Neoadjuvant Talazoparib for Patients With Operable Breast Cancer With a Germline *BRCA* Pathogenic Variant

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abstract

PURPOSE Talazoparib has demonstrated efficacy in patients with *BRCA*-positive metastatic breast cancer. This study evaluated the pathologic response of talazoparib alone for 6 months in patients with a known germline *BRCA* pathogenic variant (*gBRCA*-positive) and operable breast cancer.

METHODS Eligibility included 1 cm or larger invasive tumor and *gBRCA*-positive disease. Human epidermal growth factor receptor 2–positive tumors were excluded. Twenty patients underwent a pretreatment biopsy, 6 months of once per day oral talazoparib (1 mg), followed by definitive surgery. Patients received adjuvant therapy at physician's discretion. The primary end point was residual cancer burden (RCB). With 20 patients, the RCB-0 plus RCB-I response rate can be estimated with a 95% CI with half width less than 20%.

RESULTS Twenty patients were enrolled from August 2016 to September 2017. Median age was 38 years (range, 23 to 58 years); 16 patients were *gBRCA1* positive and 4 patients were *gBRCA2* positive. Fifteen patients had triple-negative breast cancer (estrogen receptor/progesterone receptor < 10%), and five had hormone receptor-positive disease. Five patients had clinical stage I disease, 12 had stage II, and three had stage III, including one patient with inflammatory breast carcinoma and one with metaplastic chondrosarcomatous carcinoma. One patient chose to receive chemotherapy before surgery and was not included in RCB analyses. RCB-0 (pathologic complete response) rate was 53% and RCB-0/I was 63%. Eight patients (40%) had grade 3 anemia and required a transfusion, three patients had grade 3 neutropenia, and 1 patient had grade 4 thrombocytopenia. Common grade 1 or 2 toxicities were nausea, fatigue, neutropenia, alopecia, dizziness, and dyspnea. Toxicities were managed by dose reduction and transfusions. Nine patients required dose reduction.

CONCLUSION Neoadjuvant single-agent oral talazoparib once per day for 6 months without chemotherapy produced substantial RCB-0 rate with manageable toxicity. The substantive pathologic response to single-agent talazoparib supports the larger, ongoing neoadjuvant trial (ClinicalTrials.gov identifier: [NCT03499353](https://clinicaltrials.gov/ct2/show/study/NCT03499353)).

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INTRODUCTION

Poly-(adenosine diphosphate [ADP]-ribose) polymerase (PARP) is a family of enzymes responsible for cellular activities such as DNA repair via base excision repair pathway and genetic stability.¹ The use of PARP inhibitors has been extensively evaluated in patients with multiple metastatic cancers and first achieved US Food and Drug Administration approval for advanced ovarian cancer. Although early studies also included patients with breast cancer, it was not until 2018 that PARP inhibitors were approved by the US Food and Drug Administration for a metastatic/locally advanced breast cancer indication.

Two randomized phase III trials have reported PARP inhibitor efficacy in comparison with physician's choice of chemotherapy for patients with locally advanced/metastatic breast cancer and a germline *BRCA* pathogenic variant (*gBRCA*-positive). The OlympiAD (ClinicalTrials.gov identifier: [NCT02000622](https://clinicaltrials.gov/ct2/show/study/NCT02000622)) trial evaluated olaparib at 300 mg orally twice per day versus capecitabine, eribulin, or vinorelbine. Olaparib improved progression-free survival compared with standard chemotherapy, with a hazard ratio of 0.58 (95% CI, 0.43 to 0.80).² The EMBRACA trial (ClinicalTrials.gov identifier: [NCT01945775](https://clinicaltrials.gov/ct2/show/study/NCT01945775)) evaluated talazoparib 1 mg orally once per day, also randomized versus physician's choice of chemotherapy (gemcitabine, eribulin, capecitabine,

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TABLE 1. Patient Characteristics

Characteristic	No. of Patients
Age, years	20
Median (range)	38 (23-58)
Race	
White	7
Black	5
Hispanic	5
Asian	3
<i>BRCA</i>	
1	16
2	4
Clinical stage	
I	5
II	12
III	3
Histology	
Ductal	18
Lobular	1
Metaplastic chondrosarcomatous	1
Tissue receptor subtype	
TNBC (ER and PR < 10%)	15
Hormone receptor positive (≥ 10%)	5

