doses had to be reduced. But now there's a phase 2 randomized trial called TRINITI-2 that is going to further explore the benefit of this, and hopefully this can become a new strategy for patients who may have had prior CDK 4/6 inhibition either in the adjuvant or first-line metastatic setting.



Dr. Mocharnuk:
Dr. Mayer, would you like to wrap-up this discussion and just tell us what the salient points are about PI3 kinase inhibition, as we are currently using it in the clinical setting?

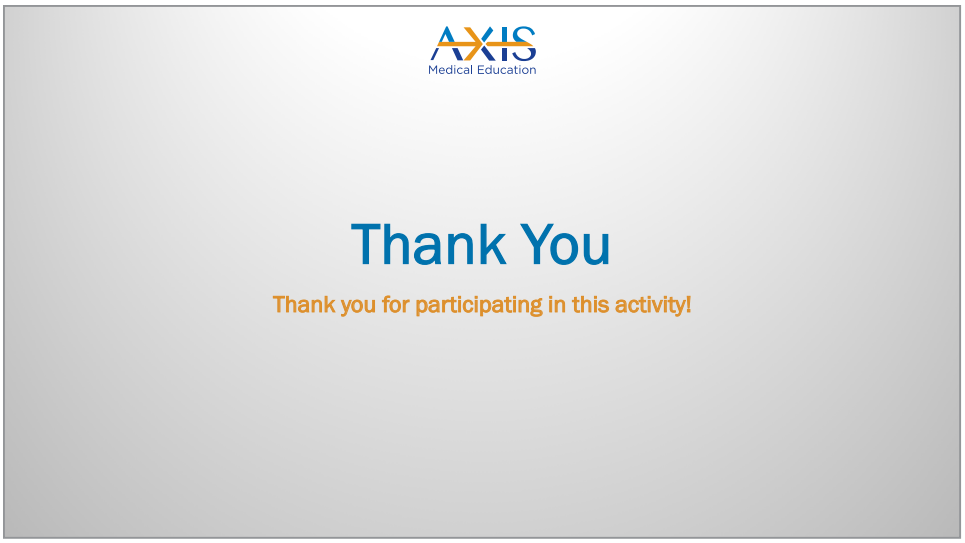
Dr. Mayer:
Certainly. So, I think my final thoughts on this subject is that genomic profiling can certainly identify meaningful alterations that could and should guide targeted treatment decisions in patients with breast cancer, certainly in the metastatic setting. And PI3 kinase pathway genomic alterations—being the most common ones found in breast cancer—are an obvious target to go after, particularly the *PIK3CA* mutations that can be found in about 40% of ER-positive primary and metastatic breast cancers.

PI3 kinase pathway activation has been associated with antiestrogen acquired resistance in ER-positive disease; and therefore, again, a perfect setting to consider medications such as mTOR inhibitors or PI3 kinase inhibitors for patients with *PIK3CA* mutations. So, this combination of these PI3 kinase inhibitors with endocrine therapy have shown to significantly prolong progression-free survival in patients with ER-positive disease beyond second line of treatment. I don't think we will see overall survival data yet, very soon, on alpelisib, but we certainly know that with everolimus we did not, unfortunately, achieve overall survival advantage. But still a solid option for patients who really are interested in delaying initiation of chemotherapy and still preserve their quality of life.



But I think, most importantly, drugs like this and strategies like this underscore the importance of considering genomic profiling in all patients with breast cancer. Because we already have several actionable genomic alterations for which we have approved agents. HER2/neu amplification is not new to anybody, and you certainly don't need to do genomic profile to find it because we can use fluorescence in situ hybridization and immunohistochemistry and other techniques. But clearly, it is a genomic alteration that has been very successfully tackled with anti-HER2 medications, as listed on the slide.

BRCA1 and *BRCA2* germline mutations really require germline profiling because PARP inhibitors now have also become FDA approved for patients with metastatic disease with *BRCA1* or *BRCA2* mutations. However, I would argue that simply just because of *ESR1* mutations that only respond to drugs with fulvestrant and do not respond to tamoxifen or aromatase inhibitors and now with *PIK3CA* mutations having alpelisib as a targeted agent that is approved showing progression-free survival advantage. For that reason alone, we should already be genomically profiling patients with metastatic breast cancer, particularly the ones with ER-positive disease.



Dr. Mocharnuk:
Thank you for this really clear and detailed review of PI3 kinase inhibition in breast cancer.

Dr. Mayer:
My pleasure, thank you.

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