TALKING PIQRAY

SOLAR 1 | Show notes

Show notes

The following papers discuss the association between PIK3CA mutations and worse patient prognosis:

- Sobhani N, Roviello G, Corona SP, et al. The prognostic value of PI3K mutational status in breast cancer: a meta-analysis. *J Cell Biochem.* 2018;119(6):4287-4292.
- Li YL, Rong M, Grieu F, Iacopetta B. PIK3CA mutations in breast cancer are associated with poor outcome. *Breast Cancer Res Treat.* 2006;96(1):91-95.
- Lai YL, Mau, BL, Cheng WH, Chen HM, Chiu HH, Tzsen CY. PIK3CA exon 20 mutation is independently associated with a poor prognosis in breast cancer patients. *Ann Surg Oncol.* 2008;15(4):1064-1069.
- Mosele F, Verret B, Jusque A, et al. Natural history and outcome of patients presenting a metastatic breast cancer with PIK3CA mutation. Abstract presented at: American Association for Cancer Research (AACR) Annual Meeting 2019; March 29-Apr 3, 2019; Atlanta, GA.

The following table lists the adverse events of PIQRAY®

ARs	PIQRAY + Fulvestrant (N=284)		Placebo + Fulvestrant (N=287)	
	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)
Gastrointestinal disorders				
Diarrhea	164 (57.7)	19 (6.7)[d]	45 (15.7)	1 (0.3)[d]
Nausea	127 (44.7)	7 (2.5)[d]	64 (22.3)	1 (0.3)[d]
Stomatitis[a]	85 (29.9)	7 (2.5)[d]	18 (6.3)	0[d]
Vomiting	77 (27.1)	2 (0.7)[d]	28 (9.8)	1 (0.3)[d]
General disorders and administration site conditions				
Fatigue[b]	120 (42.3)	15 (5.3)[d]	83 (28.9)	3 (1.0)[d]
Investigations				
Weight decreased	76 (26.8)	11 (3.9)[d]	6 (2.1)	0[d]
Metabolism and nutrition disorders				
Hyperglycemia	184 (64.8)	105 (37.0)	29 (10.1)	2 (0.7)[d]
Decreased appetite	101 (35.6)	2 (0.7)[d]	30 (10.5)	1 (0.3)[d]
Skin and subcutaneous tissue disorders				
Rash[c]	147 (51.8)	56 (19.7)[d]	21 (7.3)	1 (0.3)[d]

Transcript

Presenter	Welcome to Talking PIQRAY, discussing novel treatments for patients HR+, HER2-, and advanced breast cancer. In this episode, we hope to give you an understanding of the SOLAR-1 efficacy and safety results. SOLAR-1 is the pivotal phase 3 study leading to the approval of PIQRAY, also known as alpelisib, in combination with fulvestrant. Let's pause for a moment to get a bit more detail about PIQRAY.
Presenter	PIQRAY (alpelisib) is the first and only treatment specifically for hormone receptor positive/HER2 negative advanced breast cancer patients with a PIK3CA mutation. These mutations are particularly important as they are present in approximately 40% of these patients and are associated with a worse prognosis.[1-8] The efficacy and safety of PIQRAY was evaluated in the clinical study, SOLAR-1.
Presenter	To better understand the design of SOLAR-1, we interviewed Dr. Wolfgang Janni, Professor and Chair of Obstetrics and Gynaecology at the University Hospital of Ulm in Germany.
Presenter	Dr. Janni could you please tell us a little about the design of the SOLAR-1 study?
Dr. Janni	SOLAR-1 is a phase 3, randomized, double-blind, placebo-controlled study evaluating PIQRAY in combination with fulvestrant in postmenopausal women, and men, with hormone receptor positive, HER2/negative advanced breast cancer after disease progression.[9,10]
Presenter	Here Dr. Janni is referring to a study titled 'Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer' by Fabrice André, Eva Ciruelos, Gabor Rubovsky and their team. That paper was published in the *New England Journal of Medicine* in 2018.[9]
Presenter	Dr. Janni can you please explain more about how the study was designed? How many patients were enrolled?
Dr. Janni	In the SOLAR-1 trial, 572 patients were enrolled into two cohorts- patients with or patients without a PIK3CA mutation. The 341 patients with a PIK3CA mutation were randomized 1:1 to receive either PIQRAY plus fulvestrant or placebo plus fulvestrant.[9]
Dr. Janni	The cohort without a PIK3CA mutation consisted of 231 patients, also randomized 1:1, and were included as a separate cohort as a proof of concept. The proof of concept criteria were not met for this cohort.[10]