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; TNBC, triple-negative breast cancer.

and vinorelbine), and also showed a significant improvement in progression-free survival, with a hazard ratio of 0.54 (95% CI, 0.42 to 0.71).³ Notably, both of these trials demonstrated improvements in quality of life as well as decrease in time to meaningful deterioration for patients treated with the PARP inhibitors, in comparison with standard chemotherapy.⁴

To estimate tumor response to single-agent PARP inhibitors and assess drug effect in human tumors, a pilot trial at The University of Texas MD Anderson Cancer Center evaluated the effects of 2 months of neoadjuvant talazoparib before initiating standard neoadjuvant chemotherapy in gBRCA-positive patients with stage I to III breast cancer.⁵ The primary end point of that pilot study was to determine feasibility of accruing 20 patients over 2 years, thus measuring patient acceptance of delaying chemotherapy by 2 months for single-agent targeted therapy. Within 8 months, 13 patients were accrued to the trial. Two months of treatment with single-agent talazoparib resulted in a median decrease of tumor volume, as measured by breast ultrasound, of 88% (range, 30% to 98%). After additional evaluation of the study accrual rate, response, and lack of grade 4 toxicities, the study was halted early and the results were published. On the basis of these radiographic responses with only 2 months of therapy, this

separate study of 20 patients was proposed to evaluate a pathologic response from only talazoparib. The objective of this neoadjuvant trial was to evaluate the pathologic response and toxicity to single-agent talazoparib for 6 months in 20 patients with stage I to III breast cancer and who were gBRCA-positive before definitive surgery.

METHODS

This was a pilot study including 20 patients to obtain preliminary data to power a larger trial. Talazoparib was administered as single-agent oral dose of 1 mg per day for six cycles (each cycle was 28 days). The primary objective was pathologic response after 6 months of talazoparib. The secondary objective was evaluation of toxicity. Patients were identified for this trial if they had a germline *BRCA1* or *BRCA2* pathogenic variant as identified by a Clinical Laboratory Improvement Amendments–certified laboratory and stage I to III breast cancer. The primary tumor had to be 1 cm or larger. Imaging for each tumor included at least a mammogram and ultrasound. Biopsy was performed on suggestive nodes identified on ultrasound to confirm involvement. The tumor could have any hormone receptor (HR) status, but human epidermal growth factor receptor 2 fluorescence in situ hybridization amplified or 3+ by immunohistochemistry (as per ASCO/College of American Pathologists guideline) were excluded.⁶ Patients also were excluded if they had previous surgery, radiation, or systemic therapy for breast cancer. Exceptions were made for prior surgery for ductal carcinoma in situ or if the patient was at least 5 years from the treatment of a previous nonbreast malignancy. This trial was performed after approval by the institutional review board, and written informed consent was obtained from each participant. This trial was conducted under an institutional review board–approved protocol 2014-0045 and in accordance with relevant guidelines at The University of Texas MD Anderson Cancer Center.

Talazoparib was administered at a starting dose of 1 mg per day. Patients were considered evaluable if they received at least 4 months of talazoparib therapy and then proceeded to surgery within 6 weeks from the date of the last dose of talazoparib. One patient received 5 months of therapy, but with a lymph node enlarging she refused additional biopsy and proceeded instead to systemic chemotherapy before surgery. Her information is included for toxicity but not for the primary end point of pathologic response. Pathologic response was documented using the Residual Cancer Burden (RCB) Calculator (www.mdanderson.org/breastcancer_RCB).⁷

Toxicities were monitored and recorded per the Common Terminology Criteria for Adverse Events version 4.03. Toxicities were reported with the highest grade observed per individual. Patients could not initiate therapy if hemoglobin was less than 8.0 gm/dL. Dose reductions of 0.25 mg/d were made for grade 3 or 4 toxicity as per protocol.

