Published in final edited form as:

Int J Gynecol Cancer. 2016 February ; 26(2): 255–260. doi:10.1097/IGC.0000000000000591.

A phase II, single arm study of iniparib in patients with *BRCA1* or *BRCA2* associated advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer

Katherine M. Bell-McGuinn, MD, PhD¹, Jason A. Konner, MD¹, William P. Tew, MD¹, Martee L. Hensley, MD¹, Alexia Iasonos, PhD², Eric Charpentier, PhD³, Svetlana Mironov, MD⁴, Paul Sabbatini, MD¹, and Carol Aghajanian, MD¹

¹Department of Medicine, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York NY

²Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

³Sanofi Statistics Department, Cambridge MA

⁴Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY

Abstract

Objective—To evaluate the activity and tolerability of iniparib monotherapy in women with *BRCA1* or *BRCA2* associated advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Methods/Materials—Eligible patients had advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer, germline *BRCA1* or *BRCA2* mutation, measurable disease, and at least one prior treatment regimen of platinum/taxane chemotherapy. Patients received iniparib 8mg/kg IV on days 1 and 4 weekly, with imaging every 8 weeks. Treatment continued until disease progression or adverse events (AEs) prohibited further therapy. Common Terminology Criteria for Adverse Events (CTCAE) v3.0 was used to grade AEs. The primary endpoint was tumor response. The study was conducted with a Simon two-stage design with 12 and 23 patients planned in the first and second stage, respectively. The study was designed to distinguish between 10% versus 30% responding with a type 1 and type 2 error of 0.10.

Results—Twelve patients were treated on study, with median exposure to iniparib of 7.5 weeks. The median number of prior chemotherapeutic regimens was 7. Treatment-related AEs (10%) included asthenia (83.3%), constipation (25%), diarrhea (25%), nausea (25%), abdominal pain (16.7%), and decreased hemoglobin (16.7%). All treatment-related AEs were grade 1–2 with two exceptions: one grade 3 diarrhea and one grade 3 hypertension. One patient had stable disease lasting 2 cycles; the remaining 11 patients had progressive disease. The study did not proceed to second stage enrollment.

Conclusions—Iniparib did not show significant activity in this heavily pre-treated ovarian cancer population, all of whom had *BRCA1* or *BRCA2* mutations.

Keywords

iniparib; ovarian carcinoma; fallopian tube carcinoma; primary peritoneal carcinoma; BRCA

Introduction

Poly (ADP-ribose) polymerase (PARP) inhibitors have shown monotherapy efficacy against *BRCA1* and *BRCA2* deficient tumors *in vitro*, *in vivo*, and in clinical trials.^{1–7} This efficacy has been hypothesized to be a result of synthetic lethality: tumors deficient in *BRCA* function are uniquely sensitive to blockade of DNA single-strand break repair via PARP, which results in single strand breaks being converted to double strand breaks that are subsequently unable to be repaired via homologous recombination in the absence of *BRCA* function. Germline *BRCA1* and *BRCA2* mutations are found in up to 25% of patients with high grade serous ovarian, fallopian tube, or primary peritoneal cancer.^{8,9} Monotherapy activity of the PARP inhibitor olaparib in patients with germline *BRCA* mutations and recurrent ovarian cancer led to FDA approval in 2014 for patients with 3 or more prior therapies.¹⁰

Iniparib (4-iodo-3-nitrobenzamide) was initially reported to be a PARP inhibitor with the active metabolite (4-iodo-3-nitrosobenzamide) leading to oxidative inactivation of one zinc finger of PARP, disrupting the interaction between PARP and DNA and rendering the enzyme inactive.¹¹ Additional cell line studies comparing PARP1-competent cells to PARP1 knockdown cells showed that iniparib's inhibition of single strand DNA break repair was dependent upon PARP1 expression whereas olaparib's inhibition of single strand DNA break repair was not.¹² Further preclinical studies comparing iniparib to veliparib and olaparib failed to show expected PARP inhibitor activity of iniparib when compared to the other two agents.^{13,14} Specifically, iniparib failed to inhibit PARP enzymatic or cellular activity, potentiate temozolomide activity, sensitize cells to topoisomerase I poisons, or selectively kill homologous recombination deficient cells including in a *BRCA*-deficient setting.

