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CLINICAL TRIAL

Incidence of peripheral edema in patients receiving PI3K/mTOR/CDK4/6 inhibitors for metastatic breast cancer

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Abstract

Purpose This study evaluated development of edema in patients receiving PI3K/mTOR/CDK4/6 targeted therapy for metastatic breast cancer (MBC).

Methods We reviewed medical records of 160 patients receiving targeted therapy with PI3K/mTOR/CDK4/6 inhibitors to treat MBC ($n = 160$; 185 treatment occurrences). Clinicopathologic data, treatment details, and edema incidence were recorded.

Results Edema incidence was 43.1% (69/160) overall and 25.6% (41/160) in the upper extremity ipsilateral to the treated breast. In 185 therapy regimens administered, 6.8% of patients on a PI3K inhibitor, 8.8% of patients on an mTOR inhibitor, and 9.2% of patients on a CDK4/6 inhibitor experienced new onset or worsened preexisting upper extremity edema. Further, 9.1% of patients on a PI3K inhibitor, 18.8% of patients on an mTOR inhibitor, and 10.5% of patients on a CDK4/6 inhibitor experienced new onset or worsened preexisting edema elsewhere in the body. Multivariate logistic regression showed that, beyond the established breast cancer-related lymphedema (BCRL) risk factors [axillary lymph node dissection (Odds Ratio (OR) 2.69, $p = 0.020$), regional lymph node irradiation (OR 6.47, $p < 0.001$), and body-mass index ≥ 30 kg/m^2 (OR 3.46, $p = 0.006$)], a relative decrease in serum albumin after 3 months of treatment increased risk of developing edema (OR 2.07, $p = 0.062$). Neither duration nor type of therapy were significant risk factors for edema.

Conclusion PI3K/mTOR/CDK4/6 inhibitors may influence the development of edema, which may cause or exacerbate progression of BCRL in patients with MBC. The varied incidence of edema between therapeutic regimens warrants vigilant monitoring of patients treated with these therapies, especially those at high risk of developing BCRL.

Keywords Lymphedema · Edema · Breast cancer · Metastatic breast cancer · Targeted therapy

Introduction

Advances in detection and treatment of breast cancer (BC) have improved long-term survival in recent years [1, 2], thereby increasing research focus on minimizing toxicities of treatment and complications throughout survivorship. Breast cancer-related lymphedema (BCRL) is one such

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negative sequela that has been an increasing topic of investigation. Characterized by accumulation of protein-rich lymph fluid in the interstitial tissues of the affected upper extremity, breast, or trunk, BCRL affects approximately one in five women treated for BC in the United States [1, 3]. The risk of developing BCRL persists for a lifetime after treatment for BC. Numerous studies have identified risk factors for BCRL among patients treated for early BC, such as axillary lymph node dissection (ALND) [3–7], regional lymph node irradiation (RLNR) [3–5, 7–9], cellulitis [7, 10–12], and presenting with a body-mass index (BMI) ≥ 30 at diagnosis [6, 7, 13, 14]. While improvements in the efficacy of targeted therapies in the last two decades have increased the average lifespan of women living with metastatic breast cancer (MBC) [15], the risk factors, incidence, and time course to onset of BCRL in patients undergoing targeted therapy for MBC have not been investigated. Given that nearly 30% of women treated for early BC will develop MBC [16], it is imperative that the nature of development and progression of BCRL be defined for these patients.

Preliminary research suggests that certain targeted therapies used to treat MBC may affect risk of developing edema or lymphedema [17]. Specifically, targeted therapy regimens inhibiting the PI3K/mTOR signaling pathway, which is a cell signaling mechanism overactivated in approximately 40% of hormone receptor (HR)-positive breast cancers [18–20], include lymphedema as one of numerous side effects [17, 21, 22]. mTOR inhibitors specifically are known to hinder lymphangiogenesis, thereby increasing the burden on lymphatic vessels and potentially inducing capillary leakage and fluid accumulation within the tissues [17]. However, lymphedema incidence has yet to be investigated among patients treated with other targeted therapy regimens that inhibit similar cell signaling pathways such as the PI3K signaling pathway upstream of mTOR or the CDK4/6 cell signaling pathway.

