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Original Article – Editor's choice

Erdafitinib in Patients with High- and Intermediate-risk Non–muscle-invasive Bladder Cancer: Final Analysis of THOR-2 Study

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Abstract

Background and objective: High-risk (HR) or intermediate-risk (IR) non–muscle-invasive bladder cancer (NMIBC) carries a high probability of recurrence and/or progression. We present the final analysis results of erdafitinib in HR- or IR-NMIBC with fibroblast growth factor receptor 3/2 alterations (*FGFR3/2*alt) from the phase 2 THOR-2 study.
Methods: Cohort 1 (HR-NMIBC papillary only) with prior bacillus Calmette-Guérin was randomized 2:1 to erdafitinib or intravesical chemotherapy. Cohorts 2 (carcinoma in situ ± papillary) and 3 (IR-NMIBC) received erdafitinib. The primary endpoint was recurrence-free survival (RFS) for cohort 1. Exploratory endpoints included complete response (CR) rate and duration of response (DoR) for cohorts 2 and 3.
Key findings and limitations: In cohort 1 (n = 73), median RFS was not reached (NR) for erdafitinib (95% confidence interval [CI] 28.6 mo–not estimable [NE]) and 11.6 mo (95% CI 5.3–NE) for intravesical chemotherapy (hazard ratio 0.28 [95% CI 0.13–0.61; nominal p = 0.0007]; median follow-up, 18.5 and 16.6 mo, respectively). In cohort 2 (n = 16), CR rates were 94% (95% CI 70–100%) and 81% (95% CI 54–96%) at 8 and 32 wk, respectively; the median DoR (mDoR) was 23.3 mo (95% CI 10.0–NE; n = 15). In cohort 3 (n = 18), the CR rate was 89% (95% CI 65–99%) and mDoR was NR (95% CI 13.4 mo–NE). Most common treatment-related adverse event in pooled erdafitinib cohorts (N = 83) was hyperphosphatemia (76%). Limitations include early termination in cohort 1 and small sample size that precluded prespecified hypothesis testing.

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Conclusions and clinical implications: Oral erdafitinib demonstrated high efficacy in *FGFR3/2*alt HR-/IR-NMIBC, with a manageable safety profile.

ADVANCING PRACTICE

What does this study add?
Erdafitinib prolonged recurrence-free survival compared with intravesical chemotherapy in patients with papillary-only high-risk (HR) non–muscle-invasive bladder cancer (NMIBC) harboring fibroblast growth factor receptor 3/2 alterations (*FGFR3/2*alt) with prior bacillus Calmette-Guérin treatment (cohort 1). Furthermore, erdafitinib demonstrated encouraging antitumor activity in adults with HR carcinoma in situ ± papillary disease with *FGFR3/2*alt and intermediate-risk NMIBC and *FGFR3/2*alt (cohort 3).

Clinical Relevance
This final analysis of the multicohort phase 2 THOR-2 trial shows that oral erdafitinib achieved superior recurrence-free survival compared with intravesical chemotherapy in patients with *FGFR3/2*-altered high-risk papillary BCG-treated non–muscle-invasive bladder cancer, and demonstrated durable complete responses in those with carcinoma in situ and intermediate-risk disease. These results highlights the role of FGFR-targeted therapy as a precision oncology option in patients with non–muscle-invasive bladder cancer, a setting where systemic targeted treatments have been largely unexplored. However, the early termination of the trial and small sample sizes limit the generalizability of the findings, underscoring the need for larger, confirmatory studies before widespread adoption in clinical practice. Associate Editor: Gianluca Giannarini, MD.

Patient Summary
Patients with intermediate-risk (IR) or high-risk (HR) non–muscle-invasive bladder cancer with fibroblast growth factor receptor alterations are at a high likelihood of recurrence and/or progression. Oral erdafitinib in patients with HR or IR non–muscle-invasive bladder cancer harboring fibroblast growth factor receptor 3/2 alterations demonstrated meaningful efficacy. Safety outcomes were manageable and consistent with prior clinical studies.

1. Introduction

Bladder cancer is the tenth most common malignancy worldwide [1,2]. At diagnosis, 75% of patients have non–muscle-invasive bladder cancer (NMIBC) [3]. Both intermediate-risk (IR) and high-risk (HR) NMIBC are characterized by local recurrence (5-yr probability, ∼67% and 70%, respectively) [4] and progression (5-yr probability, ∼4–12% and ∼10–51%, respectively). For IR-NMIBC, standard therapy includes transurethral resection of bladder tumor (TURBT) followed by intravesical treatment [5]. For HR-NMIBC, TURBT is followed by intravesical bacillus Calmette-Guérin (BCG) [6,7]. Radical cystectomy is the standard of care for patients with BCG-unresponsive HR-NMIBC [6,7] but is associated with high morbidity [8], relatively high mortality [8], and diminished health-related quality of life [9,10].