This study was conducted early in the clinical development of iniparib to assess monotherapy efficacy and tolerability in patients with recurrent *BRCA1* or *BRCA2* associated advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Methods

Eligibility

Eligible patients had histologically or cytologically confirmed advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (stage III or IV), a confirmed germline *BRCA1* or *BRCA2* deleterious mutation, and at least one prior regimen of platinum and taxane based therapy. A Karnofsky performance status greater than or equal to 70% was required along with an estimated life expectancy of at least 16 weeks and one or more measurable lesions

by RECIST criteria. Patients were excluded for any of the following laboratory parameters: absolute neutrophil count < 1500/ μ L, platelet count < 100,000/ μ L, hemoglobin < 8.5 g/dL, serum bilirubin > 2.0 times the upper limit of normal (ULN), aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 times ULN (AST or ALT > 5 times ULN for subjects with liver metastases), or serum creatinine > 1.5 times ULN. Additional exclusion criteria included the following: any anti-cancer therapy within 21 days prior to day 1; another malignancy within 3 years of day 1 except adequately treated carcinoma in situ of the cervix, ductal carcinoma in situ (DCIS) of the breast, or basal or squamous cell skin cancer; active viral infection including HIV/AIDS, hepatitis B or hepatitis C; active central nervous system or brain metastases; history of seizures or current treatment with anti-epileptic medications; and persistent grade 2 or greater toxicities from prior therapy, excluding alopecia.

Treatment Plan

Patients received iniparib intravenously at a dose of 8mg/kg twice weekly. The doses were administered on days 1 and 4 of each week. Scheduling delays were permitted only if doses of iniparib would remain separated by 2 treatment-free days. Iniparib was held for any grade 3 or 4 toxicity until it resolved to < grade 2. Iniparib was then resumed at the same dose for toxicities unrelated to study drug and reduced for toxicities at least possibly related to study drug. Two dose reductions were allowed: reduction to iniparib 5.6 mg/kg for the first occurrence followed by reduction to 4.0 mg/kg for the second occurrence. A third occurrence of grade 3 or 4 toxicity led to discontinuation of protocol therapy.

One cycle was defined as 8 weeks of treatment. During cycle 1, patients were evaluated every other week with a complete history and physical exam, performance status assessment, and blood work that included a complete blood count, coagulation studies, comprehensive metabolic panel, and magnesium level. Patients had a baseline CT or MRI scan within 4 weeks of starting treatment and a repeat scan during week 8 of each cycle. Patients could continue on therapy as long as there was stable or responding disease per RECIST criteria and no unacceptable toxicities.

Statistical Design

The primary endpoint of the study was objective response rate. This was defined by RECIST criteria as the total of complete and partial responses (CR+PR). Patients were evaluated for response at the end of the first cycle of therapy. Enrollment followed a Simon optimal two-stage statistical design with a maximum of 35 patients.¹⁵ Twelve patients were enrolled in the first stage. If 2/12 patients in the first stage had a CR or PR, 23 additional patients would be enrolled in the second stage. If at least 6/35 patients had a response at the end of the trial, the study would be declared positive. The study was powered to see a difference between a 10% and 30% response rate with a type 1 error = 0.10 and a type 2 error = 0.10.

Secondary endpoints included clinical benefit rate defined as CR+PR+stable disease (SD), clinical outcome including progression-free survival (PFS) and overall survival (OS), CA125 response defined as a decrease to a normal range (0–35) with a confirmatory value followed at the next cycle, and safety and tolerability. Safety was described by tabulating toxicities

using the NCI Common Terminology Criteria for Adverse Events (version 3.0). Tolerability was defined as the ability to adhere to twice-weekly dosing without missing more than two doses out of 16.

Results

Twelve patients were enrolled on the study (Table 1). The median number of prior chemotherapeutic regimens was 7 (range, 5 to 14). None of the patients had received a prior PARP inhibitor. Three of the 12 patients (25%) had a treatment-free interval of 6 months from their last platinum therapy. Six patients (50%) had parenchymal liver involvement at the time of enrollment. The median exposure to iniparib was 7.5 weeks (range, 3.5 to 15.5 weeks).