With preliminary evidence that certain targeted therapies may influence risk of developing edema, some have proposed that this population be screened for arm volume changes and edema-related symptoms throughout treatment and after cessation. This recommendation was first proposed in a 2014 review by Kaplan et al. about the management of adverse events of mTOR inhibitors; the authors suggested that patients undergoing therapy with mTOR inhibitors be monitored for lymphedema throughout their treatment and that patients with preexisting lymphatic conditions should avoid the use of mTOR inhibitors altogether [17, 21]. Given that peripheral edema is a known adverse side effect of mTOR inhibitors, the goal of this study is to elucidate how the incidence and nature of edema and lymphedema varies among patients treated for MBC with PI3K, mTOR, and CDK4/6 targeted therapies.

Methods

Patient population and data collection

We queried 198 patients from a single academic institution (Massachusetts General Hospital) who were treated with PI3K/mTOR inhibitors or CDK4/6 inhibitors to treat MBC as standard of care or as part of a clinical trial between May 2011 and August 2016. Patients being treated as a part of clinical trial were identified via enrollment in a Dana Farber/Harvard Cancer Center study (10–262, 11–10, 13–121, 13–283, and 13–367), while patients being treated as standard of care were identified via a query of the Research Patient Data Registry. We excluded patients who did not complete at least one full cycle of targeted therapy for a final cohort of 160 patients who underwent a total of 185 treatment regimens with the therapies of interest. Demographic, clinicopathologic, and treatment-related characteristics were collected via medical record review (IRB approval number: 2005P001038). The incidence of edema was assessed by reviewing the clinical reports of the patient's treating oncologists, primary care provider, or physical therapists.

Statistical methods

Statistical analysis was conducted with R Version 2.15 (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org). Logistic regression models were used to assess the association between clinical risk factors and the development of edema during, after, or exacerbated by the initiation of the targeted therapeutics. Trends in serum albumin levels and time on trial were analyzed as continuous variables. All other clinical parameters were treated as dichotomous variables. Univariate analysis was used as an exploratory method, but primary statistical inference was based on multivariate analysis. Multivariate models were derived using backwards selection, starting with a model including all variables with $p < 0.20$ in the univariate analysis as well as known confounders, and sequentially removing non-significant variables until only variables with $p < 0.05$ remained. Two proportion z-tests with continuity correction were used to compare the incidence of upper extremity edema in groups with different numbers of BCRL-related risk factors.

Results

Patient population

Of the 160 primary breast cancers in this cohort, 88.1% were HR-positive and human epidermal growth factor receptor 2 (HER2)-negative, 6.9% were HR-positive/

HER2-positive, 3.1% were HR-negative/HER2-positive, and 1.3% were triple-negative breast cancers (TNBC). In this cohort, 63.8% of patients had history of unilateral breast surgery (25.0% lumpectomy; 38.8% mastectomy) and 20.6% had history of bilateral breast surgery (1.3% bilateral lumpectomy; 18.1% bilateral mastectomy; 1.3% mastectomy with contralateral lumpectomy). Of note, 15.0% of women did not have breast surgery. Further, 70.0% had history of unilateral nodal surgery (18.8% sentinel lymph node biopsy (SLNB); 51.3% ALND) and 6.9% had history of bilateral nodal surgery (1.9% bilateral SLNB; 5.0% ALND with contralateral SLNB). Moreover, 34.4% had history of RLNR whereas 48.8% did not. Details pertaining to BC treatment and pathological characteristics are outlined in Table 1.

These 160 patients participated in 185 treatments with any of the therapies, all of which were administered in combination with endocrine therapy. The median age at initiation of targeted therapy was 58 years (range 34–90 years), median BMI was 25.7 kg/m^2 (range 16.4–48.4), and median serum albumin level at the first dose was 4.3 g/dL (range 2.8–5.3 g/dL) (Table 2). The median duration of targeted therapy was 5.5 months (Range 0.9–48.3 months). Of the 185 treatment occurrences, 68.1% (n = 126) utilized only one targeted therapy agent [19.5% (36) with PI3K-α inhibitor; 19.5% (36) with PI3K-β-sparing therapy; 20.0% (37) with mTOR inhibitor; 9.2% (17) with CDK4/6 inhibitor]. The remaining 31.9% (59) of treatment occurrences utilized two targeted therapy agents in combination [8.6% (16) with PI3K-α inhibitor in combination with CDK4/6 inhibitor; 23.3% (43) with mTOR inhibitor in combination with CDK4/6 inhibitor]. Reasons for terminating treatment were primarily disease progression (84.3%; 156/185) or drug-related toxicity (13.5%; 25/185). Two patients discontinued therapy with an mTOR inhibitor (everolimus) due to severity of edema, which improved upon ceasing therapy. Information relating to targeted therapy regimens is detailed in Table 2.