Fibroblast growth factor receptor 3/2 alterations (*FGFR3/2*alt), which include mutations and fusions, have been shown to operate as potential oncogenic drivers in NMIBC [11]. Most common mutations occur in *FGFR3*, and are reported in >31% and ∼ 70% of patients with HR- and IR-NMIBC, respectively [12,13].

When THOR-2 was designed (June 2020), treatment options for patients with BCG-unresponsive HR-NMIBC were limited [14–16]. Several therapies have since been approved [16], including nadofaragene firadenovec-vncg [17] and nogapendekin alfa inbakicept-pmln [18].

Erdafitinib (JNJ-42756493) is an oral pan-FGFR1-4 inhibitor with demonstrated clinical activity in patients with solid tumors harboring *FGFR*alt [19]. In the USA, erdafitinib 8 mg/d is approved for previously treated adults with locally advanced or metastatic urothelial carcinoma who have susceptible *FGFR3*alt [20].

THOR-2 was a multicohort phase 2 trial assessing the safety and efficacy of erdafitinib in patients with HR- or IR-NMIBC and select *FGFR3/2*alt. Cohort 1 evaluated whether erdafitinib improved recurrence-free survival (RFS) over intravesical chemotherapy (IC) in patients with recurrent BCG-treated, papillary-only HR-NMIBC. Previous results from cohort 1 at a median follow-up of 13.4 mo showed prolonged RFS with erdafitinib versus IC in this population [13]. Herein, we report the final analysis of THOR-2 with longer follow-up data from cohort 1. Additionally, exploratory cohort 2, comprising patients with carcinoma in situ (CIS) ± papillary disease, was evaluated due to differences from HR-NMIBC in disease etiology and molecular drivers, and exploratory marker-lesion cohort 3 assessed on-target efficacy of erdafitinib in patients with IR-NMIBC.

2. Patients and methods

2.1. Study design and patients

THOR-2 (an open-label, global, multicenter, phase 2 study) comprised cohort 1 (randomized) and two single-arm exploratory cohorts (Fig. 1). Patients were ≥18 yr old, were treated with BCG, and had select *FGFR3/2*alt results by local or central assessment, as described in the Supplementary material. Patients were required to have one or more of the following mutations: *R248C*, *S249C*, *G370C*, and *Y373C*, or one or more of the following gene fusions: *FGFR2-BICC1*, *FGFR2-CASP7*, *FGFR3-TACC3*, and *FGFR3-BAIAP2L1*. Cohort 1 enrolled patients with HR-NMIBC papillary-only disease including BCG-experienced and BCG-unresponsive patients. Cohort 2 included patients with histologically confirmed, BCG-unresponsive HR-NMIBC CIS with *FGFR3/2*alt with or without a papillary tumor, who had refused or were ineligible for cystectomy (Supplementary material). Cohort 3 patients had histologically confirmed, recurrent low-grade IR-NMIBC, <5% risk of progression at 2 yr, and >50% risk of recurrence using the European Organisation for Research and Treatment of Cancer risk calculator. Patients had resection of all visible bladder tumors except one 5–10 mm tumor marker lesion for direct assessment of on-target efficacy.

THOR-2 was approved by the ethics committee, and patients gave informed consent to participate.

2.2. Procedures

Patients in cohort 1 were randomized 2:1 to either erdafitinib or IC [13]. In cohorts 2 and 3, patients received oral erdafitinib at 6 mg/d in 28-d cycles. Erdafitinib was continued for maximum 2 yr or until HR disease recurrence, intolerable toxicity, consent withdrawal, investigator decision, or study closure, with exceptions detailed in the Supplementary material. IC comprised instillations of mitomycin C/hyperthermic mitomycin C 40 mg or gemcitabine 2000 mg once weekly for four or more induction doses, followed by monthly maintenance for ≥6 mo.

2.3. Endpoints

The primary endpoint for cohort 1 was RFS. The secondary endpoints for all cohorts were pharmacokinetics and safety. For cohort 2, exploratory endpoints were complete response (CR) rates at 8 and 32 wk, and duration of response (DoR). A CR was defined as having at least a negative cystoscopy and negative (including atypical) urine cytology or a positive cystoscopy with biopsy-proven benign or low-grade NMIBC and negative cytology, and DoR was defined as the interval between initial documentation of a CR and the first documented evidence of progression, HR-NMIBC recurrence, or death from any cause.

