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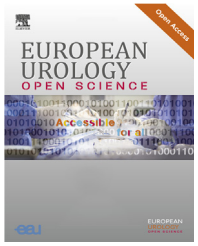

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Bladder Cancer

Management of Fibroblast Growth Factor Inhibitor Treatment–emergent Adverse Events of Interest in Patients with Locally Advanced or Metastatic Urothelial Carcinoma

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Abstract

Background: Erdafitinib is indicated for the treatment of adults with locally advanced/metastatic urothelial carcinoma and susceptible *FGFR3/2* alterations progressing on/after one or more lines of prior platinum-based chemotherapy.
Objective: To better understand the frequency and management of select treatment-emergent adverse events (TEAEs) to enable optimal fibroblast growth factor receptor inhibitor (FGFRi) treatment.
Design, setting, and participants: Longer-term efficacy and safety results of the BLC2001 (NCT02365597) trial in patients with locally advanced and unresectable or metastatic urothelial carcinoma were studied.
Intervention: Erdafitinib schedule of 8 mg/d continuous in 28-d cycles, with uptitration to 9 mg/d if serum phosphate level was <5.5 mg/dl and no significant TEAEs occurred.
Outcome measurements and statistical analysis: Adverse events were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. The Kaplan-Meier methodology was used for the cumulative incidence of the first onset of TEAEs by grade. Time to resolution of TEAEs was summarized descriptively.

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Results and limitations: At data cutoff, the median treatment duration was 5.4 mo among 101 patients receiving erdafitinib. Select TEAEs (total; grade 3) were hyperphosphatemia (78%; 2.0%), stomatitis (59%; 14%), nail events (59%; 15%), non–central serous retinopathy (non-CSR) eye disorders (56%; 5.0%), skin events (55%; 7.9%), diarrhea (55%; 4.0%), and CSR (27%; 4.0%). Select TEAEs were mostly of grade 1 or 2, and were managed effectively with dose modifications, including dose reductions or interruptions, and/or supportive concomitant therapies, resulting in few events leading to treatment discontinuation. Further work is needed to determine whether management is generalizable to the nonprotocol/general population.
Conclusions: Identification of select TEAEs and appropriate management with dose modification and/or concomitant therapies resulted in improvement or resolution of most TEAEs in patients, allowing for continuation of FGFRi treatment to ensure maximum benefit.
Patient summary: Early identification and proactive management are warranted to mitigate or possibly prevent erdafitinib side effects to allow for maximum drug benefit in patients with locally advanced or metastatic bladder cancer.

1. Introduction

Erdafitinib, a pan–fibroblast growth factor receptor inhibitor (pan-FGFRi) [1], is indicated for the treatment of adults with locally advanced or metastatic urothelial carcinoma (UC) and susceptible *FGFR3/2* alterations who have progressed on/after one or more prior lines of platinum-based chemotherapy [2]. This indication is based on the primary results of the phase 2 BLC2001 trial [3].

The specific mechanism of action of erdafitinib and other members of the (FGFRi) class is to counteract the physiological role of the FGF/FGFR axis [4]. This leads to specific toxicities distinct from those observed with broader tyrosine kinase inhibition, including hyperphosphatemia, alopecia, dry skin, stomatitis, nail disorders (onycholysis, nail loss, and paronychia), and eye disorders including central serous retinopathy (CSR) detected with and without routine optical coherence tomography (OCT) testing [5–8]. Any-grade toxicity rates with erdafitinib and other FGFRis across trials in patients with UC and cholangiocarcinoma (CCA) were reported to be 31–77% for hyperphosphatemia, 7–58% for stomatitis, 15–61% for diarrhea, 18% for nail events, 21–23% for palmar-plantar erythrodysesthesia, and 13–41% for ocular events [4].

In a long-term follow-up analysis of BLC2001 [9], the overall safety profile of erdafitinib was consistent with that observed in the primary analysis [3]. Here, we further examine long-term safety, focusing on the frequency and management of select treatment-emergent adverse events (TEAEs; ie, most common and FGFRi class-effect TEAEs) to enable optimal erdafitinib treatment.