All 12 (100%) patients experienced at least one adverse event of any grade regardless of causality (Table 2). Treatment-related AEs (any grade) occurring in 10% of patients included asthenia (83.3%), constipation (25%), diarrhea (25%), nausea (25%), abdominal pain (16.7%), and decreased hemoglobin (16.7%). The majority of treatment-related AEs were grade 1–2. Two treatment-related grade 3 AEs were reported: diarrhea and hypertension. There were no treatment-related grade 4 or 5 AEs. Overall, treatment was well tolerated, with 11 of 12 patients receiving all planned doses. One patient missed 2 of 14 doses secondary to grade 3 and 4 elevation of AST and ALT, respectively. The elevation of her AST and ALT was considered to be more likely related to her underlying liver metastases than the protocol therapy.

In this heavily pretreated population with advanced ovarian cancer, many AEs (any grade, incidence 50%), regardless of causality, were reported: hypoalbuminemia (100%); hyperglycemia (91.7%); asthenia and decreased hemoglobin (each 83.3%); increased activated partial thromboplastin time (66.7%); constipation, hyperbilirubinemia, increased AST, increased alkaline phosphatase, and increased international normalized ratio (each 58.3%); and hyponatremia and abdominal pain (each 50%). Grade 3 or higher AEs, regardless of causality, were observed in 7 (58.3%) patients. These events included increased ALT, increased alkaline phosphatase, and increased international normalized ratio (each 16.7%), and malignant pleural effusion, lymphopenia, hyponatremia, hypertension, diarrhea, hyperbilirubinemia, increased activated partial thromboplastin time, increased AST, and death (each 8.3%).

Five (41.7%) patients experienced a serious adverse event (SAE) while on study. Four SAEs were unrelated to study drug and included grade 2 hematuria, grade 3 hyperbilirubinemia, grade 3 malignant pleural effusion, and death due to disease progression. One SAE of grade 3 hypertension was reported as related to study drug. No AEs led to permanent treatment discontinuation.

Among the 12 patients who received the study drug, no complete or partial responses were seen. One patient had stable disease that lasted 1 cycle; she came off treatment after cycle 2 due to progression of disease. She was one of the 3 platinum sensitive patients on the trial and the only patient who experienced a decline in her CA125 level on study. The remaining

11 patients had progressive disease during or after 1 cycle of treatment. Nine of the 11 patients had a documented rise in CA125 while on study. Two patients did not get a repeat CA125 at the time of protocol therapy discontinuation. Median PFS was 1.6 months (range, 0.7 to 3.6 months), with 6 of 12 patients (50%) discontinuing treatment prior to 1 cycle secondary to symptoms or signs of progression that led to early radiologic assessment confirming progression. Median OS was 11.4 months (range, 1.9 to 41.0 months), with 3 of 12 patients (25%) surviving less than 3 months. The study was discontinued at Stage 1 of the Simon's two-stage design due to lack of observed responses; no safety concerns were noted.

Discussion

Iniparib failed to show monotherapy efficacy in this study. No partial or complete responses were seen. One of the 12 patients had stable disease, ultimately coming off study for disease progression after 2 cycles. Iniparib was well tolerated, with the majority of treatment-related AEs being grade 1–2. There were only two treatment-related grade 3 AEs, - diarrhea and hypertension; both occurred in patients in whom these were pre-existing conditions that were exacerbated during study treatment.