For cohort 3, exploratory endpoints included CR rate, DoR, and the best overall response. A CR was defined as complete disappearance of the marker lesion with no new lesion or no viable tumor seen on histopathological examination, and negative urine cytology (atypical cytology would not qualify as a CR); a partial response was defined as marker lesion reduction by 50%; DoR was defined as the interval between initial documentation of response and the first documented evidence of progression, recurrence, or death due to any cause; and the best overall response was defined as the best response documented after the start of study treatment.

2.4. Assessments

Patients were assessed for disease response by cystoscopy and bladder mapping for the detection of new lesions, local

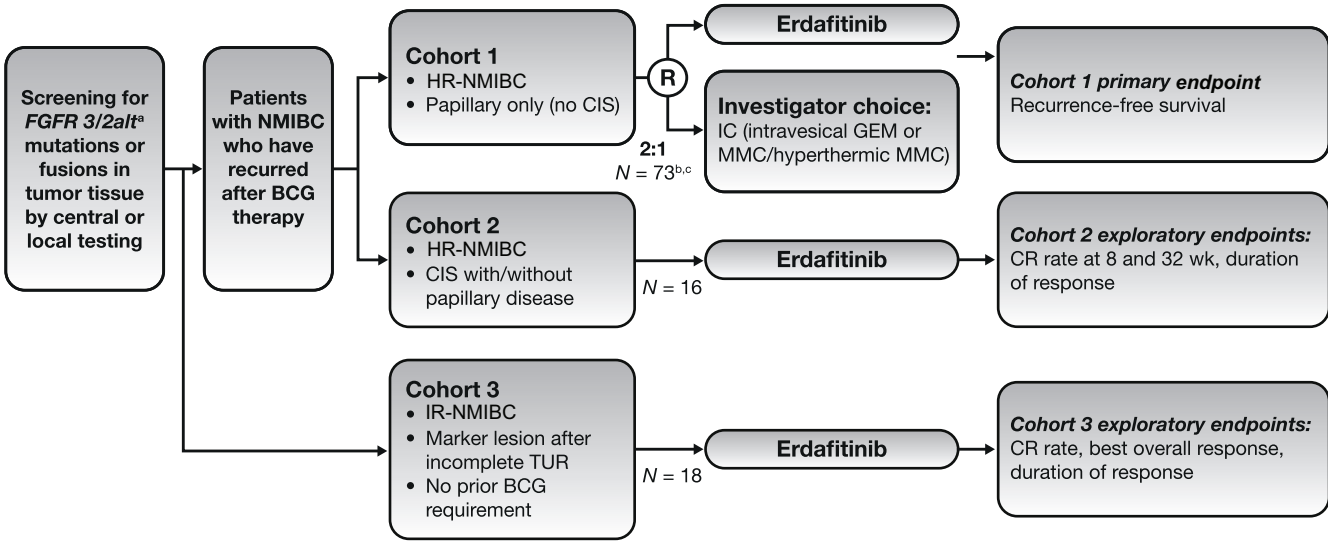

Fig. 1 – THOR-2 study design. alt = alterations; BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; CR = complete response; FGFR = fibroblast growth factor receptor; GEM = gemcitabine; HR = high risk; IC = intravesical chemotherapy; IR = intermediate risk; MMC = mitomycin C; NMIBC = non–muscle-invasive bladder cancer; TUR = transurethral resection. [a] Alterations include mutations or fusions. [b] Number of patients randomized at clinical cutoff of 7 August 2024. [c] The study was terminated early due to poor accrual in cohort 1, which resulted in smaller-than-planned sample sizes across all cohorts. Reasons for slow accrual included the COVID-19 pandemic, intermittent global shortage of BCG leading to patients not receiving adequate BCG, limited tumor tissue availability in the NMIBC population resulting in molecular testing challenges, and concerns from urologists and patients about potential systemic toxicities. Originally published in the study of Catto et al [13].

assessment of urine cytology, and computed tomography/-magnetic resonance imaging urogram.

For cohorts 1 and 2, cystoscopy was performed at screening, on cycle 3 day 1 (3 mo), and then every 12 (±1) wk for up to 2 yr of treatment or until HR disease recurrence or progression. For cohort 3, cystoscopy was performed at screening, then on cycle 2 day 1 (1 mo ± 2 d), cycle 3 day 1, and cycle 4 day 1 (±1 wk) or until CR, whichever occurred first.

Further details of assessments are provided in the Supplementary material.

2.5. Statistical analysis

Cohort 1 did not achieve target enrollment of ~240 patients owing to poor accrual, resulting in study termination in December 2022. The resulting sample size of cohort 1 was 73 patients, and the statistical analysis plan was amended to remove all prespecified hypothesis testing. Power calculations are described in Supplementary Table 1. All reported *p* values are nominal. Descriptive subgroup analyses were performed, but with no correction for multiplicity. The 95% confidence intervals (CIs) are presented but should not be used in place of hypothesis testing [13]. For cohorts 2 and 3, CR rates were calculated with associated two-sided 95% CIs. The Kaplan-Meier method was used to estimate median RFS and DoR with 95% CIs. Further details are provided in the Supplementary material.