2. Patients and methods

2.1. Study design

Longer-term efficacy and safety results of the BLC2001 (NCT02365597) trial in patients with locally advanced and unresectable or metastatic UC were described recently [9]. Briefly, eligible adult patients had measurable disease according to the Response Evaluation Criteria in Solid Tumors version 1.1, one or more *FGFR3* mutations or *FGFR2/3* fusions per prespecified panel by central laboratory testing, had a history of disease progression during or after one or more lines of systemic chemotherapy or within 12 mo after neoadjuvant/adjuvant chemotherapy or were cisplatin ineligible and chemotherapy naïve, had Eastern Cooperative Oncology Group performance status $\leq$2, and had adequate bone marrow, liver, and kidney function (creatinine clearance, $\geq$40 ml/min/1.73 m^2).

2.2. Treatment

Patients received 8 mg/d oral erdafitinib, with uptitration to 9 mg/d permitted on day 15 of cycle 1 for those without adverse events (AEs) considered to be related to treatment by the investigator, if they had not reached the target serum phosphate level of 5.5 mg/dl (1.8 mmol/l). Patients continued erdafitinib treatment at 8 mg/d if their serum phosphate levels on day 14 were within 5.5–<7.0 mg/dl (1.8–2.3 mmol/l; target range). Patients continued to receive erdafitinib until disease progression or unacceptable AEs, as determined by the investigator. At the discretion of the investigator and the sponsor, patients with investigator-assessed disease progression could continue erdafitinib treatment.

2.3. Assessments and statistical methods

Safety was assessed in treated patients (safety population) through clinical laboratory testing and physical and ophthalmological examinations as of the August 9, 2019, data cutoff. Investigators assessed and graded AEs using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Select TEAEs (ie, the most common and FGFRi class-effect TEAEs) identified for this analysis were hyperphosphatemia, nail events, skin events, CSR events, non-CSR eye disorders, stomatitis, and diarrhea. The most significant dose modification action taken for a TEAE was recorded; thus, TEAEs that led to interruption followed by reduction were reported as reductions. Events that recurred within 3 d of each other were considered a single, continuous event, with the entire duration included in the time-to-resolution calculation. Time to resolution was defined as the time from the day of the onset of a TEAE of any grade, through changes in grade, to the day of the event's resolution (with recurrence $\leq$3 d). Events that changed in

grade, per patient, were reported independently in the Kaplan-Meier analysis for each respective grade. Patients without a corresponding event of a particular grade are censored in the time-to-event analysis for that grade at the last dose date plus 30 d, data cutoff, or the end of study date, whichever was first. Patients may have had more than one TEAE in the higher-level categories of nail events, skin events, non-CSR eye disorders, and CSR, which comprise multiple preferred terms. Resolution data are presented only for the most common preferred terms in these higher-level categories to accurately reflect patient experience for each TEAE preferred term. Concomitant medication duration was reported by class of agents used to treat select TEAEs, with missing end dates imputed with respective nonmissing TEAE end dates; records with both missing concomitant medication and TEAE end dates were excluded.

3. Results

3.1. Patient characteristics

A total of 101 patients were treated with the 8 mg/d uptitration regimen, which reflects the safety data reported herein (Supplementary Fig. 1). At the data cutoff date (August 9, 2019), the median treatment duration was 5.4 mo among 101 patients who received erdafitinib 8 mg/d uptitration, and the median follow-up (estimated based on the time from the first dose date to the censoring date for progression-free survival) [9] was 24.0 mo. Progressive disease was the primary reason for treatment discontinuation ($n = 76$). Seventeen patients discontinued due to AEs, and five continued treatment. Patient demographic and baseline characteristics, as reported previously [9], are described in Supplementary Table 1.

3.2. Overall safety

Overall safety data have been reported [9]. The most common select TEAEs were hyperphosphatemia (78%), stomatitis (59%), and nail events (59%; Table 1). The median onset time, frequencies of dose reduction, interruption, discontinuation, and median time treatment was withheld for select TEAEs are shown in Table 2. The incidence of the first onset of select TEAEs displays a temporal sequence with either an acute peak onset (eg, hyperphosphatemia or diarrhea) or a delayed peak onset (eg, CSR or nail events; Fig. 1).