Transcript

Presenter	Thank you Dr. Janni for this explanation. So, SOLAR-1 became the first phase 3 trial to lead to a treatment approved specifically for advanced breast cancer patients with the PIK3CA mutation.
Presenter	Dr. Janni, can you now please describe the primary and secondary endpoints in the SOLAR-1 study.
Dr. Janni	In SOLAR-1, the primary endpoint was investigator-assessed progression free survival, or PFS, in the cohort with a PIK3CA mutation, per RECIST 1.1.[9,10] Secondary endpoints included overall survival and overall response rate for those patients with a PIK3CA mutation.[9-11]
Presenter	Ah I understand. So, it was the RECIST 1.1 methodology that was used to understand how effective PIQRAY was in changing tumor burden.
Presenter	To guide us through the results of the study we turned to Dr. Stephen Chia. Dr. Chia is a medical oncologist with the British Columbia Cancer Agency and Professor of Medicine at the University of British Columbia in Canada. Thank you, Dr. Chia, for taking the time to help us to understand the results on SOLAR-1 Study. Can you please outline some of those results for us?
Dr. Chia	We see in the PIK3CA mutation cohort the median progression free survival nearly doubled from 5.7 months to 11 months with PIQRAY plus fulvestrant versus fulvestrant and placebo.[10]
Presenter	Nearly doubled? That's great to hear for patients. Were there any other results of note, Dr. Chia?
Dr. Chia	Separation of the progression free survival curve was apparent as early as 2 months.[10]
Dr. Chia	Furthermore, the increase in median progression free survival observed in patients in the PIK3CA cohort taking PIQRAY plus fulvestrant was consistent across selected subgroups.[9]

Transcript

Presenter	The subgroups include patients with lung and/ or liver metastases, Bone-only disease, Prior CDK4/6 treatment, prior chemotherapy, first line and second line of advanced anticancer treatment, as well as different endocrine status. About 40% of patients who are diagnosed with hormone receptor positive, HER2-, advanced breast cancer will have this PIK3CA mutation.[1-4] Testing for these mutations is important because they are associated with a worse prognosis.[5-8] This connection with a worse prognosis has been detailed in four separate papers published between 2006 and 2019. Again, we include links to these in the show notes at www.piqray.com. The reason I bring this up is because PIQRAY does offer hope to these patients. In this next section, you will hear the story of a hypothetical patient, portrayed by an actor, talking about her experience of her diagnosis.
Presenter	Phyllis is a 63-year-old post-menopausal woman. She's a busy professional who had already completed adjuvant aromatase inhibiting or AI therapy. However, seven months after completing this treatment, she found she was persistently coughing and experiencing chest pain. Imaging confirmed a small tumor in the right pulmonary lobe. A biopsy reconfirmed her status as HR+/ HER2-. An additional test indicated the presence of the PIK3CA mutation.
Actor 1 (Phyllis)	Relapsing so quickly after finishing treatment was a shock. I thought the cancer was under control.
Presenter	Relapsing is a shock to any patient, and relapsing so quickly after adjuvant treatment can be especially disappointing.
Phyllis	I keep thinking, why did this happen? After additional tests my Oncologist told me my cancer tested positive for a PIK3CA mutation. I needed to know if there was a treatment available for this type of cancer.