Two important lessons were learned to help guide future early phase studies. First, as discussed by others, care should be taken to seek out and understand the pre-clinical data of a drug prior to clinical investigations.¹⁶ While there was reported basic science data from environmental and chemistry based laboratories suggesting the inhibition of PARP activity by iniparib prior to its development, data from pre-clinical cancer models was not readily available. The phase I trial of iniparib in advanced heavily pretreated (mean number of prior regimens > 6) solid tumor patients showed a best response of stable disease in 6/23 patients.¹⁷ Studies showing the inability of iniparib to produce expected PARP inhibition effects were reported in 2012, well after completion of this study.^{13,14}

In the event that iniparib had been an effective PARP inhibitor, there was still a chance that efficacy would not have been seen in this study given the fact that all of the enrolled patients had advanced disease. Prior to the design of this study, the activity of olaparib in heavily pre-treated germline *BRCA* ovarian cancer patients had been presented.¹⁸ Given those favorable results, this study had no limits on prior lines of therapy. While the median or mean number of lines of prior therapy in the published olaparib studies has been 3–4, this study enrolled much more heavily pre-treated patients who may not have responded even to an active drug given the point in their disease course.^{4–6,10} In fact, 3 of 12 patients (25%) died within 3 months of study enrollment, while eligibility required a life expectancy of 16 weeks. Of the 8 patients who continued their care at our study center after disease progression on iniparib therapy, 3 (25%) were referred to hospice within 1 month of study discontinuation and 2 (16.7%) progressed on their next line of therapy and were referred to hospice within 3 months of study discontinuation. Three patients (25%) had a partial response to paclitaxel alone (1 patient) or to paclitaxel and bevacizumab (2 patients) as their next line of therapy, with responses lasting 2.5–5 months. Two of these 3 patients then experienced rapidly progressive disease, and each received an additional 3 lines of inactive therapy. One of the 3 patients had prolonged stable disease on multiple lines of therapy lasting 2 years. For future

trials, investigators should consider limiting the total lines of therapy in eligibility criteria so as not to deem a potentially active drug inactive.

Acknowledgments

Funding: Sanofi funded this trial, NCT00677079.

References

1. Bryant HE, Schultz N, Thomas HD, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature*. 2005; 434:913–917. [PubMed: 15829966]
2. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature*. 2005; 434:917–921. [PubMed: 15829967]
3. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from *BRCA* mutation carriers. *N Engl J Med*. 2009; 361(2):123–134. [PubMed: 19553641]
4. Fong PC, Yap TA, Boss DS, et al. Poly (ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. *J Clin Oncol*. 2010; 28:2512–2519. [PubMed: 20406929]
5. Audeh MW, Carmichael J, Penson RT, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. *Lancet*. 2010; 376:245–251. [PubMed: 20609468]
6. Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol*. 2011; 12:852–861. [PubMed: 21862407]
7. Coleman RL, Sill MW, Bell-McGuinn K, et al. A phase II evaluation of the potent, highly selective PARP inhibitor veliparib in the treatment of persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who carry a germline BRCA1 or BRCA2 mutation – an NRG Oncology/Gynecologic Oncology Group study. *Gynecol Oncol*. 2015 Epub ahead of print.
8. Alsop K, Fereday S, Meldrum C, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. *J Clin Oncol*. 2012; 30:2654–2663. [PubMed: 22711857]
9. Pennington KP, Walsh T, Harrell MI, et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. *Clin Cancer Res*. 2014; 20:764–775. [PubMed: 24240112]
10. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and germline *BRCA 1/2* mutation. *J Clin Oncol*. 2015; 33:244–250. [PubMed: 25366685]
11. Mendeleyev J, Kirsten E, Hakam A, et al. Potential chemotherapeutic activity of 4-iodo-3-nitrobenzamide. *Biochem Pharmacol*. 1995; 50:705–714. [PubMed: 7669074]
12. Ma W, Halweg CJ, Menendez D, et al. Differential effects of poly(ADP-ribose) polymerase inhibition on DNA break repair in human cells are revealed with Epstein-Barr virus. *Proc Natl Acad Sci*. 2012; 109:6590–6595. [PubMed: 22493268]
13. Liu X, Shi Y, Maag DX, et al. Iniparib nonselectively modifies cysteine-containing proteins in tumor cells and is not a *bona fide* PARP inhibitor. *Clin Cancer Res*. 2012; 18:510–523. [PubMed: 22128301]
14. Patel AG, De Lorenzo SB, Flatten KS, et al. Failure of iniparib to inhibit poly(ADP-ribose) polymerase *in vitro*. *Clin Cancer Res*. 2012; 18:1655–1662. [PubMed: 22291137]
15. Simon R. Optimal 2-stage trial design for phase II trials. *Controlled Clinical Trials*. 1989; 10:1–10. [PubMed: 2702835]
16. Mateo J, Ong M, Tan DSP, et al. Appraising iniparib, the PARP inhibitor that never was – what must we learn? *Nat Rev Clin Oncol*. 2013; 10:688–696. [PubMed: 24129347]