3.3. Hyperphosphatemia

Serum phosphate levels were monitored over the course of treatment (Supplementary Fig. 2), with the mean values peaking 6 wk after the start of treatment and generally decreasing thereafter.

Seventy-nine (78%) patients developed hyperphosphatemia, with a median time to onset of 20 (interquartile range [IQR], 14–29) d; of these patients, 77 (76%) had grade 1 or 2 events (Tables 1 and 2; cumulative incidence, Fig. 2). The median phosphate values for dose interruption and dose reduction due to hyperphosphatemia were 7.16 (IQR, 7.00–7.70) and 7.30 (IQR, 6.50–8.50) mg/dl, respectively. The most common therapy for hyperphosphatemia among the 31 (39%) of 79 patients with hyperphosphatemia was the use of various phosphate binders (94%; median duration 72 [IQR, 44–121] d; Supplementary Table 2). By data cutoff, resolution of one or more hyperphosphatemia events was observed in 74 (94%) patients. The median time to resolution of hyperphosphatemia was 17 (IQR, 9–37) d.

3.4. Long-term sequelae of hyperphosphatemia

The incidence of any TEAEs considered potential sequelae of prolonged hyperphosphatemia was similar in patients with prolonged hyperphosphatemia (≥5.5 mg/dl for >1 mo; seven of 21 [33%]) and those without (29 of 80 [36%]; Supplementary Table 3). Patients with prolonged hyperphosphatemia had a higher incidence of anemia (29% vs 20%) and renal impairment (14% vs 6.3%) than those without prolonged hyperphosphatemia, and a lower incidence of hypotension (4.8% vs 7.5%). The incidence of all other TEAEs that were considered potential sequelae of prolonged hyperphosphatemia was nonexistent for patients with prolonged hyperphosphatemia versus those without: hyperparathyroidism (0 vs 2.5%), hypocalcemia (0 vs 5.0%), and renal failure (0 vs 2.5%). No events of calcinosis or calciphylaxis were reported. Cumulative incidence curves of the first onset of TEAEs considered potential sequelae of prolonged

Table 1 – Incidence of select TEAEs

	Grade 1 *n* (%)	Grade 2 *n* (%)	Grade 3 *n* (%)	Total *n* (%)	UpT *n* (%)	No UpT *n* (%)
				N = 101	*N* = 41	*N* = 60
Hyperphosphatemia	54 (54)	23 (23)	2 (2.0)	79 (78)	27 (66)	52 (87)
Stomatitis	21 (21)	25 (25)	14 (14)	60 (59)	23 (56)	37 (62)
Nail events[a]	22 (22)	23 (23)	15 (15)	60 (59)	25 (61)	35 (58)
Non-CSR eye disorders[a]	28 (28)	23 (23)	5 (5.0)	57 (56)[b]	21 (51)	36 (60)
Skin events[a]	25 (25)	22 (22)	8 (7.9)	55 (55)	23 (56)	32 (53)
Diarrhea	34 (34)	17 (17)	4 (4.0)	55 (55)	24 (59)	31 (52)
CSR	12 (12)	11 (11)	4 (4.0)	27 (27)	12 (29)	15 (25)

CSR = central serous retinopathy; TEAE = treatment-emergent adverse event; UpT = uptitration.

[a] The three most frequently occurring TEAEs in each of the categories, grouped by higher-level terms, were onycholysis (19%), paronychia (19%), and nail dystrophy (17%) for nail events; dry eye (28%), vision blurred (18%), and conjunctivitis (13%) for non-CSR eye disorders; dry skin (34%), palmar-plantar erythrodysesthesia syndrome (25%), and erythema (7.9%) for skin events; and chorioretinopathy (7.9%), retinal detachment (5.9%), and vitreous detachment (5.9%) for CSR events.

[b] One grade 4 TEAE occurred: cataract (grade 1 cataract was present at baseline). No other grade 4 or grade 5 TEAEs occurred.