TABLE 2. Tumor Responses per Patient

<i>BRCA 1 or BRCA 2</i>	Tissue Receptor	Clinical Stage	Surgery	RCB	Systemic Therapy After Surgery	Dose of Talazoparib at End of Study, mg	Highest-Grade Toxicity
1	TNBC	T2N3a	N/A	Did not go to surgery	N/A	1	2
1	TNBC	T2N1	SM	III	AC+PTX	0.75	3
1	TNBC	T2N0	BM	I	AC+PTX	0.5	3
1	HR positive	T1cN0	SM	0	TC	0.5	3
1	TNBC	T3N1c	UM	III	AC+PTX	1	2
1	TNBC	T2N0	BM	0	Declined chemotherapy	1	2
1	TNBC	T2N1	BM	0	AC+PTX	1	1
2	TNBC	T1cN0	BM	0	Declined chemotherapy	1	1
1	TNBC	T2N0	BM	II	AC+PTX	0.5	3
1	TNBC	T2N1	BM	0	AC+PTX	0.5	4
1	HR positive	T1cN0	BM	II	Endocrine only	1	3
1	TNBC	T4dN2	UM	0	AC+PTX	0.5	3
1	TNBC	T2N1	BM	II	AC+PTX	1	1
1	TNBC	T1cN0	BM	0	Declined chemotherapy	0.75	3
2	Invasive lobular HR positive	T1cN0	SM	0	Endocrine only	0.25	3
1	TNBC	T2N0	UM	II	AC+PTX	0.5	3
2	TNBC/metaplastic (chondrosarcomatous)	T2N0	BM	0	TC	1	1
1	TNBC	T2N0	BM	II	AC+PTX	1	2
1	HR positive	T1cN1	UM	0	Endocrine only	1	1
2	HR positive	T2N1	BM	I	Endocrine only	1	2

Abbreviations: AC+PTX, doxorubicin and cyclophosphamide, preceded by or followed by weekly paclitaxel; BM, bilateral mastectomy; HR, estrogen receptor and/or progesterone receptor $\geq 10\%$; N/A, not applicable; RCB, residual cancer burden; SM, segmental mastectomy; TC, docetaxel and cyclophosphamide; TNBC, triple-negative breast cancer; UM, unilateral mastectomy.

RESULTS

Nineteen patients completed 6 months of therapy before surgery, and one patient received 5 months of therapy and then received chemotherapy before surgery. Patients participated in this study beginning in August 2016, and the last patient started treatment in September 2017. Patient characteristics are listed in Table 1. All patients were women, although men were eligible to participate in this study.

For the 19 patients who had pathologic response outcome data, 10 had RCB-0 (pathologic complete response [pCR]), which correlates to no invasive disease in breast and lymph nodes. Two patients had an RCB-I, five had RCB-II, and three had RCB-III. The RCB-0/pCR rate was 53% (95% CI, 32% to 73%) and RCB-0/I was 63% (95% CI, 41% to 81%). RCB-0 and RCB-I were seen across both *BRCA1* and *BRCA2* as well as in HR-positive and triple-negative breast cancer (TNBC). In these subgroups, the percentages of RCB-0/I were: TNBC 57% (95% CI, 29% to 82%), HR positive 80% (95% CI, 28% to 99%), T1 tumors 83%

(95% CI, 36% to 100%), and T2 or greater 54% (95% CI, 25% to 81%). For patients with *BRCA1*-positive disease, RCB-0/I disease was 53% (95% CI, 27% to 79%), and all of the *BRCA2* patients had RCB-0/I response (95% CI, 40% to 100%). Of note, the one patient with metaplastic chondrosarcomatous carcinoma, one patient with invasive lobular carcinoma, and a third patient with inflammatory breast cancer all had a pCR/RCB-0 response to talazoparib. Table 2 lists the response per patient, with information regarding their clinical stage, HR status, pathologic response, and systemic therapy after surgery.

Toxicity

There were 12 grade 3 toxicities and one grade 4 toxicity. Anemia and nausea were the most common toxicities experienced, and a full list of recorded toxicities can be found in Table 3. Eight patients required transfusions during the course of the therapy. Figure 1 demonstrates hemoglobin levels as trended over time for the eight patients who required transfusions. A total of 29 units were