Table 1 Breast cancer treatment and pathological characteristics

	Count	Percent
Hormone receptor status (n = 160)		
HR+/HER2−	141	88.1
HR+/HER2+	11	6.9
HR−/HER2+	5	3.1
TNBC	2	1.3
Not applicable	1	0.6
Breast surgery (n = 160)		
Unilateral	102	63.8
Lumpectomy	40	25
Mastectomy	62	38.8
Bilateral	33	20.6
Lumpectomy	2	1.3
Mastectomy	29	18.1
Mastectomy with contralateral lumpectomy	2	1.3
None	24	15
Not available	1	0.6
Nodal surgery (n = 160)		
Unilateral	112	70.0
SLNB	30	18.8
ALND	82	51.3
Bilateral	11	6.9
SLNB	3	1.9
ALND with contralateral SLNB	8	5.0
None	26	16.3
Not available	11	6.9
Radiation therapy (n = 160)		
RLNR	55	34.4
No RLNR	78	48.8
Not available	27	16.9

HR Hormone receptor, *HER2* human epidermal growth factor receptor 2, *TNBC* triple-negative breast cancer, *SLNB* sentinel lymph node biopsy, *ALND* axillary lymph node dissection, *RLNR* regional lymph node radiation

Cumulative incidence of edema

In this cohort, 43.1% (69/160) of women experienced edema either before or after their treatment with targeted therapy in one or more areas of the body; 25.6% (41/160) of women developed edema in the upper extremity at risk for BCRL (i.e., the arm ipsilateral to the affected side), 20.0% (32/160) developed edema in a lower extremity, 6.9% (11/160) developed pedal edema, and 1.9% (3/160) developed edema in the chest wall. To understand the influence of targeted therapy on edema development or progression, we evaluated the incidence of newly developed or worsened preexisting edema relative to the first dose of therapy (C1D1). Among the 160 patients, 19 completed at least one full cycle of two different therapy regimens relevant to this analysis and 3 completed at least one full cycle of three different therapies for a total of 185 therapy regimens in this analysis.

Edema was present in the affected upper extremity at C1D1 in 15.2% (28/185) of instances, which was noted to be worsened during therapy in 2.2% (4) of instances. Edema developed in the affected upper extremity upon initiation of therapy in 5.4% (10) of instances and within 3 months of cessation of therapy in 3.2% (6) of instances. There was edema present in another anatomical location (lower extremity, pedal, chest wall) at C1D1 in 4.9% (9) of instances, which was noted to be worsened during therapy in 0.5% (1) of instances. Edema developed upon initiation of therapy in 13.0% (24) of instances and within 3 months of cessation

Table 2 Targeted therapy treatment summary

	Median (range)	
Age at C1D1 (years)	58 (34, 90)	
BMI at C1D1 (kg/m^2)	25.7 (16.4, 48.4)	
Serum albumin level at C1D1 (g/dL)	4.3 (2.8, 5.3)	
Duration of time on trial (months)	5.5 (0.9, 48.3)	
	Count	Percent
Targeted therapy type ($n = 160$[a])		
PI3K targeted therapy	88	55.0
PI3K-α inhibitors	52	32.5
PI3K-β sparing therapy	36	22.5
CDK4/6 inhibitors	76	47.5
mTOR inhibitors	80	50.0
Targeted therapy regimen ($n = 185$[b])		
PI3K-*α* inhibitor only	36	19.5
PI3K-*β* sparing therapy only	36	19.5
PI3K-*α* inhibitor + CDK4/6 inhibitor	16	8.6
mTOR inhibitor only	37	20.0
CDK4/6 inhibitor only	17	9.2
CDK4/6 inhibitor + mTOR inhibitor	43	23.3
Reason for terminating treatment ($n = 185$[b])		
Disease progression	156	84.3
Toxicity	25	13.5
Edema	2	1.1
Death	1	0.5
Other/not noted	1	0.5