Table 2 – Summary of onset, management, and resolution of individual select TEAEs

	Hyperphosphatemia	Stomatitis	Nail events	Non-CSR eye disorders	Skin events	Diarrhea	CSR
Developed select TEAE, *n*/*N* with ≥1 TEAE (%)	79/101 (78)	60/101 (59)	60/101 (59)	57/101 (56)	55/101 (55)	55/101 (55)	27/101 (27)
Time to first onset of select TEAE (d), median (IQR)	20 (14–29)	32 (18–85)	69 (50–89)	50 (28–80)	42 (22–83)	14 (8–23)	53 (32–100)
Had dose modification for select TEAE, *n*/*N* with TEAE (%)[a]							
Dose reduction	11/79 (14)	19/60 (32)	20/60 (33)	15/57 (26)	11/55 (20)	0	13/27 (48)
Dose interruption	24/79 (30)	27/60 (45)	17/60 (28)	10/57 (18)	13/55 (24)	6/55 (11)	8/27 (30)
Discontinuation	1/79 (1.3)	2/60 (3.3)	1/60 (1.7)	3/57 (5.3)	3/55 (5.5)	1/55 (1.8)	3/27 (11)
Received treatment for select TEAE, *n*/*N* with TEAE (%)	31/79 (39)	44/60 (73)	34/60 (57)	34/57 (60)	31/55 (56)	30/55 (55)	5/27 (19)
Time treatment was withheld for select TEAE (d), median (IQR)[b]	13 (7–16)	16 (7–32)	14 (14–14)[c] 18 (12–21)	NA	3 (3–3)[d] 25 (15–35)	5 (3–11)	22 (21–24)[e]
Resolution of ≥1 event of select TEAE by data cutoff, *n*/*N* with TEAE (%)	74/79 (94)	48/60 (80)	6/19 (32)[c] 11/19 (58)	21/28 (75)[f]	19/34 (56)[d] 12/25 (48)	50/55 (91)	6/8 (75)[e]
Time to resolution of select TEAE (d), median (IQR)	17 (9–37)	34 (22–75)	122 (100–237)[c] 75 (16–138)	44 (29–91)[f]	42 (15–91)[d] 93 (41–121)	20 (7–34)	27 (17–133)[e]

CSR = central serous retinopathy; IQR = interquartile range; NA = not available; TEAE = treatment-emergent adverse event.
[a] The most significant dose modification action taken for a TEAE was recorded; thus, TEAEs that led to interruption followed by reduction were reported as reductions.
[b] For each of the subsequent rows, data for the select TEAEs grouped by higher-level terms are the most common events.
[c] Data for nail events represent two separate preferred terms (onycholysis [top] and paronychia [bottom]).
[d] Data for skin events represent two separate terms (dry skin [top] and palmar-plantar erythrodysesthesia [bottom]).
[e] Data for chorioretinopathy (other CSR-related TEAEs are shown in Supplementary Table 4).
[f] Data for non-CSR eye disorders represent the preferred term of dry eye.