17. Kopetz S, Mita MM, Mok I, et al. First in human phase I study of BSI-201, a small molecule inhibitor of poly ADP-ribose polymerase (PARP) in subjects with advanced solid tumors. *J Clin Oncol*. 2008; 26(15S):3577.
18. Yap TA, Boss DS, Fong PC, et al. First in human phase I pharmacokinetic (PK) and pharmacodynamic (PD) study of KU-0059436 (ku), a small molecule inhibitor of poly ADP-ribose polymerase (PARP) in cancer patients (p), including BRCA1/2 mutation carriers. *J Clin Oncol*. 2007; 25(18S):3529.

Table 1

Patient Clinical Characteristics

Characteristic	No. of Patients (N = 12)		%
Age, years			
Median		53	
Range		(42–74)	
Race			
White	12		100
Karnofsky performance status			
100	0		0
80–90	12		100
Time since diagnosis, months			
Median		61	
Range		(29–96)	
No. of prior chemotherapy regimens			
Median		7	
Range		(5–14)	
Platinum sensitivity			
Progression < 6 months from last platinum	9		75
Progression ≥ 6 months from last platinum	3		25
Baseline CA125, units/mL			
Median		785.5	
Range		(25–7666)	
BRCA mutation			
BRCA1	9		75
BRCA2	3		25
Histology			
High grade serous carcinoma	11		92
Poorly differentiated carcinoma, favor serous	1		8

Table 2

Adverse Events (any cause). *

	Any	Grade 3	Grade 4	Grade 5
Event	n (%)	n (%)	n (%)	n (%)
Any Event	12 (100)	8 (66.7)	1 (8.3)	1 (8.3)
Hypoalbuminemia	12 (100)	0 (0)	0 (0)	0 (0)
Hyperglycemia	11 (91.7)	0 (0)	0 (0)	0 (0)
Asthenia	10 (83.3)	0 (0)	0 (0)	0 (0)
Anemia	10 (83.3)	0 (0)	0 (0)	0 (0)
Increased activated partial thromboplastin time	8 (66.7)	1 (8.3)	0 (0)	0 (0)
Constipation	7 (58.3)	0 (0)	0 (0)	0 (0)
Hyper bilirubinemia	7 (58.3)	1 (8.3)	0 (0)	0 (0)
Increased aspartate aminotransferase	7 (58.3)	1 (8.3)	0 (0)	0 (0)
Increased alkaline phosphatase	7 (58.3)	2 (16.7)	0 (0)	0 (0)
Increased international normalized ratio	7 (58.3)	2 (16.7)	0 (0)	0 (0)
Abdominal pain	6 (50)	0 (0)	0 (0)	0 (0)
Hyponatremia	6 (50)	1 (8.3)	0 (0)	0 (0)
Nausea	4 (33.3)	0 (0)	0 (0)	0 (0)
Increased alanine aminotransferase	4 (33.3)	1 (8.3)	1 (8.3)	0 (0)
Diarrhea	3 (25)	1 (8.3)	0 (0)	0 (0)
Hypokalemia	3 (25)	0 (0)	0 (0)	0 (0)
Increased creatinine	3 (25)	0 (0)	0 (0)	0 (0)
Leukopenia	3 (25)	0 (0)	0 (0)	0 (0)
Cough	2 (16.7)	0 (0)	0 (0)	0 (0)
Dyspnea	2 (16.7)	0 (0)	0 (0)	0 (0)
Edema, peripheral	2 (16.7)	0 (0)	0 (0)	0 (0)
Neutropenia	2 (16.7)	0 (0)	0 (0)	0 (0)
Pain, extremity	2 (16.7)	0 (0)	0 (0)	0 (0)
Pain, flank	2 (16.7)	0 (0)	0 (0)	0 (0)
Pyrexia	2 (16.7)	0 (0)	0 (0)	0 (0)
Reflux gastritis	2 (16.7)	0 (0)	0 (0)	0 (0)
Thrombocytopenia	2 (16.7)	0 (0)	0 (0)	0 (0)
Urinary incontinence	2 (16.7)	0 (0)	0 (0)	0 (0)
Vomiting	2 (16.7)	0 (0)	0 (0)	0 (0)
Abdominal distention	1 (8.3)	0 (0)	0 (0)	0 (0)
Increased amylase	1 (8.3)	0 (0)	0 (0)	0 (0)
Anorexia	1 (8.3)	0 (0)	0 (0)	0 (0)
Anxiety	1 (8.3)	0 (0)	0 (0)	0 (0)
Arthralgia	1 (8.3)	0 (0)	0 (0)	0 (0)