C1D1 cycle 1 day 1, first dose of targeted therapy, *PI3K-α/PI3K-β* phosphoinositide 3-kinase-alpha/beta, *mTOR* mammalian target of rapamycin, *CDK4/6* cyclin-dependent kinase 4/6

[a]Refers to 160 unique patients

[b]Refers to 185 unique patient-targeted therapy combinations

of therapy in 4.3% (8) of instances. Timing and duration of edema is outlined in Table 3. To understand how edema incidence differs by therapy type, we stratified patients by type of therapy and assessed the timing of edema development relative to C1D1. See Fig. 1.

Univariate and multivariate logistic regression summary

By univariate analysis, history of ALND [Odds Ratio (OR) 3.51, $p = 0.001$] or RLNR (OR 6.24, $p < 0.001$) increased the risk of upper extremity edema (UEE) in the arm at risk for BCRL for patients on any therapy. Additionally, a BMI ≥ 30 kg/m^2 at the time of the first dose of therapy was significantly associated with UEE in the arm at risk for BCRL (OR 2.04, $p = 0.057$) and developing edema elsewhere in the body (OR 2.49, $p = 0.010$).

By multivariate analysis, history of RLNR and having a BMI ≥ 30 kg/m^2 at C1D1 was significantly associated with developing UEE in the arm at risk for BCRL (OR 6.47, $p < 0.001$ and OR 3.46, $p = 0.006$, respectively) and in any anatomical location (OR 3.64, $p < 0.001$ and OR 2.95, $p = 0.005$, respectively). History of ALND or experiencing a relative decrease in serum albumin after 3 months of targeted therapy was significantly associated with developing UEE in the arm at risk for BCRL (OR 2.69, $p = 0.020$ and OR 2.07, $p = 0.062$, respectively). No therapy emerged as a significant predictor of edema when compared to other therapies. Complete univariate and multivariate regression results are outlined in Table 4.

We also evaluated the incidence of BCRL (characterized by UEE in the arm at risk for BCRL) upon stratification of the cohort by number of established risk factors for BCRL patients possessed, namely ALND, RLNR, and BMI ≥ 30 kg/m^2 (Fig. 2). While none of the patients without any established risk factors ($n = 38$) were noted to have BCRL prior to C1D1, one patient developed BCRL upon starting therapy. Of the 70 patients with only one established risk factor for BCRL, 10.0% (7) had BCRL before C1D1 and 11.4% (8) developed BCRL upon initiation of therapy. Of the 43 patients with exactly two known BCRL-associated risk factors, 23.3% (10) had BCRL before C1D1, 7.0% (3)

Table 3 Timing and duration of onset upper extremity edema (UEE) or edema in any other location (non-UEE)