3. Results

3.1. Patients

Enrollment began on June 9, 2020. A total of 1714 patients were screened for molecular eligibility, of whom 1258 (73%) had adequate tumor samples for testing and 431 (34%) had *FGFR3/2alt* (Supplementary Fig. 1). Data for patients with CIS disease morphology who had inadequate samples are provided in Supplementary Table 2.

Of 73 patients with HR-NMIBC papillary-only disease and *FGFR3/2alt* enrolled in cohort 1, 49 were randomized to erdafitinib and 24 to IC (Supplementary Fig. 2). At data cutoff on August 7, 2024, 43 patients (88%) treated with erdafitinib and 17 (71%) with IC had discontinued study treatment. Patient characteristics of cohort 1 are available in Supplementary Table 3 and have been published [13].

Cohort 2 comprised 16 patients with CIS ± papillary disease. The median age was 68.5 yr (Supplementary Table 3). The most common reasons for treatment discontinuation were HR recurrent disease (31%) and study termination by the sponsor (31%; Supplementary Fig. 3).

Cohort 3 comprised 18 patients (median age 63.5 yr) with low-grade IR-NMIBC (Supplementary Table 3). The most common reason for treatment discontinuation was study termination by the sponsor (39%; Supplementary Fig. 4).

At study termination, responding patients from all three cohorts could continue erdafitinib in a long-term extension scheme.

3.2. Efficacy

At the final analysis of cohort 1, the median follow-up periods were 18.5 and 16.6 mo for the erdafitinib and IC groups, respectively, inclusive of 36 censored patients in the erdafitinib group and ten in the IC group. Median RFS was not reached (NR) for erdafitinib (95% CI 28.6 mo–not estimable [NE]) and 11.6 mo (5.3–NE) for IC, with an estimated hazard ratio of 0.28 (95% CI 0.13–0.61; nominal $p = 0.0007$; Fig. 2). The RFS benefit observed with erdafitinib was consistent across subgroups based on prior BCG therapy (BCG experienced vs BCG unresponsive) and tumor stage (Ta vs T1; Supplementary Fig. 5).

In cohort 2, the median follow-up was 18.6 mo. The CR rates at 8 and 32 wk were 94% (95% CI 70–100%; $n = 15/16$) and 81% (95% CI 54–96%; $n = 13/16$), respectively. In 15 responders, the median DoR was 23.3 mo (95% CI 10.0–NE), with nine ongoing responses at data cutoff, five with recurrence or progression after initial response, and one censored for consent withdrawal (Fig. 3).

In cohort 3, the median follow-up was 16.6 mo. At the 3-mo assessment, the CR rate was 89% (95% CI 65–99%), one

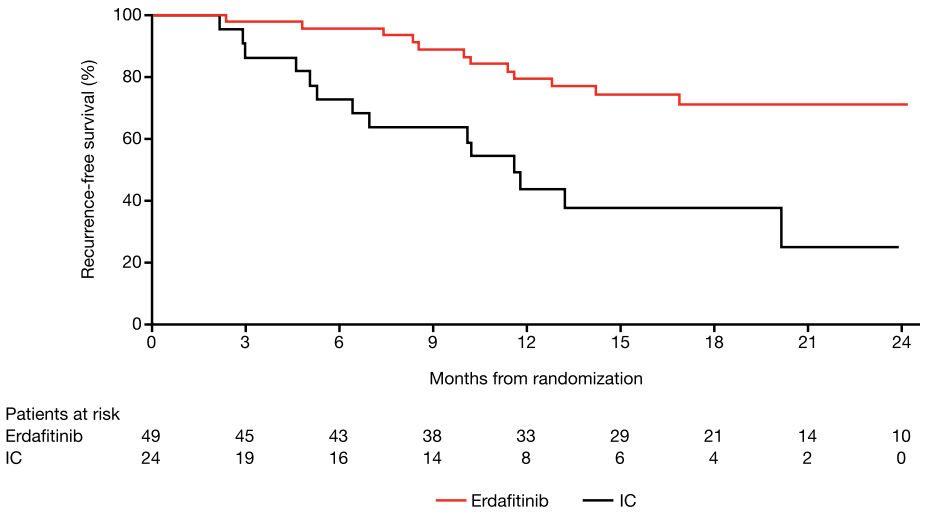

Fig. 2 – Longer-term recurrence-free survival rates plotted using the Kaplan-Meier method in randomized participants from cohort 1 (high-risk non–muscle-invasive bladder cancer papillary only). IC = intravesical chemotherapy.