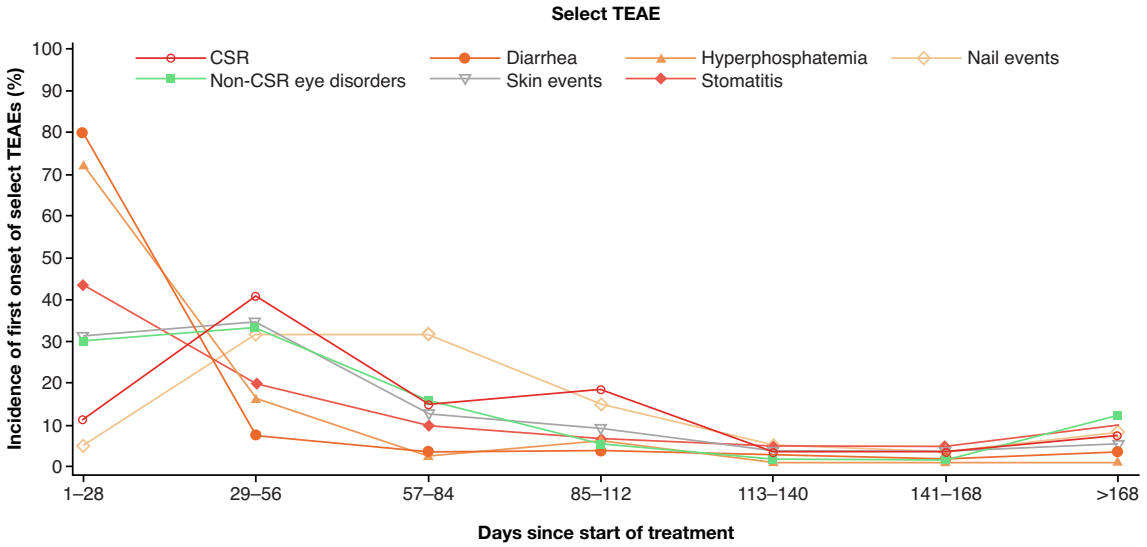

Fig. 1 – Incidence of the first onset of select treatment-emergent adverse events. CSR = central serous retinopathy; TEAE = treatment-emergent adverse event.

hyperphosphatemia, by grade, are shown in Supplementary Figure 3.

3.5. *Dermatological events*

3.5.1. *Nail events*

Sixty (59%) patients developed nail events, with a median time to onset of 69 (IQR, 50–89) d; of these patients, 45 (45%) had grade 1 or 2 events (Tables 1 and 2; cumulative incidence, Fig. 3A). Among the 34 (57%) of 60 patients with nail events receiving concomitant medications, the most common therapies were systemic antibacterials (38%; median duration 15 [IQR, 11–24] d) and dermatological antifungals (35%; median duration 59 [IQR, 35–214] d). The most commonly reported nail events were onycholysis and paronychia ($n = 19$, 19% for each). The median time treatment was withheld for onycholysis ($n = 2$ with dose interruption) and paronychia ($n = 6$ with dose interruption) was 14 (IQR, 14–14) and 18 (IQR, 12–21) d, respectively. By data cutoff, resolution of one or more onycholysis events was observed in six (32%) patients, and resolution of one or more paronychia events was observed in 11 (58%) patients.

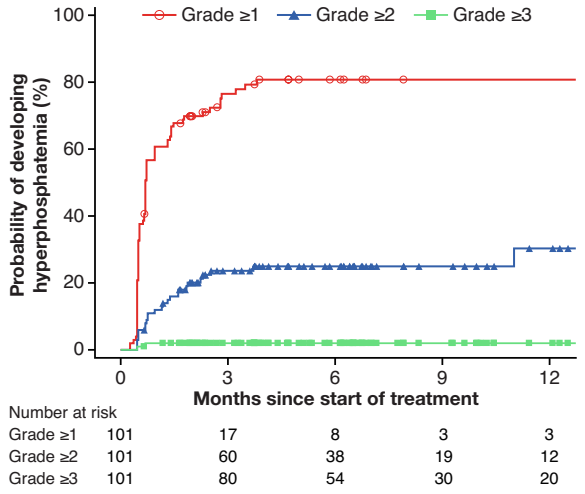

Fig. 2 – Cumulative incidence of the first onset of hyperphosphatemia by grade using the Kaplan-Meier method.

The median time to resolution of onycholysis and paronychia was 122 (IQR, 100–237) and 75 (IQR, 16–138) d, respectively.

3.5.2. Skin events

Fifty-five (55%) patients developed skin events, with a median time to onset of 42 (IQR, 22–83) d; of these patients, 47 (47%) had grade 1 or 2 events (Tables 1 and 2; cumulative incidence, Fig. 3B). Among the 31 (56%) of 55 patients with skin events receiving concomitant medications, the most common therapies were emollients and protective agents (45%; median duration 111 [IQR, 65–156] d) and systemic corticosteroids (29%; median duration 63 [IQR, 21–74] d). The most commonly reported skin event was dry skin ($n = 34$, 34%) followed by palmar-plantar erythrodysesthesia ($n = 25$, 25%). The median time treatment was withheld for palmar-plantar erythrodysesthesia ($n = 9$ with dose interruption) was 25 (IQR, 15–35) d. By data cutoff, resolution of one or more palmar-plantar erythrodysesthesia events was observed in 12 (48%) patients. The median time to resolution of palmar-plantar erythrodysesthesia was 93 (IQR, 41–121) d.