TABLE 3. Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Total
Hematologic toxicities					
Anemia	4	3	8	—	15
Decreased WBCs	8	4	—	—	12
Neutropenia	—	4	3	—	7
Thrombocytopenia	—	—	—	1	1
Nonhematologic toxicities					
Nausea	14	1			15
Fatigue	14				14
Alopecia	11				11
Dizziness	6				6
Dyspnea	5				5
Hyperglycemia	5				5
Pain (other)	4	1			5
Pain in breast	4				4
Increased transaminases	4				4
Mucositis	4				4
Vomiting	2	1			3
UTI		2	1		3
Hypomagnesemia	3				3
Sinusitis		2			2
Headache	2				2
Constipation	2				2
Diarrhea	2				2
Hypernatremia	2				2
Increased creatinine	1				1
Hypokalemia	1				1
Headache	1				1
Increased phosphorous	1				1
Increased BUN	1				1
Hypophosphatemia	1				1
Anxiety	1				1
Vaginal bleeding	1				1
Bronchitis		1			1
Hyperphosphatemia	1				1
Flatulence	1				1

Abbreviations: BUN, blood urea nitrogen; UTI, urinary tract infection.

transfused, with 1 to 2 units per transfusion mostly post cycles 2 through 6 of talazoparib. One patient required 1 unit one time, three patients required 2 units one time, two patients required 2 units twice, and two patients required 2 units three times. None of the patients reported a change in their menstrual cycles while taking talazoparib.

Dose Reductions

Eleven patients completed therapy at the full dose of 1 mg, two patients completed at a reduced dose of 0.75 mg, six

patients completed the study at a dose level of 0.5 mg, and one patient completed the study at a dose level of 0.25 mg. All of the dose reductions were the result of hematologic toxicity.

Compliance

Nine patients experienced dose delays, with a median delay of 17 days (range, 8 to 41 days). Eleven patients received doses as scheduled. Nine patients missed one to three doses that were not planned or protocol mandated during the study, and no patients missed more than three doses that were not planned or protocol mandated.

DISCUSSION

This trial of 20 *gBRCA*-positive patients who received single-agent oral talazoparib before definitive surgery for early-stage breast cancer demonstrated the ability of a single targeted agent to achieve pCR in a *gBRCA*-positive patient population. Given the excellent prognosis associated with achieving pCR and RCB-I with standard chemotherapy,⁸ the 53% rate of pCR and 63% rate of pCR/RCB-I with single-agent talazoparib is encouraging. Additional studies, however, are needed to determine if pCR to PARP inhibitor therapy has the same favorable prognosis as that seen with chemotherapy. Importantly, excellent pathologic responses were seen across *BRCA* mutation types, in both HR-positive and TNBC tumors, as well as subtypes known for chemotherapy resistance to neoadjuvant therapy, such as inflammatory breast cancer, metaplastic cancer, and invasive lobular carcinoma. Although the numbers are small, the preliminary data suggest that patients with HR-positive and *BRCA*-positive tumors may respond better, a suggestion also seen in the EMBRACA trial.

The response to neoadjuvant chemotherapy in patients with *gBRCA*-positive cancer has been described in multiple series. In a cohort of patients with *gBRCA*-positive breast cancer from The University of Texas MD Anderson Cancer Center, 26 (46%) of 57 patients achieved a pCR with mostly third-generation chemotherapy regimens.⁹ Silver et al¹⁰ described 28 women with TNBC who received four cycles of cisplatin at 75 mg/m² every 21 days, with a pCR rate of 22%. Both of the *gBRCA*-positive patients in this cohort had a pCR. Byrski et al¹¹ reported a trial of 107 women with a *gBRCA1* mutation who received cisplatin 75 mg/m² every 3 weeks for four cycles. The overall pCR rate was 61%. The toxicity reported in the article described early discontinuation of therapy in five patients and mostly grade 1 and 2 toxicities, including tinnitus. Interestingly, in a subset of 50 *gBRCA*-positive patients from the GeparSixto (ClinicalTrials.gov identifier: [NCT0146880](#)) trial, pCR was 66.7% and was not improved with the addition of carboplatin.¹² The INFORM (ClinicalTrials.gov identifier: [NCT01670500](#)) trial has completed accrual, and results are anticipated to directly compare platinum versus doxorubicin and cyclophosphamide (AC) chemotherapy in patients with *gBRCA*-positive breast cancer.

FIG 1. Hemoglobin in the eight patients who required transfusions.