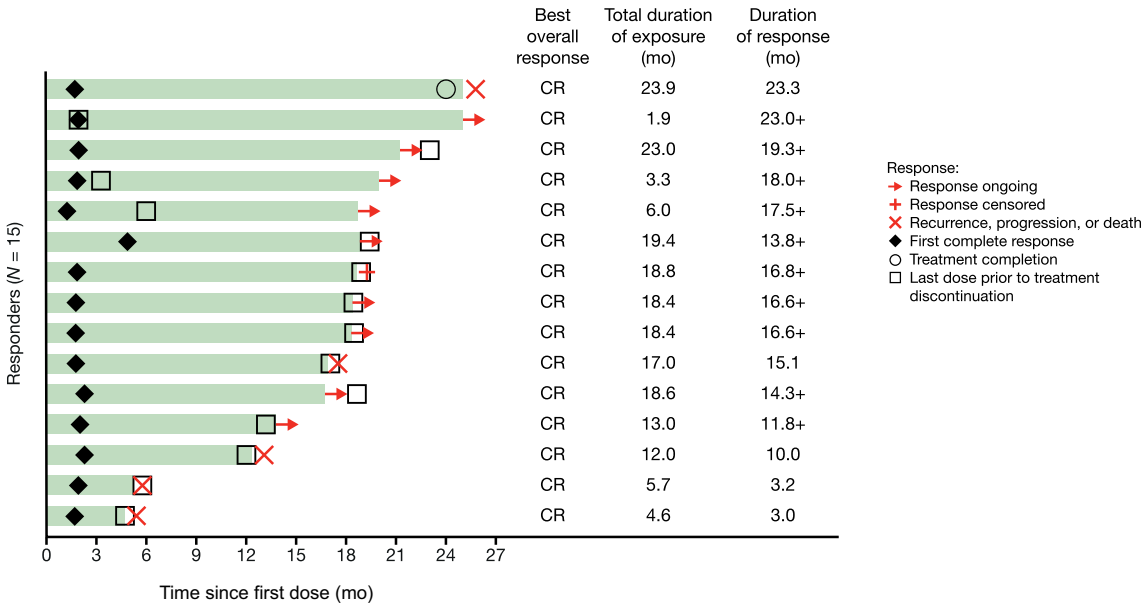

Fig. 3 – Swimmer plot for treatment duration and response in cohort 2 (high-risk carcinoma in situ ± papillary). Duration of response is defined as the interval between the date of initial documentation of a CR and the first documented evidence of progressive disease, recurrence, or death due to any cause. CR = complete response.

patient achieved a partial response (6%), and one patient recurred with high-grade NMIBC. The median time to response was 1.2 mo (interquartile range [IQR] 1.0–1.8). In 17 responders, median DoR was NR (95% CI 13.4 mo–NE), with nine responses ongoing at data cutoff. Four responders were censored due to consent withdrawal, and four experienced recurrence or progression (Fig. 4).

3.3. *Safety*

Patients in cohort 1 received erdafitinib and IC for a median of 12.8 mo (IQR 5.4–20.3) and 6.2 mo (IQR 5.9-14.4), respectively. In cohorts 1 and 2, 15 (31%) and zero patients, respectively, reported treatment-emergent adverse events (TEAEs) leading to discontinuation, and 23 (47%) and four