3.6. Central serous retinopathy

Twenty-seven (27%) patients developed CSR, with a median time to onset of 53 (IQR, 32–100) d; of these patients, 23 (23%) had grade 1 or 2 events (Tables 1 and 2; cumulative incidence, Fig. 4). Among the five (19%) of 27 patients with CSR receiving concomitant medications, the most common therapy was the use of ophthalmologicals (60%, mostly artificial tears; median duration 112 [IQR, 23–113] d). The most commonly reported CSR event was chorioretinopathy (CR; $n = 8$, 8%). The median time treatment was withheld for CR ($n = 3$ with dose interruption) was 22 (IQR, 21–24) d. By data cutoff, resolution of one or more CR events was observed in six (75%) patients. The median time to resolution of CR was 27 (IQR, 17–133) d. In addition to CR, CSR encompasses several TEAEs that could potentially overlap in an individual patient (eg, retinal detachment and vitreous detachment). Supplementary Table 4 provides a summary of their frequency of occurrence and resolution.

3.7. Non-CSR eye disorders

Fifty-seven (56%) patients developed non-CSR eye disorders, with a median time to onset of 50 (IQR, 28–80) d; of these patients, 51 (50%) had grade 1 or 2 events (Tables 1 and 2; cumulative incidence, Supplementary Fig. 4). Among the 34 (60%) of 57 patients with non-CSR eye disorders receiving concomitant medications, the most common therapy was the use of ophthalmologicals (85%, mostly eye lubricants/artificial tears; median duration 51 [IQR, 30–143] d). The most commonly reported non-CSR eye event

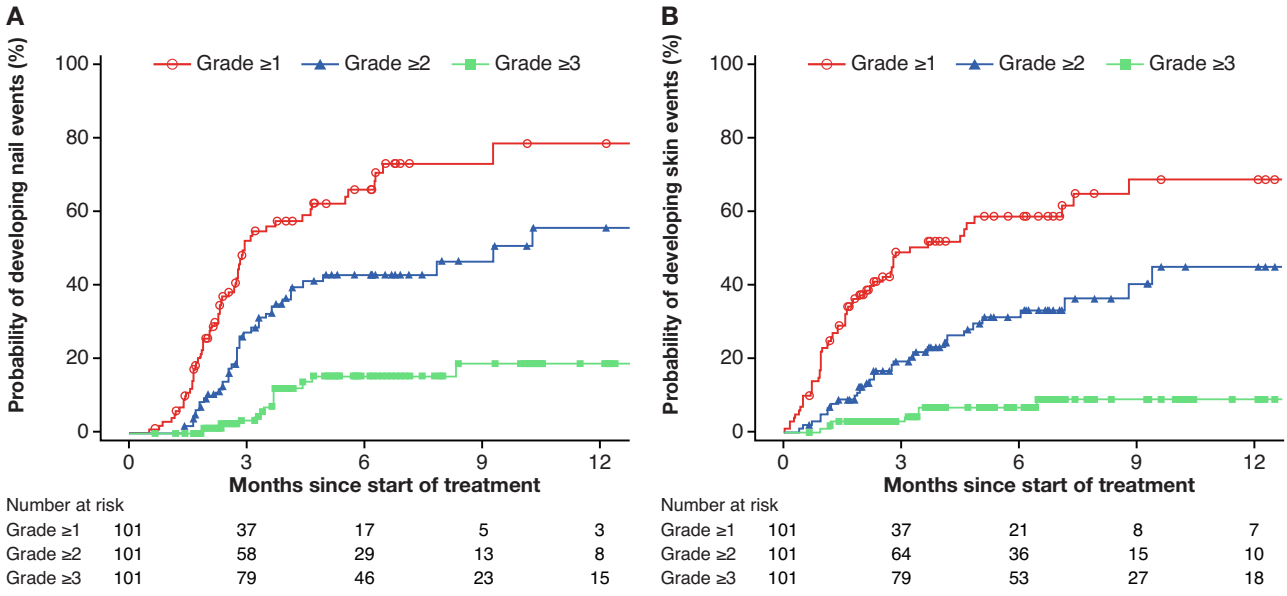

Fig. 3 – Cumulative incidence of the first onset of (A) nail and (B) skin events by grade using the Kaplan-Meier method.

