Erdafitinib in Patients With Advanced Solid Tumors With *FGFR* Alterations (RAGNAR): Results of Tumor-Specific Analyses and Secondary Cohorts

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ABSTRACT

PURPOSE Erdafitinib, a pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor, is approved for second-line treatment of locally advanced or metastatic urothelial carcinoma with susceptible *FGFR3* alterations. Primary histology-agnostic analysis from the phase II RAGNAR study (ClinicalTrials.gov identifier: NCT04083976) indicated a clinical benefit with erdafitinib in Broad Panel Cohort (BPC) patients. We present tumor-specific updated efficacy and safety results from the BPC and tumor-agnostic findings from the Exploratory and Pediatric Cohorts of RAGNAR.

METHODS The Broad Panel, Exploratory, and Pediatric Cohorts enrolled patients with target (selected) *FGFR* alterations, nontarget *FGFR* alterations, and any *FGFR* alterations, respectively. Adults and pediatric patients (6 years and older) with advanced, unresectable, or metastatic disease who progressed after ≥1 prior line of systemic therapy and exhausted standard therapies were eligible. Erdafitinib 3-8 mg once daily (with possible uptitration) was administered orally until disease progression or intolerable toxicity.

RESULTS Objective response rates (ORRs) in the BPC were 10.0% (3 of 30) for high-grade glioma, 26.1% (6 of 23) for non–small cell lung cancer, 28.6% for (2 of 7) low-grade glioma, 31.3% (5 of 16) for breast cancer, 33.3% (5 of 15) for head and neck squamous cell carcinoma, 55.6% (10 of 18) for pancreatic cancer, and 100% (5 of 5) for salivary gland cancer. The ORR was 3.8% (2 of 53) in the Exploratory Cohort. In the Pediatric Cohort (n = 11), there were one responder and seven patients with durable stable disease. Treatment-related adverse events (TRAEs) were consistent with the known safety profile of erdafitinib. Pediatric-specific TRAEs included epiphysiolysis and limb fracture.

CONCLUSION Encouraging activity was observed for erdafitinib across tumor types in patients with advanced malignancies and selected *FGFR* alterations who have exhausted treatment options. More limited activity was observed for erdafitnib in the Exploratory Cohort.

ACCOMPANYING CONTENT

- Data Sharing Statement
- Data Supplement
- Protocol

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INTRODUCTION

Genetic alterations encoding the fibroblast growth factor receptor (FGFR) family of receptor tyrosine kinases are involved in key cellular processes and have been identified as potentially oncogenic across tumor types.[1] *FGFR* alterations are detected in 1.3%-31.7% of patients across tumor types, with highest prevalence in urothelial cancer.[2] Some tumor types with specific *FGFR* alterations may be sensitive to FGFR inhibition.[3] Patients with advanced, unresectable, or metastatic solid tumors who have exhausted standard-of-care therapies have a poor prognosis and represent a significant unmet need. FGFR inhibition has been studied as a treatment option for patients with advanced *FGFR*-altered tumors.[4]

Erdafitinib, an oral pan-FGFR tyrosine kinase inhibitor, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma with susceptible *FGFR3* genetic alterations whose disease has progressed on or

CONTEXT

Key Objective

Erdafitinib is approved for *FGFR3*-altered urothelial carcinoma and has previously demonstrated histology-agnostic clinical benefit in initial results from the phase II RAGNAR study. Our objective was to investigate whether erdafitinib demonstrates clinically meaningful antitumor activity beyond urothelial carcinoma across multiple advanced solid tumor types harboring selected *FGFR* alterations in updated results from RAGNAR.

Knowledge Generated

Erdafitnib demonstrated objective responses across multiple tumor types with selected *FGFR* alterations in the Broad Panel Cohort (glioma, non–small cell lung cancer, breast cancer, head and neck cancer, pancreatic cancer, salivary gland cancer), whereas erdafitnib showed generally limited activity in tumors with nontarget *FGFR* alterations in the Exploratory and Pediatric Cohorts.