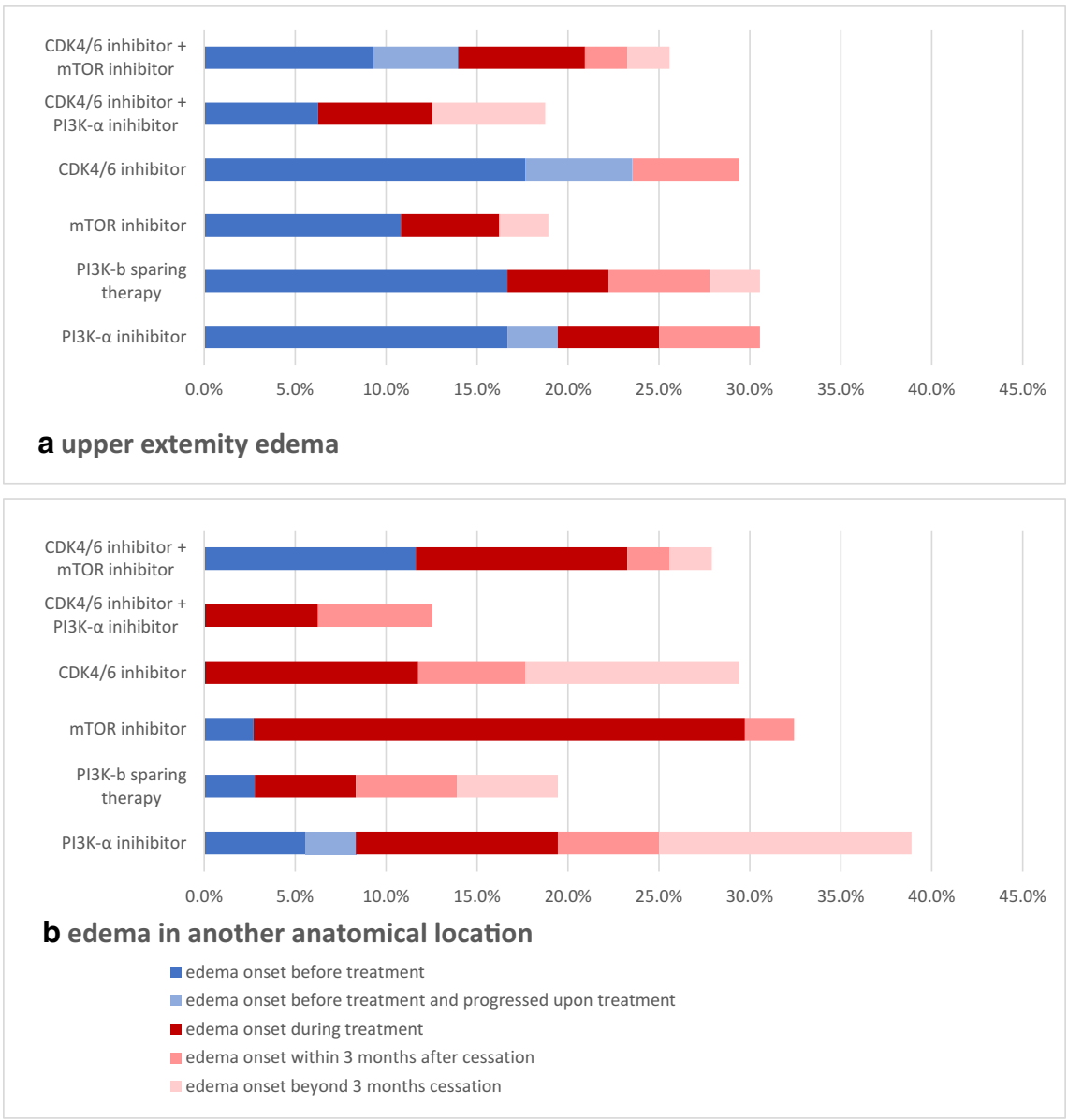
	PI3K-α inhibitor	PI3K-b sparing therapy	mTOR inhibitor	CDK4/6 inhibitor	CDK4/6 inhibitor + PI3K-α inhibitor	CDK4/6 inhibitor + mTOR inhibitor
UEE onset During Treatment (*n*)	2	2	2	–	1	3
Median time to onset after C1D1 (days)	220	33	36.5	–	14	105
Edema resolved (*n*)	–	–	–	–	–	2
Median time to resolution (days)						77
Edema persisted until death	2	2	1	–	1	1
Managing edema at most recent follow up (*n*)	–	–	1	–	–	–
UEE onset after cessation of treatment (*n*)	2	3	1	1	1	2
Median time to onset after cessation (days)	29.5	68	156	7	587	83
Edema resolved (*n*)	–	1	–	–	–	1
Median time to resolution (days)		24				21
Edema persisted until death (*n*)	2	2	1	1	1	1
Managing edema at most recent follow up (*n*)	–	–	–	–	–	–
Non-UEE onset during treatment (*n*)	4	2	10	2	1	5
Median time to onset after C1D1 (days)	24	49	210	274.5	20	95
Edema resolved (n)	1	–	2	–	–	4
Median time to resolution (days)	46		96			325.5
Edema persisted until death	3	2	5	1	1	–
Managing edema at most recent follow up (*n*)	–	–	3	1	–	1
Non-UEE onset after cessation of treatment (*n*)	7	4	1	3	1	2
Median time to onset after cessation (days)	144	147.5	30	307	463	367.5
Edema resolved (*n*)	2	–	–	1	–	–
Median time to resolution (days)	723.5			230		
Edema persisted until death (*n*)	3	4	–	2	1	1
Managing edema at most recent follow up (*n*)	1	–	–	–	–	–
Unknown (*n*)	1	–	1	–	–	1