Given earlier signs of efficacy for patients with *gBRCA*-positive metastatic breast cancer in multiple phase I and II trials, PARP inhibitors have also been evaluated in the neoadjuvant setting for treatment of early-stage breast cancer.¹³ The I-SPY 2 (ClinicalTrials.gov identifier: [NCT01042379](#)) trial evaluated the neoadjuvant combination of the PARP inhibitor veliparib with carboplatin and paclitaxel, followed by AC using a Bayesian-based adaptive randomization design to compare response to standard taxane plus anthracycline therapy.¹³ The estimated pCR rate for the experimental arm was 33% versus 22% (control) in unselected patients and 51% versus 26% in TNBC, respectively. Given these findings, the BrighTNess (ClinicalTrials.gov identifier: [NCT02032277](#)) trial evaluated three neoadjuvant therapeutic strategies: paclitaxel alone, paclitaxel and carboplatin, and paclitaxel, carboplatin, and veliparib, followed by AC in each arm.¹⁴ Approximately 15% of the patients in BrighTNess also were *gBRCA* positive. Although the study was not designed to evaluate differences between the three arms, the arms with carboplatin had a higher pCR, which was not further improved with the addition of veliparib. Notably, combining chemotherapies with PARP inhibitors at dosing levels that still inhibit PARP has been challenging because of overlying hematologic toxicities.

Although therapy was administered in a treatment-naïve, newly diagnosed patient population, toxicities were similar to those previously described in patients treated with

talazoparib in the metastatic setting. The most common toxicities seen were anemia and nausea. Anemia was manageable by dosing delay, dose reduction, and transfusion, when indicated. Transfusions were administered in eight of the treated patients, because the drug could not be resumed until the hematologic toxicity resolved to a grade 1. Most transfusions were required during cycles 2 through 6; it is important to monitor serial hematologic profiles throughout treatment with talazoparib. Given the relatively substantial number of patients requiring transfusions, it will be critical not only to monitor this in the larger national trial but also to determine if there is an underlying mechanism for patients with little to no anemia versus those requiring multiple transfusions. Most nonhematologic toxicities were grade 1 and manageable with appropriate supportive treatment.

The study has several limitations. First, this was a small, single-institution trial designed to evaluate the ability to accrue and estimate pCR rates to a neoadjuvant trial of talazoparib in a select patient population of *gBRCA*-positive patients, resulting in wide confidence intervals for pCR prediction. As such, a larger confirmatory trial is needed to more accurately determine single-agent pCR rates. Second, although toxicity was followed and carefully recorded at each study visit, there were no patient-reported outcome (PRO) instruments used for this study. PROs would be of interest in the larger, confirmatory trial given the significant improvements noted in the PROs in the EMBRACA trial.⁴ In

addition, although patients were asked whether they noticed a change in their menstrual cycles at clinic visits, the trial included no objective measurements, such as checking anti-Müllerian hormone levels pre and post therapy. Such measurements will be critical, because many *gBRCA*-positive patients develop cancer at younger age, and fertility is an important part of the treatment and survivorship plan. Finally, because this is a single-arm study, treatment can be compared only to historic pathologic response rates and hence cannot directly compare single-agent PARP inhibition versus platinum chemotherapy.

Another important question unanswered by this pilot trial is the optimal postsurgical treatment plan for patients. For the six patients with HR-positive disease, five proceeded to adjuvant endocrine therapy only and one to adjuvant docetaxel and cyclophosphamide followed by endocrine therapy. For these younger patients with TNBC, whether to omit chemotherapy after a pCR cannot be answered by this study, because many did receive adjuvant chemotherapy; this question merits additional investigation. Outcomes and long-term symptoms in a larger, multicenter trial are needed to determine if single-agent talazoparib is sustainable as a de-escalation of therapy.

To the best of our knowledge, this study is the first to show a single-agent, targeted therapy achieved pCR in patients with *gBRCA*-positive breast cancer, including TNBC and HR-positive breast cancer, without the addition of chemotherapy. Other neoadjuvant trials have failed to show significant benefit for PARP inhibition. However, these trials