Relevance

Encouraging activity was observed for erdafitinib across tumor types in patients with advanced malignancies and selected *FGFR* alterations who have exhausted treatment options. Erdafitinib showed limited activity in patients with advanced solid tumors and nontarget *FGFR* alterations.

after ≥1 line of PD-(L)1 inhibitor therapy. Erdafitinib has not been approved for pediatric use in any tumor type. The primary analysis of the tumor-agnostic RAGNAR phase II clinical study demonstrated that erdafitinib provides clinical benefit in patients with advanced solid tumors with *FGFR* alterations across 16 tumor types in the Broad Panel Cohort (BPC; median follow-up, 17.9 months; objective response rate [ORR], 30% [64 of 217]; duration of response [DOR], 6.9 months) and in the Cholangiocarcinoma (CCA) Expansion Cohort (median follow-up, 20.4 months; ORR, 60% [21 of 35]; DOR, 5.6 months).[5,6]

We report additional follow-up from key tumor types enrolled in the BPC, including low-grade glioma (LGG) and high-grade glioma (HGG), non–small cell lung cancer (NSCLC), breast cancer, pancreatic cancer, head and neck squamous cell carcinoma (HNSCC), and salivary gland cancer (SGC). We also report previously presented tumor-agnostic results from the Exploratory Cohort (nontarget *FGFR* alterations) and the Pediatric Cohort (any *FGFR* alterations).[7,8]

METHODS

Patients and Study Design

RAGNAR (ClinicalTrials.gov identifier: NCT04083976) was an open-label, single-arm, phase II, international study. Briefly, eligible adult (18 years and older) and pediatric patients (6-17 years old) with advanced, unresectable, or metastatic cancer who had disease progression on ≥1 line of systemic therapy and had no available alternative standard therapy were enrolled. Pediatric patients with newly diagnosed disease were also eligible. Eligibility criteria (including central molecular eligibility screening and profiling) for patients in each cohort are summarized below and presented in detail in the Supplementary Methods. In brief, *FGFR* alterations were classified as target or nontarget using prespecified criteria, including an intact FGFR kinase domain; alterations not meeting these criteria were evaluated in the Exploratory Cohort.

1. BPC: Adult and pediatric patients (12 years and older) with target *FGFR* mutations and *FGFR* gene fusion with intact kinase domain;
2. Exploratory Cohort: Adults with nontarget *FGFR* mutations that were not specified for the BPC;
3. Pediatric Cohort: Children with any *FGFR* mutations (exclusive of valine gatekeeper and resistance alterations), *FGFR* gene fusions, or *FGFR* internal tandem duplications.

Patients 15 years and older received oral erdafitinib 8 mg once daily with possible uptitration to 9 mg once daily at cycle 1 day 14. Adolescents 12-14 years old received erdafitinib 5 mg once daily with possible uptitration to 6 mg or further to 8 mg once daily based on cycle 1 day 14 and cycle 2 day 7 serum phosphate levels. Children 6-11 years old received erdafitinib 3 mg once daily with possible uptitration to 4 mg once daily or further to 5 mg once daily based on cycle 1 day 14 and cycle 2 day 7 serum phosphate levels. Treatment continued daily on a continuous 21-day cycle until disease progression, intolerable toxicity, withdrawal of consent, or investigator decision to discontinue treatment.

Outcomes and Statistical Analysis

Efficacy and safety evaluations included patients who received ≥1 dose of erdafitinib and are presented by tumor histology. Prespecified efficacy evaluations were ORR (primary end point), disease control rate (DCR), clinical benefit rate (CBR), DOR, progression-free survival (PFS), and overall survival (OS). ORR, DCR, CBR, DOR, and PFS were per the

Independent Review Committee (IRC) for the BPC and per investigator assessment for the Exploratory and the Pediatric Cohorts. Treatment-emergent adverse events and treatment-related adverse events (TRAEs) were summarized descriptively. Efficacy and safety outcomes, statistical design, and data review monitoring are detailed in Supplementary Methods; tumor-specific enrollment and evaluation followed prespecified protocol criteria. Interim reviews for each BPC histologic subgroup were conducted at predefined enrollment milestones to evaluate activity against prespecified ORR benchmarks (≤15% null; ≥35% alternative).[5]

Ethical Compliance

RAGNAR was performed according to the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable regulatory requirements. Review boards of participating institutions and countries approved the study and all protocol amendments. Patients or their legally acceptable representatives provided written informed consent before enrollment.

RESULTS

Patients were enrolled between December 5, 2019 and December 4, 2023. All efficacy and safety analyses are based on a clinical cutoff of August 15, 2022. Baseline demographics and disease characteristics and study disposition are reported in the Supplementary Results; Data Supplement, Fig S1 and Table S1.