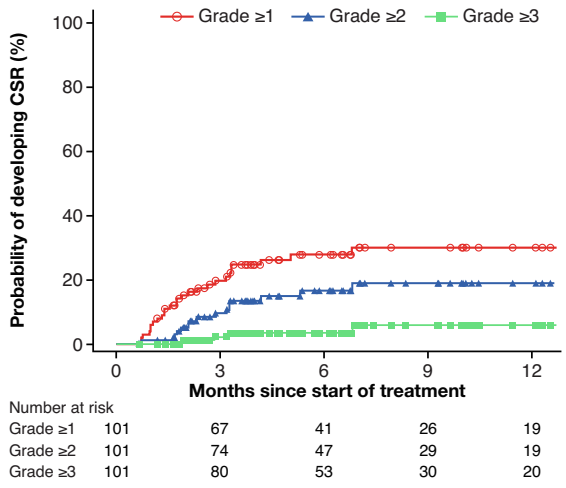

Fig. 4 – Cumulative incidence of the first onset of central serous retinopathy (CSR) by grade using the Kaplan-Meier method.

was dry eye (n = 28, 28%). By data cutoff, resolution of one or more dry eye events was observed in 21 (75%) of 28 patients. The median time to resolution of dry eye was 44 (IQR, 29–91) d.

3.8. Gastrointestinal TEAEs

3.8.1. Stomatitis

Sixty (59%) patients developed stomatitis, with a median time to onset of 32 (IQR, 18–85) d; of these patients, 46 (46%) had grade 1 or 2 events (Tables 1 and 2; cumulative incidence, Supplementary Fig. 5A). Among the 44 (73%) of 60 patients with stomatitis receiving concomitant medications, the most common therapy was the use of stomatological preparations (45%; median duration 65 [IQR, 27–137] d), including magic mouthwash (9%) and systemic corticosteroids (30%). By data cutoff, resolution of one or more stomatitis events was observed in 48 (80%) patients. The median time to resolution of stomatitis was 34 (IQR, 22–75) d.

3.8.2. Diarrhea

Fifty-five (55%) patients developed diarrhea, with a median time to onset of 14 (IQR, 8–23) d; of these patients, 51 (50%) had grade 1 or 2 events (Tables 1 and 2; cumulative incidence, Supplementary Fig. 5B). Among the 30 (55%) of 55 patients with diarrhea receiving concomitant medications, the most common therapies included antidiarrheals (97%; median duration 29 [IQR, 12–91] d), primarily loperamide hydrochloride/loperamide (87%). Resolution of one or more diarrhea events by data cutoff was observed in 50 (91%) patients. The median time to resolution of diarrhea was 20 d (IQR, 7–34).

4. Discussion

Patients treated with erdafitinib in the BLC2001 study exhibited common class-effect TEAEs known to be associated with FGFRi. Dose interruption and reduction guidelines were provided to investigators as guidance during the conduct of the study and are provided here (Supplementary Table 5), as they may be beneficial for the general care of patients being treated with FGFRi. Overall, the select TEAEs were managed effectively with erdafitinib dose modifications, including reductions or interruptions, and/or supportive concomitant therapies, resulting in few events leading to treatment discontinuation. Additionally, low-grade events occur earlier than more severe grade 3 events. These data suggest that identification of the select TEAEs and appropriate management with dose modification and concomitant therapies resulted in resolution of most TEAEs, may avoid more severe events, and may have prevented treatment discontinuation thereby ensuring maximum benefit with erdafitinib.

Hyperphosphatemia is a known class effect of FGFRi mediated by blockade of FGF23 inhibition of phosphate reabsorption [10,11]. Based on this off-tumor physiology, serum phosphate is carefully monitored as a pharmacokinetic/pharmacodynamic marker for erdafitinib and infigratinib [3,12,13]. The lower rate of hyperphosphatemia observed in patients who had uptitration may be explained by lower phosphate levels on erdafitinib due to lower FGFR target engagement than the group that did not require uptitration. Treatment with continuous erdafitinib was well tolerated, with a decrease in phosphate levels over time, and allows for improved clinical activity in patients. Further, hyperphosphatemia is seen in patients with chronic kidney disease, due to a decreased ability to excrete excess phosphate, acid, and potassium [14]. As adequate kidney function was an inclusion criterion for BLC2001, the risks of hyperphosphatemia associated with FGFRi treatment in patients with chronic kidney disease were not assessed in the study, so caution should be practiced in this setting.