UEE Upper extremity edema, *PI3K-α/PI3K-β* phosphoinositide 3-kinase-alpha/beta, *mTOR* mammalian target of rapamycin, *CDK4/6* cyclin-dependent kinase 4/6

of whom experienced exacerbation of edema and symptoms upon initiation of therapy. An additional 16.3% (7) developed BCRL upon initiation of therapy. Lastly, of the 9 patients with exactly three known BCRL-associated risk factors, 66.7% (6) had BCRL before C1D1, one of whom experienced exacerbation of BCRL volume and symptoms upon initiation of therapy. An additional 22.2% (2) developed BCRL upon initiation of therapy.

Discussion

Recent advances in prospective BCRL research have elucidated risk factors for BCRL and its course of development [3, 5–7, 23]. However, the risk and incidence of BCRL has yet to be investigated in patients with MBC or in those receiving targeted therapeutics such as PI3K, mTOR, and CDK4/6 inhibitors to treat metastatic disease. Women with



Legend: PI3K-α/PI3K-β, phosphoinositide 3-kinase-alpha/beta; mTOR, mammalian target of rapamycin; CDK4/6, cyclin-dependent kinase 4/6.

Fig. 1 Incidence of **a** upper extremity edema and **b** edema in another anatomical location relative to initiation of treatment with unique targeted therapy regimens. *PI3K-α/PI3K-β* phosphoinositide 3-kinase-alpha/beta, *mTOR* mammalian target of rapamycin, *CDK4/6* cyclin-dependent kinase 4/6

BCRL report a significantly compromised quality of life (QOL) compared to women who do not develop it [24], and edema can be particularly threatening to mobility and QOL in patients with metastatic disease and those receiving end-of-life care. Given that approximately 40% of HR-positive breast cancers are modulated by a mutant form of PIK3CA [18–20] which activates the PI3K/mTOR signaling pathway, and considering that preliminary studies describe lymphedema as an adverse side effect of targeted therapies such as mTOR inhibitors and CDK4/6 inhibitors, it is imperative to understand if and how these therapies influence risk of developing edema or BCRL.

To our knowledge, this is the first study investigating peripheral edema and BCRL in a cohort of women treated with these therapies. In 185 administered regimens of targeted therapy, new UEE developed in the arm at risk for BCRL during treatment in 5.4% (10) of instances and in another anatomical location in 13.0% (24) of instances. UEE

Table 4 Regression summary of patients with edema

Factor	Edema in any location				Upper extremity edema			
	Univariate		Multivariate		Univariate		Multivariate	
	OR	*p* value	OR	*p* value	OR	*p* value	OR	*p* value
BMI ≥ 30 kg/m^2 vs. BMI < 30	2.49	0.010	2.95	0.005	2.04	0.057	3.46	0.006
Age ≥ 55 vs. age < 55	0.86	0.624	–	–	0.47	0.029	–	–
SLNB vs. none	1.91	0.228	–	–	2.60	0.260	–	–
ALND vs. SLNB/none	1.31	0.366	–	–	3.51	0.001	2.69	0.020
RLNR vs. no RLNR	3.05	< 0.001	3.64	< 0.001	6.24	< 0.001	6.47	< 0.001
Hormone (+) vs. hormone (-)	1.95	0.432	–	–	0.87	0.872	–	–
Her2 (+) vs. her2 (-)	1.73	0.272	–	–	1.49	0.454	–	–
Albumin < 4.0 vs. albumin ≥ 4.0	1.05	0.923	–	–	1.08	0.830	–	–
Decrease in albumin at 3 months (g/dL)	1.32	0.364	–	–	1.74	0.102	2.07	0.062
Time on trial (months)	1.00	0.011	1.00	0.016	1.00	0.119	–	–
PI3K inhibitor vs. not	0.99	0.987	–	–	1.28	0.467	–	–
PI3K-α inhibitor vs. not	1.18	0.617			1.07	0.850	–	–
PI3K-β sparing therapy vs. not	0.80	0.557			1.33	0.483	–	–
mTOR inhibitor vs. not	0.95	0.859	–	–	0.73	0.352	–	–
CDK 4/6 inhibitor vs. not	0.92	0.794	–	–	0.92	0.806	–	–
CDK 4/6 inhibitor + PI3K-α inhibitor vs. not	0.57	0.316	–	–	0.64	0.495	–	–
CDK 4/6 inhibitor + mTOR inhibitor vs. not	1.05	0.887	–	–	0.98	0.950	–	–