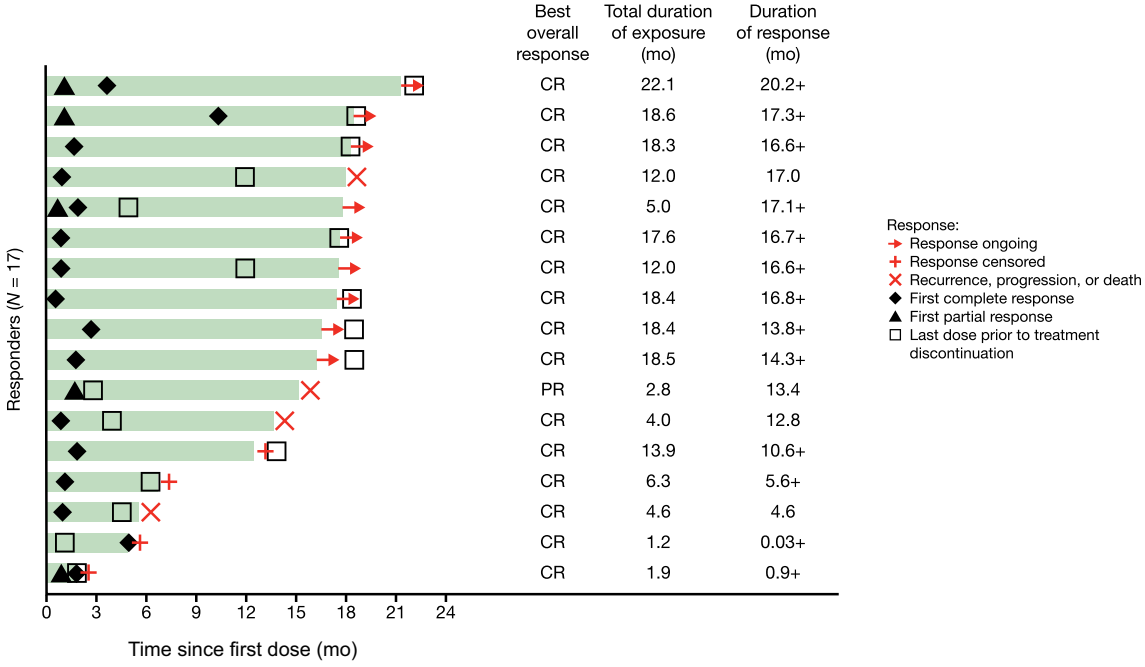

Fig. 4 – Swimmer plot for treatment duration and response in cohort 3 (intermediate-risk non–muscle-invasive bladder cancer). Duration of response is defined as the interval between the date of initial documentation of a response and the first documented evidence of progressive disease, recurrence, or death due to any cause. CR = complete response.

(17%), respectively, reported grade ≥3 TEAEs (Supplementary Table 4).

Cohort 2 (n = 16) patients received erdafitinib for a median of 15.0 mo (IQR 5.4–18.7). Three (19%) reported TEAEs leading to discontinuation; 12 (75%) reported grade ≥3 TEAEs.

Patients in cohort 3 (n = 18) received erdafitinib for a median of 12.0 mo (IQR 4.2–18.4). Four (22%) reported TEAEs leading to discontinuation; four (22%) reported grade ≥3 TEAEs (Supplementary Table 4). No TEAEs led to death in any cohort.

The most common treatment-related adverse event among the pooled cohorts (N = 83) receiving erdafitinib was hyperphosphatemia, occurring in 63 (76%) patients (Table 1).

TEAEs representing class effects of fibroblast growth factor receptor (FGFR) inhibitors in patients receiving erdafitinib by cohort are shown in Supplementary Tables 5–7. Central serous retinopathy (CSR) is a TEAE associated with FGFR class effect. CSR TEAEs were reported in 20 (41%), four (25%), and three (17%) patients in cohorts 1, 2, and 3, respectively, with grades 1–2 being the most reported maximum toxicity (18/20 [90%], 4/4 [100%], and 3/3 [100%], respectively). CSR events resolved in most patients (12/20 [60%]) in cohort 1 and in all patients (4/4 [100%]) in cohort 2 with dose modifications; in cohort 3, two CSR events remained unresolved at study end. Eight patients in cohort 1 had ongoing unresolved CSR events: three were associated with treatment withdrawal and five were not resolved at data cutoff. For the two patients in cohort 3 with unresolved CSR events, treatment was withdrawn in one and the other was unresolved at data cutoff.

Visual acuity is described in Supplementary Tables 8 and 9. Among the pooled cohorts of patients with baseline to worst postbaseline visual acuity data (n = 56), 22 had worsened. Among the pooled cohorts with at least one visual acuity record after the occurrence of worst postbaseline visual acuity (n = 42), 16 had improved at their last assessment.

3.4. Pharmacokinetics

A summary of descriptive statistics for erdafitinib plasma concentration data at cycle 2 day 1 (before dose administration) for each cohort is provided in Supplementary Table 10.

4. Discussion

The THOR-2 final analysis showed prolonged RFS benefit with erdafitinib versus IC in papillary-only HR-NMIBC patients. Erdafitinib also elicited high CR rates that were durable in patients with CIS ± papillary disease, demonstrating efficacy of FGFR-targeted therapy in a challenging-to-treat population [14]. The on-target effect of erdafitinib demonstrated by a high CR rate in the IR-NMIBC population provides a proof of concept of erdafitinib as an ablative targeted treatment in this setting.

The choice of IC (gemcitabine and mitomycin C/hyperthermic mitomycin C) as a comparator in cohort 1 is supported by current treatment practice and clinical data [21]. While retrospective clinical data for intravesical gemcitabine and docetaxel in patients with HR-NMIBC after BCG failure show a 74% CR rate [22], there are currently no therapies approved by the US Food and Drug Administration (FDA) for papillary-only HR-NMIBC with recurrence after BCG [6]. Consequently, there remains an unmet need for safe and effective therapies. This analysis from a median follow-up of 18.5 mo demonstrated continued benefit in patients with papillary-only HR-NMIBC harboring *FGFR3/2*alt who had early recurrence after BCG therapy and benefit across subgroups, consistent with prior findings [13].