Transcript

Presenter	After the early progression of Phyllis' breast cancer, and with the confirmation of her mutation, it is worth it to reinforce that PIK3CA mutations are a common indicator of poor prognosis.[5-8] PIQRAY specifically addresses PIK3CA mutations for women like her. PIQRAY improves her prognosis and allows Phyllis to get back to enjoying the job she loves.
Presenter	It helps, I think, to hear stories like Phyllis'. I understand, Dr. Chia, that there were further results from the SOLAR-1 study. What were other results worth noting, apart from the progression-free survival?
Dr. Chia	In addition to the progression free survival efficacy, in patients with a PIK3CA mutation who had measurable disease the overall response rate nearly doubled, from 16% to 35.7% with PIQRAY plus fulvestrant versus fulvestrant alone.[9,10]
Presenter	We've heard about the design of the SOLAR-1 Study from Dr. Wolfgang Janni, and Dr. Stephen Chia shared the efficacy results of the study with us. We have also heard what this can mean for patients when we heard Phyllis' story.
Presenter	However, healthcare providers have to consider other factors when deciding whether to prescribe a treatment to a patient, like the safety profile of the treatment. Dr. Chia can you talk to us about the most common adverse reactions associated with PIQRAY?
Dr. Chia	The most common adverse reactions in patients taking PIQRAY plus fulvestrant were hyperglycemia, diarrhea, rash, nausea, fatigue, asthenia, decreased appetite, stomatitis, vomiting and weight reduction.[10]
Dr. Chia	Serious adverse reactions associated with PIQRAY include hypersensitivity such as anaphylactic reaction, severe cutaneous reactions, hyperglycemia, and pneumonitis.[10]
Presenter	You can find a link to a table that lists the adverse reactions in show notes at www.piqray.com.

Transcript

Presenter	Dr. Chia, PI3 kinase inhibition has certain expected reactions, doesn't it?
Dr. Chia	Hyperglycemia is an expected, on-target effect of PI3K inhibition.[10,12]
Presenter	Interesting. We'll have an upcoming episode on Mechanism of Action where we delve into this in more detail. Tell me, do the adverse reactions lead to many people giving up treatment with PIQRAY + fulvestrant?
Dr. Chia	Of note 25% of patients being treated with PIQRAY plus fulvestrant discontinued treatment due to adverse events compared to 5% treated with placebo plus fulvestrant.[10]
Presenter	And finally, on adverse reactions, what most frequently caused patients to discontinue treatment?
Dr. Chia	The most frequent adverse reactions leading to treatment discontinuation of PIQRAY plus fulvestrant were hyperglycemia, rash, diarrhea, and fatigue.[10]
Presenter	Many thanks to both Dr. Wolfgang Janni for introducing us to SOLAR-1 and how the study was designed, and Dr. Stephen Chia for sharing all those efficacy and safety results from SOLAR-1 with us.
Presenter	So that is it from this episode of Talking PIQRAY. I really enjoyed bringing you through the details of the SOLAR-1 study and learning more about the efficacy and safety of PIQRAY. We will further episodes available that examine topics such as Mechanism of Action amongst others, so please join us again.
Presenter	Dr. Chia received honoraria from AstraZeneca, Hoffmann-LaRoche, Novartis and Pfizer, and has a consultancy/ advisory role with GlaxoSmithKline at the time of recording. Dr. Janni receives grant support from Novartis at the time of recording. Before you go, we have some safety information about PIQRAY that we would like to share with you.

Important Safety Information FROM THE PIQRAY EU SmPC

Important Safety Information FROM THE PIQRAY EU SmPC

The most common ADRs and the most common grade 3 / 4 ADRs (reported at a frequency >20% and ≥2% respectively) were plasma glucose increased, creatinine increased, gamma-glutamyltransferase increased, rash, lymphocyte count decreased, nausea, alanine aminotransferase increased, anaemia, fatigue, lipase increased, decreased appetite*, stomatitis, vomiting*, weight decreased, hypocalcaemia, plasma glucose decreased*, activated partial thromboplastin time prolonged*, alopecia** diarrhoea, hypokalaemia, hypertension, nausea, creatinine increased, and mucosal inflammation (*<2% grade 3/4 ADRs reported, ** no grade 3/4 ADRs reported).