C1D1 cycle 1 day 1, first dose of targeted therapy, *BMI* body-mass index, *SLNB* sentinel lymph node biopsy, *ALND* axillary lymph node dissection, *RLNR* regional lymph node radiation, *PI3K* phosphoinositide 3-kinase, *mTOR* mammalian target of rapamycin, *CDK4/6* cyclin-dependent kinase 4/6

that developed during targeted therapy treatment improved upon holding or decreasing doses in two patients on mTOR inhibitors and one patient on an mTOR inhibitor in combination with a CDK4/6 inhibitor. Edema that developed elsewhere on the body during targeted therapy treatment improved upon holding or decreasing doses in three patients on mTOR inhibitors and one patient on an mTOR inhibitor in combination with a CDK4/6 inhibitor. Further, edema worsened upon initiation of therapy in 16.7% (4/24) of patients who had preexisting UEE and in 11.1% (1/9) of patients who had preexisting edema in another location.

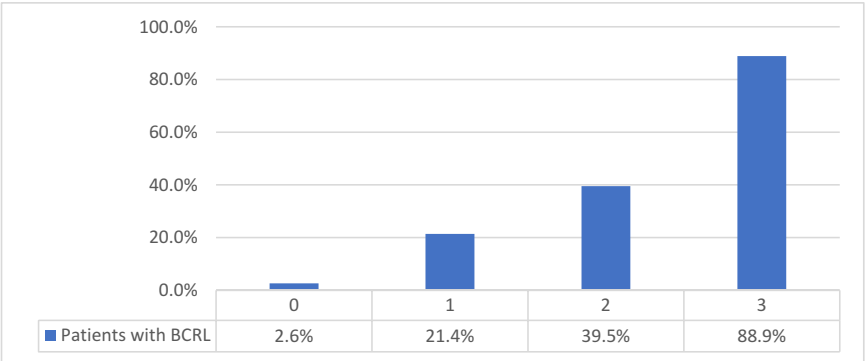


Fig. 2 Incidence of Upper Extremity Edema in the arm at risk for BCRL by number of BCRL-associated risk factors. Columns represent the proportion of patients in that group who developed upper extremity edema in the arm at risk for BCRL

Columns represent the proportion of patients in that group who developed upper extremity edema in the arm at risk for BCRL.

Though no therapy was significantly more associated with edema compared to the others on multivariate analysis, the incidence of edema varies depending on the treatment. Thus, it is important to monitor for development or progression of edema in patients undergoing treatment with these therapies.

Multivariate logistic regression revealed that a decrease in serum albumin after 3 months of targeted therapy was significantly associated with development of UEE (OR 2.07, $p = 0.062$). This may warrant closer monitoring of serum

albumin levels for patients treated with targeted therapies, as they may influence a patient's risk of developing edema or BCRL. It is important for the relationship between serum albumin and onset or progression of edema to be better defined to allow for informed risk assessment.

Though the risk factors of BCRL have been well identified in patients treated for early BC [3, 6, 7], it is unclear how the edema-inducing effects of PI3K/mTOR/CDK4/6 targeted therapies may influence risk of developing BCRL in patients with MBC. While treatment with a targeted therapy was administered to a patient with preexisting BCRL in 15.2% (28/185) of treatment instances, BCRL developed during treatment in 4.9% (9) of instances and within 3 months after cessation of treatment in 3.2% (6) of instances. The variation in incidence of new or worsened UEE after initiation of therapy may warrant more vigilant screening for BCRL patients in this population.