At the start of THOR-2, treatment options were also limited for patients with BCG-unresponsive CIS ± papillary disease; the available treatment options were associated with low CR rates (18–41%) [14,15,23]. Since then, nadofaragene firadenovec-vncg [17,24] and nogapendekin alfa inbakicept-pmln [18] have been approved by the FDA [16,25], with anytime CR rates of 34–71%. In our study, erdafitinib demonstrated encouraging and durable efficacy (CR rates: 94% and 81% at 8 and 32 wk, respectively).

Current treatment for IR-NMIBC presenting as papillary tumors involves TURBT followed by intravesical treatment [5], which prevents on-target efficacy assessment. This population has a reported *FGFR*alt prevalence rate of 73% [12]. In THOR-2, erdafitinib demonstrated remarkable and durable efficacy (89%) in these patients.

Durable responses were observed in nine patients each in cohorts 2 and 3 who discontinued erdafitinib in the absence of recurrence or progression, suggesting a sustained antitumor effect.

Safety results were consistent with the known safety profile for erdafitinib [26]. Plasma concentrations of erdafitinib were generally comparable across all three cohorts and consistent with previous reports [27]. There were no grade ≥3 toxicities for hyperphosphatemia and skin, and a generally lower rate of grade ≥3 nail toxicities in cohorts 1 and 3 of THOR-2 compared with studies investigating erdafitinib in the locally advanced and metastatic setting (starting dose 8 mg and uptitration to 9 mg) [26,28]. This finding was consistent with the lower dose used in our study (6 mg). CSR was observed in 17–41% of patients across cohorts receiving erdafitinib versus 14–21% in other studies [29–31]. This higher frequency potentially results from the requirement of surveillance optical coherence tomography scans in THOR-2, while for-cause ophthalmological assessments were required in other studies [29–31], which may have led to the identification of subclinical cases of CSR in THOR-2 that mostly resolved with appropriate dose modifications.

To potentially reduce systemic toxicities associated with erdafitinib, TAR-210, a novel targeted-releasing system that provides sustained intravesical delivery of erdafitinib, is under investigation in patients with recurrent, BCG-experienced HR- and IR-NMIBC (Ta/T1) with a history of only low-grade papillary disease [32]. Phase 1 data suggest that TAR-210 is safe and well tolerated [32].

THOR-2 had some limitations. The study was terminated early due to poor accrual in cohort 1, which resulted in smaller-than-planned sample sizes across all cohorts. While

Table 1 – TRAEs across cohorts, using ≥10% TRAE cutoff of all erdafitinib-treated patients (cohorts 1–3) or patients treated with intravesical chemotherapy