	Any	Grade 3	Grade 4	Grade 5
Event	n (%)	n (%)	n (%)	n (%)
Back pain	1 (8.3)	0 (0)	0 (0)	0 (0)
Chest pain	1 (8.3)	0 (0)	0 (0)	0 (0)
Chills	1 (8.3)	0 (0)	0 (0)	0 (0)
Death	1 (8.3)	0 (0)	0 (0)	1 (8.3)
Depressed mood	1 (8.3)	0 (0)	0 (0)	0 (0)
Dizziness	1 (8.3)	0 (0)	0 (0)	0 (0)
Dry mouth	1 (8.3)	0 (0)	0 (0)	0 (0)
Dry skin	1 (8.3)	0 (0)	0 (0)	0 (0)
Dysgeusia	1 (8.3)	0 (0)	0 (0)	0 (0)
Epistaxis	1 (8.3)	0 (0)	0 (0)	0 (0)
Exfoliative rash	1 (8.3)	0 (0)	0 (0)	0 (0)
Hearing impaired	1 (8.3)	0 (0)	0 (0)	0 (0)
Hematuria	1 (8.3)	0 (0)	0 (0)	0 (0)
Hemorrhage, anal	1 (8.3)	0 (0)	0 (0)	0 (0)
Hemorrhage, rectal	1 (8.3)	0 (0)	0 (0)	0 (0)
Hot flush	1 (8.3)	0 (0)	0 (0)	0 (0)
Hypercalcemia	1 (8.3)	0 (0)	0 (0)	0 (0)
Hyperkalemia	1 (8.3)	0 (0)	0 (0)	0 (0)
Hypernatremia	1 (8.3)	0 (0)	0 (0)	0 (0)
Hypertension	1 (8.3)	1 (8.3)	0 (0)	0 (0)
Hypomagnesemia	1 (8.3)	0 (0)	0 (0)	0 (0)
Insomnia	1 (8.3)	0 (0)	0 (0)	0 (0)
Lymphopenia	1 (8.3)	1 (8.3)	0 (0)	0 (0)
Malignant pleural effusion	1 (8.3)	1 (8.3)	0 (0)	0 (0)
Muscular weakness	1 (8.3)	0 (0)	0 (0)	0 (0)
Musculoskeletal chest pain	1 (8.3)	0 (0)	0 (0)	0 (0)
Musculoskeletal disorder	1 (8.3)	0 (0)	0 (0)	0 (0)
Musculoskeletal pain	1 (8.3)	0 (0)	0 (0)	0 (0)
Peripheral sensory neuropathy	1 (8.3)	0 (0)	0 (0)	0 (0)
Postnasal drip	1 (8.3)	0 (0)	0 (0)	0 (0)
Pruritis	1 (8.3)	0 (0)	0 (0)	0 (0)
Skin laceration	1 (8.3)	0 (0)	0 (0)	0 (0)
Stomatitis	1 (8.3)	0 (0)	0 (0)	0 (0)
Tinnitus	1 (8.3)	0 (0)	0 (0)	0 (0)
Venous injury	1 (8.3)	0 (0)	0 (0)	0 (0)
Vision blurred	1 (8.3)	0 (0)	0 (0)	0 (0)

* By Common Terminology Criteria for Adverse Events (version 3.0).