To understand how the risk of developing BCRL may differ in this population compared to those with early BC, we stratified patients noted to have BCRL at any point by the number of known BCRL risk factors they possessed, including ALND, RLNR, and having a BMI ≥30 at C1D1. The 38 women who possessed none of these risk factors were at extremely low risk for developing BCRL [3, 7], yet one patient developed BCRL during treatment with targeted therapy. The incidence of BCRL among the 70 women with one known risk factor was 21.4%, which approximates the incidence of BCRL in our larger cohort of patients treated for early BC [1, 3, 7]. Among the 43 women with exactly two BCRL risk factors in this cohort, 39.5% (17) developed BCRL; this incidence is nearly twice as high as the 19.0% 2-year cumulative incidence of BCRL in a large, prospective cohort of women with exactly two BCRL-related risk factors who were rigorously screened for BCRL throughout BC treatment with both quantitative and qualitiative measures [25]. Finally, 88.9% (8/9) of women with all three risk factors developed BCRL. While six of these patients developed BCRL before targeted therapy treatment, one patient's BCRL progressed upon starting therapy and an additional two patients developed BCRL during treatment with a PI3K/mTOR or CDK4/6 inhibitor. Given that the median duration of treatment in this study was only 5.5 months, it should not be assumed that BCRL onset during treatment with one of the targeted therapies is a coincidence. The risk increase associated with each additional BCRL-related risk factor in this cohort of women implies the need for more informed risk education among patients being treated with certain targeted therapies. Further, the varying rates of BCRL between this cohort and patients with early BC may indicate potential involvement of these therapies on BCRL risk; nonetheless, we acknowledge that patients with MBC may be at increased risk of BCRL due to the location and progression of their disease.

We acknowledge the limitations of this study, the major limitation being that incidence of edema or BCRL was collected by retrospective chart review of treating oncologists' documentation, and hence the lack of methodical screening for edema and BCRL. Further, this cohort was relatively small and was stratified by different targeted therapy regimens. We recognize that patients with MBC may be heavily pre-treated with other systemic therapies; however, this is the case with many patients being treated for MBC. We also note that the proportion of women with history of ALND (51.3%) is higher in this cohort than in our larger cohort treated for early BC [23], which increases this cohort's risk of developing BCRL. However, ALND is associated with later-stage disease; thus, these patients would be more likely to progress to MBC than those with early BC, thereby reflecting the greater occurrence of ALND in this cohort.

Given the implications of this analysis, we have implemented a standardized BCRL screening plan at MGH for women on targeted therapies akin to these. This screening plan mirrors our well-validated BCRL screening protocol [26] but allows replacement of a pre-surgical baseline perometer measurement with a measurement taken prior to initiation of therapy. In addition to volumetric measurements, our screening methods incorporate patient-reported symptoms and an attending oncologist's clinical examination. The lack of knowledge about the influence of targeted therapies on the risk of developing edema or BCRL warrants more rigorous research among this population, and thus we screen these patients more frequently.

Knowing the chronic and burdensome impact that edema and BCRL can have on physical mobility, emotional well-being, and overall QOL [24], we recommend a large, prospective clinical study incorporating vigilant and standardized screening in women with MBC undergoing treatment with PI3K/mTOR inhibitors, CDK4/6 inhibitors, and other specialized treatments in the clinical testing phase. Such a study has the potential to clarify the involvement of these therapies on the development or progression of BCRL and may allow us to define the unique risks within this population. The implications of this research will guide patient education, including individualized risk assessment of developing BCRL, which can be debilitating and can dramatically decrease QOL in later stages of disease. Lastly, it is crucial that all patients undergoing targeted therapy for treatment of MBC be screened for edema and BCRL to allow for earliest possible detection and treatment [17].

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Compliance with ethical standards

Conflict of interest Aditya Bardia serves as a consultant for Genentech/Roche, Immunomedics, Novartis, Pfizer, Merck, Radius Health, Spectrum Pharma, and Taiho Pharmeceutical. Aditya Bardia reports institutional grants from Genentech/Roche, Immunomedics, Novartis, Pfizer, Merck, Radius Health, Mersana, and Innocrin, as well as personal funding from Biothernostics. Steven J. Isakoff serves as a consultant for Myriad, Puma, Immunomedics, and Mylan, and reports funding from Genentech, Pharmamar, Abbvie, OncoPep, Merck, AstraZeneca. Dejan Juric serves as a consultant for Novartis, Genentech, Eisai, Ipsen, and EMD Serono. Dejan Juric reports grants from Novartis, Genentech, Eisai, EMD Serono, Takeda, Celgene, and Placon Therpaeutics, as well as personal funding from Novartis, Genentech, Eisai, Ipsen, and EMD Serono. The remaining authors have no conflicts to disclose.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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