Safety set	IC	Erdafitinib			
	Cohort 1 HR-NMIBC papillary only (n = 23)	Cohort 1 HR-NMIBC papillary only (n = 49)	Cohort 2 HR-NMIBC CIS ± papillary (n = 16)	Cohort 3 IR-NMIBC (n = 18)	Total erdafitinib cohorts (N = 83)
Patients with ≥1 TRAEs, n (%)	9 (39)	49 (100)	15 (94)	18 (100)	82 (99)
Preferred term, *n* (%)					
TRAEs in ≥10% of patients					
Hyperphosphatemia	0	36 (73)	9 (56)	18 (100)	63 (76)
Diarrhea	0	27 (55)	7 (44)	11 (61)	45 (54)
Dry mouth	0	23 (47)	9 (56)	13 (72)	45 (54)
Stomatitis	0	22 (45)	8 (50)	5 (28)	35 (42)
Dysgeusia	0	10 (20)	7 (44)	10 (56)	27 (33)
Dry skin	0	12 (24)	7 (44)	7 (39)	26 (31)
Nail dystrophy	0	16 (33)	2 (13)	4 (22)	22 (27)
Fatigue	1 (4)	9 (18)	3 (19)	7 (39)	19 (23)
Nail disorder	0	7 (14)	6 (38)	5 (28)	18 (22)
Onycholysis	0	10 (20)	3 (19)	5 (28)	18 (22)
Palmar-plantar erythrodysesthesia syndrome	0	6 (12)	5 (31)	7 (39)	18 (22)
Constipation	0	6 (12)	4 (25)	6 (33)	16 (19)
Alopecia	0	8 (16)	2 (13)	5 (28)	15 (18)
Central serous chorioretinopathy	0	11 (22)	2 (13)	2 (11)	15 (18)
Decreased appetite	0	10 (20)	2 (13)	3 (17)	15 (18)
Dry eye	0	11 (22)	4 (25)	4 (22)	19 (23)
Weight decreased	0	7 (14)	2 (13)	5 (28)	14 (17)
Paronychia	0	8 (16)	2 (13)	4 (22)	14 (17)
Alanine aminotransferase increased	1 (4.3)	6 (12)	2 (13)	3 (17)	11 (13)
Nasal dryness	0	4 (8)	2 (13)	5 (28)	11 (13)
Aspartate aminotransferase increased	1 (4)	6 (12)	1 (6)	3 (17)	10 (12)
Patients with ≥1 grade ≥3 TRAEs, n (%)	1 (4)	16 (33)	9 (56)	3 (17)	28 (33)
Preferred term, *n* (%)					
Stomatitis	0	6 (12)	2 (13)	0	8
Diarrhea	0	1 (2)	0	1 (6)	2
Glossitis	0	2 (4)	0	0	2
Nail toxicity	0	1 (2)	1 (6)	0	2
Alanine aminotransferase increased	1 (4)	1 (2)	1 (6)	0	2
Onychomadesis	0	0	2 (13)	0	2
Abdominal pain	0	0	0	1 (6)	1
Acute kidney injury	0	0	1 (6)	0	1
Aspartate aminotransferase increased	0	1 (2)	0	0	1
Cataract	0	0	1 (6)	0	1
Chronic kidney disease	0	0	1 (6)	0	1
Colitis ulcerative	0	1 (2)	0	0	1
Constipation	0	1 (2)	0	0	1
Detachment of macular retinal pigment epithelium	0	1 (2)	0	0	1
Diabetes mellitus	0	1 (2)	0	0	1
Dry mouth	0	0	1 (6)	0	1
Gastritis	0	0	0	1 (6)	1
Hyponatremia	0	1 (2)	0	0	1
Hypotension	0	0	1 (6)	0	1
Keratitis	0	1 (2)	0	0	1
Maculopathy	0	1 (2)	0	0	1
Nail bed inflammation	0	0	1 (6)	0	1
Nail dystrophy	0	2 (4)	0	0	2
Nail disorder	0	0	1 (6)	0	1
Pulmonary sepsis	0	0	1 (6)	0	1
Renal impairment	0	0	1 (6)	0	1
Syncope	0	1 (2)	0	0	1
Urosepsis	0	0	1 (6)	0	1
Weight decreased	0	1 (2)	0	0	1

CIS = carcinoma in situ; HR = high risk; IC = intravesical chemotherapy; IR = intermediate risk; NMIBC = non–muscle-invasive bladder cancer; TRAE = treatment-related adverse event.

a statistical difference using a nominal *p* value was observed, prespecified hypothesis testing between erdafitinib and IC could not be completed as designed originally owing to early termination. The exploratory cohorts were underpowered, lacked a direct comparator, and had limited follow-up times. While termination accounted for 20–39% cases of erdafitinib discontinuation across cohorts, responding patients from all cohorts could continue erdafitinib in a long-term extension scheme.

5. Conclusions

Erdafitinib prolonged RFS versus IC in patients with papillary-only HR-NMIBC harboring *FGFR3/2*alt and demonstrated encouraging antitumor activity in adults with CIS ± papillary disease with *FGFR3/2*alt, and IR-NMIBC and *FGFR3/2*alt. The observed antitumor activity of erdafitinib in THOR-2 supports continued research, including ongoing studies with TAR-210, a novel targeted releasing system, and additional larger clinical studies with longer follow-up.

Previous presentations of data are as follows:

Cohort 1 in: Catto JWF, et al. Erdafitinib in BCG-treated high-risk non–muscle-invasive bladder cancer. *Ann Oncol* 2024;35(1):98–106.

Cohort 2 in: Catto JWF, et al. Updated efficacy and safety of oral erdafitinib in patients with bacillus Calmette-Guérin–unresponsive, high-risk, non–muscle-invasive bladder cancer with *FGFR3/2* alterations in THOR-2 cohort 2. Presented at the 24th Annual Meeting of the Society of Urologic Oncology; November 29 to December 1, 2023; Washington, DC, USA.

Cohort 3 in: Daneshmand S, et al. Marker lesion study of oral erdafitinib in patients with intermediate-risk non–muscle-invasive bladder cancer with *FGFR3/2* alterations in THOR-2: updated cohort 3 results. Presented at the 24th Annual Meeting of the Society of Urologic Oncology; November 29 to December 1, 2023; Washington, DC, USA.

***Author contributions*:** Siamak Daneshmand had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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able at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for study data access can be submitted through the Yale Open Data Access (YODA) project site at http://yoda.yale.edu.

Supplementary data

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