Piqray can cause serious side effects such as severe hypersensitivity, severe cutaneous reactions, hyperglycemia, pneumonitis, diarrhoea, and osteonecrosis of the jaw.

The following should be taken into consideration prior to or during treatment with Piqray:

Piqray should be permanently discontinued in patients with serious hypersensitivity reactions.

Piqray should not be initiated in patients with a history of severe cutaneous reactions, should be interrupted if signs or symptoms of severe cutaneous reactions are present, and permanently discontinued if a severe cutaneous reaction is confirmed.

Fasting glucose and HbA1c levels should be monitored frequently in the first 4 weeks of treatment, and patients should be advised of the signs and symptoms of hyperglycaemia.

In case of new or worsening respiratory symptoms, the patient should be evaluated for pneumonitis.

Patients should be advised to notify their physician if diarrhoea occurs.

Caution should be exercised when Piqray and bisphosphonates or denosumab are used together or sequentially. Piqray should not be initiated in patients with ongoing osteonecrosis of the jaw.

The efficacy and safety of Piqray has not been studied in patients with symptomatic visceral disease.

Animal studies suggest that Piqray may cause fetal harm in pregnant women. Therefore, as a precaution, women of childbearing potential should use effective contraception while receiving Piqray during treatment and at least 1 week after stopping treatment. Women should not breast feed for at least 1 week after the last dose of Piqray. Piqray may affect fertility in males and females.

Please see full Prescribing Information for Piqray, available at: www.piqray.com

References: 1. The Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. *Nature*. 2012;490(7418): 61-70. **2.** Tolaney S, Toi M, Neven P, et al. Clinical Significance of PIK3CA and ESR1 mutations in ctDNA and FFPE Samples From the MONARCH 2 Study of Abemaciclib Plus Fulvestrant. Presented at: 2019 American Association for Cancer Research (AACR) Annual Meeting; March 29-April 3, 2019; Atlanta, GA. **3.** Di Leo A, Johnston S, Seok Lee K, et al. Buparlisib plus fulvestrant in postmenopausal women with hormone-receptor-positive, HER2-negative, advanced breast cancer progressing on or after mTOR inhibition (BELLE-3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2018;19(1):87-100. **4.** Moynahan ME, Chen D, He W, et al. Correlation between PIK3CA mutations in cell-free DNA and everolimus efficacy in HR+, HER2- advanced breast cancer: results from BOLERO-2. *Br J Cancer*. 2017;116(6):726-730. **5.** Sobhani N, Roviello G, Corona SP, et al. The prognostic value of PI3K mutational status in breast cancer: a meta-analysis. *J Cell Biochem*. 2018;119(6):4287-4292. **6.** Li YL, Rong M, Grieu F, Iacopetta B. PIK3CA mutations in breast cancer are associated with poor outcome. *Breast Cancer Res Treat*. 2006;96(1):91-95. **7.** Lai YL, Mau, BL, Cheng WH, Chen HM, Chiu HH, Tzsen CY. PIK3CA exon 20 mutation is independently associated with a poor prognosis in breast cancer patients. *Ann Surg Oncol*. 2008;15(4):1064-1069. **8.** Mosele F, Verret B, Jusque A, et al. Natural history and outcome of patients presenting a metastatic breast cancer with PIK3CA mutation. Abstract presented at: American Association for Cancer Research (AACR) Annual Meeting 2019; March 29-Apr 3, 2019; Atlanta, GA. **9.** André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. *N Engl J Med*. 2019;380(20):1929-1940. **10.** PIQRAY® (alpelisib) Core Data Sheet: Version 1.0. Novartis Pharma AG; November 2018. **11.** André F et al. Presented at: 2018 European Society for Medical Oncology (ESMO) Congress; October 19-23, 2018; Munich, Germany. **12.** Goncalves MD, Hopkins BD, Cantley LC. Phosphatidylinositol 3-kinase, growth disorders and cancer. *N Engl J Med*. 2018;379 (21):2052-2062.

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PIQRAY® (alpelisib) tablets

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