evaluated PARP and chemotherapy combination trials and were not specific to a *gBRCA*-positive-only population. Also, they may have limited applicability, because the chosen PARP inhibitor, veliparib, is not as strong a PARP inhibitor or a PARP trapper, as is talazoparib.¹⁵ In addition, combining PARP inhibition plus chemotherapy has the challenge of overlapping toxicities, requiring consequent dose reductions. There are multiple other ongoing studies evaluating the use of PARP inhibition in combination with chemotherapy, such as the PARTNER (ClinicalTrials.gov identifier: [NCT03499353](https://clinicaltrials.gov/ct2/show/study?term=NCT03499353)) trial and the GeparOla trial (ClinicalTrials.gov identifier: [NCT02789332](https://clinicaltrials.gov/ct2/show/study?term=NCT02789332)), or as part of adjuvant therapy for patients with residual disease in the OlympiA trial (ClinicalTrials.gov identifier: [NCT02032823](https://clinicaltrials.gov/ct2/show/study?term=NCT02032823)). These and other trials are currently accruing and will enhance our understanding of how PARP inhibitors can further affect the treatment of early breast cancer.

In conclusion, this pilot trial of neoadjuvant talazoparib starting at 1 mg orally once per day for 6 months was used before surgery for early breast cancer, resulting in a pCR rate of 53% and RCB-O/I rate of 63%. The toxicities were mostly hematologic and managed by dosing delay, dose reduction, and blood transfusions. In addition, the 2-month window study with a strong biologic rationale, which quickly can lead into a full neoadjuvant therapy, as done in this instance with talazoparib, may be a novel strategy for developing and de-escalating therapy in the neoadjuvant space. This trial is completing the ongoing larger, multicenter trial (ClinicalTrials.gov identifier: [NCT03499353](https://clinicaltrials.gov/ct2/show/study?term=NCT03499353)).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Neoadjuvant Talazoparib for Patients With Operable Breast Cancer With a Germline *BRCA* Pathogenic Variant**

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Travel, Accommodations, Expenses: Physician Education Resource, Med Learning Group, Medscape

Marion E. Scoggins

Research Funding: General Electric (Inst)

Rashmi K. Murthy

Consulting or Advisory Role: Puma Biotechnology, Genentech

Research Funding: Genentech (Inst), Daiichi Sankyo (Inst), Cascadian Therapeutics (Inst), Pfizer (Inst), EMD Serono (Inst), Seattle Genetics (Inst)

Senthil Damodaran

Honoraria: Novartis

Consulting or Advisory Role: Tempus, Taiho Pharmaceutical, Pfizer

Research Funding: EMD Serono, Guardant Health

Travel, Accommodations, Expenses: Phillips Gilmore Oncology Communications

Sarah M. DeSnyder

Research Funding: ImpediMed

Carlos H. Barcenas

Speakers' Bureau: Genomic Health

Research Funding: Puma Biotechnology (Inst)

Vicente Valero

Honoraria: Genentech

Consulting or Advisory Role: Genentech

Travel, Accommodations, Expenses: Genentech

Gary J. Whitman

Stock and Other Ownership Interests: Pfizer

Elizabeth A. Mittendorf

Honoraria: Physician Education Resource

Consulting or Advisory Role: Peregrine Pharmaceuticals, TapImmune, Sella Life Sciences, Merck, Genomic Health

Research Funding: Galena Biopharma (Inst), Genentech (Inst), AstraZeneca (Inst), EMD Serono (Inst)

Alastair M. Thompson

Honoraria: Novartis (I)

Honoraria: Pfizer

Research Funding: Genentech (Inst)

Travel, Accommodations, Expenses: Novartis (I), Pfizer

Nuhad Ibrahim

Honoraria: Celgene, Roche, Novartis

Consulting or Advisory Role: Immunomedics

Speakers' Bureau: Celgene, Roche, Novartis

Research Funding: Nektar Therapeutics

Travel, Accommodations, Expenses: Roche, Novartis

Stacy L. Moulder

Honoraria: Novartis, Pfizer (I)

Research Funding: Oncocyte (Inst), Pfizer (Inst), Novartis (Inst), Genentech (Inst), Takeda (Inst), Bayer (Inst), EMD Serono (Inst), Genentech (Inst)

Travel, Accommodations, Expenses: Novartis, Pfizer (I)

Banu K. Arun

Consulting or Advisory Role: Bright Pink, AbbVie

Research Funding: AbbVie (Inst), PharmaMar (Inst), AstraZeneca (Inst), InVivo (Inst)

Travel, Accommodations, Expenses: AstraZeneca

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