Events of calcinosis and calciphylaxis were not reported in this study, but cases have been reported with FGFRi treatment [15,16], and may be related to changes in underlying serum phosphate known to be associated with FGFRis [11] or to the role of FGF/FGFR signaling in skeletal development [17]. There are also other underlying clinical risk factors that can contribute to the development of calciphylaxis and calcinosis, including but not limited to female sex, obesity, and diabetes [18–21]. Therefore, clinicians should consider a patient's underlying risk factors for calciphylaxis and calcinosis, and counsel patients accordingly.

CSR developed in 27% of patients, with most commonly reported events of CR, retinal detachment, and vitreous detachment. Additional FGFRis have shown similar findings of CSR. Rogaratinib treatment led to a serious treatment-related adverse event of retinopathy in one patient with UC (2%) on routine OCT testing [5]. Serous retinal detachment was found during OCT monitoring in 4% of patients with CCA and UC treated with pemigatinib [8]. In patients with CCA treated with derazantinib, grade ≥3 TEAEs included non-CSR monitored ocular events (7%) [6]. Different degrees of reported retinopathy may be related to variability in monitoring across clinical trials (ie, routine OCTs vs OCT in response to clinical symptoms or abnormal Amsler grid test). There may also be age-related differences in CSR occurrence. For example, patients in our study were

on average 10 yr older than CCA cohorts, and that could impact TEAEs. The underlying mechanism of CSR in patients treated with FGFRi is unclear, but other inhibitors of the MEK/MAP kinase pathways have been associated with CSR, such as transient MEK inhibitor–associated grade 1/2 bilateral retinopathies (40–65%) in patients with metastatic melanoma [22].

Nail disorders are the most concerning TEAEs that arise during long-term erdafitinib dosing. Treatments for symptom management of grade 2/3 nail onycholysis or onychodystrophy include over-the-counter nail strengthener/nail lacquer and silver nitrate application weekly, and topical antibiotics and vinegar soaks. For signs of infection (periungal edema/erythema/tenderness or discharge), bacterial cultures should be obtained with initiation of oral antibiotics (cefadroxil 500 mg twice daily, ciprofloxacin 500 mg twice daily, or sulfamethoxazole/trimethoprim twice daily) for 2 wk. For cases of severe or refractory infection, intravenous antibiotics should be considered, along with dermatological or surgical evaluation.

A potential study limitation is generalizability to the nonprotocol/general population given the sample size. This safety analysis does not include any description of potential correlation between the select TEAEs and efficacy. Additionally, the absence of dosing details for concomitant medications, the small number of patients who received specific therapies or supportive measures, and investigator discretion in the management of TEAEs limit the ability to precisely assess the efficacy of such interventions for the management of erdafitinib-related toxicities.

5. Conclusions

Erdafitinib is being studied in a phase 3 randomized, controlled trial (NCT03390504) in patients with previously treated advanced UC as monotherapy versus an immune checkpoint inhibitor (programmed cell death protein 1) or chemotherapy. Erdafitinib is also being investigated in a randomized phase 1/2 trial in the first-line cisplatin-ineligible metastatic UC setting in combination with the programmed cell death protein 1 inhibitor cetrelimab (NCT03473743) and as monotherapy versus intravesical chemotherapy in a randomized phase 2 trial (NCT04172675) in high-risk, non–muscle-invasive bladder cancer recurring after treatment with bacillus Calmette-Guérin. These additional studies and ongoing studies with other FGFRi will continue to inform optimal management of FGFRi TEAEs with dose modification and concomitant therapies in different patient populations and settings. Pending such additional information from clinical studies, multidisciplinary management may be recommended to manage select higher-grade TEAEs in metastatic UC patients with FGFRi to prevent the onset, or minimize the severity, of the select TEAEs and optimize patient compliance and outcome.

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Study concept and design: Siefker-Radtke, Rezazadeh Kalebasty, O'Hagan.
Acquisition of data: All authors.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
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Appendix A. Supplementary data

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