Efficacy

Broad Panel Cohort

Gliomas. Patients with LGG (n = 7) had a median age of 22.0 (range, 12-32) years and a median of 1 (range, 1-4) prior line of anticancer therapy (Data Supplement, Table S1). One patient with LGG was also included in the Pediatric Cohort. At a median follow-up of 4.17 (95% CI, 1.41 to not evaluable [NE]) months, the IRC ORR was 28.6% (2 of 7 [95% CI, 3.7 to 71.0]; Tables 1 and 2). There was one complete response (CR) lasting 21.68 months (censored at last disease assessment) in a patient with dysembryoplastic neuroepithelial tumor with a *FGFR1* mutation (pathogenic comutations in *KRAS* and *PIK3CA*; Figs 1, 2, and 3A and Table 1). There was one partial response (PR) of 2.60 months (censored at initiation of new anticancer therapy) in a patient with a *FGFR2* fusion (no coalterations; Figs 1 and 2A; Table 1). Three patients had stable disease (SD; Figs 1 and 2A), including one lasting >4 months. The DCR was 71.4%, and the CBR was 42.9%. Median DOR, PFS, and OS were not reached; median PFS and OS were NE [95% CI, 2.76 to NE] months and NE [95% CI, 5.72 to NE] months, respectively (Table 1).

Patients with HGG (n = 30) had a median age of 54.5 (range, 13-70) years and a median of 2 (range, 1-6) prior lines of anticancer therapy (Data Supplement, Table S1). One patient with HGG was also included in the Pediatric Cohort. At a median follow-up of 18.04 (95% CI, 13.50 to NE) months, the IRC ORR was 10.0% (3 of 30 [95% CI, 2.1 to 26.5]; Tables 1 and 2). All three responses were PRs, lasting for 15.90, 10.15, and 7.00 months (Fig 2B). The PRs occurred in one patient with *FGFR1* fusion (pathogenic comutations of *CDK4*, *MDM2*, *EGFR*, and *PTPN11* amplifications) and two patients with *FGFR3* alterations (*CDKN2A* pathogenic coalteration, including one patient with additional genetic fusions; Figs 1 and 2B; Table 1). Fourteen patients had SD (Figs 1 and 2; Table 1), including seven patients with SD lasting >4 months. The DCR was 56.7%, and the CBR was 33.3%. The median PFS was 3.86 (95% CI, 2.96 to 5.26) months, and the median OS was 6.34 (95% CI, 3.75 to 10.74) months (Table 1).

NSCLC. Patients with NSCLC (n = 23, including squamous NSCLC, n = 14 and nonsquamous NSCLC, n = 9) had a median age of 63.0 (range, 50-79) years and a median of 2 (range, 1-7) prior lines of anticancer therapy (Data Supplement, Table S1). At a median follow-up of 10.87 (95% CI, 2.83 to NE) months, the IRC ORR was 26.1% (6 of 23 [95% CI, 10.2 to 48.4]), including one CR and five PRs (Tables 1 and 2; Figs 1 and 2C). The ORR was 21.4% (3 of 14 [95% CI, 4.7 to 50.8]) in squamous NSCLC and 33.3% (3 of 9 [95% CI, 7.5 to 70.1]) in nonsquamous NSCLC. The median DOR was 4.62 (95% CI, 2.33 to NE) months, with a median DOR of 3.65 months (95% CI, 2.33 to NE) in squamous NSCLC and 5.59 months (95% CI, 2.83 to NE) in nonsquamous NSCLC. The CR was maintained for 16.56 months in a patient with nonsquamous NSCLC (censored at last disease assessment). The ORR was 28.6% in patients with *FGFR2* alterations (one mutation, one fusion) and 25.0% in patients with *FGFR3* alterations (one mutation, three fusions; Table 2). Eleven patients achieved SD, including three patients with SD lasting >4 months (Figs 1 and 2C; Table 1). The DCR was 73.9% (squamous NSCLC, 85.7%; nonsquamous NSCLC, 55.6%), and the CBR was 39.1% (squamous NSCLC, 28.6%; nonsquamous NSCLC, 55.6%). The overall median PFS was 4.11 (95% CI, 2.37 to 6.93) months, and the overall median OS was 10.45 (95% CI, 4.37 to 14.82) months (Table 1). The median PFS was 4.11 (95% CI, 2.37 to NE) months, and the median OS was 10.45 (95% CI, 2.37 to 14.59) months for patients with squamous NSCLC. The median PFS was 4.07 (95% CI, 1.38 to NE) months, and the median OS was 9.86 (95% CI, 2.33 to NE) months for patients with nonsquamous NSCLC.

Breast cancer. Sixteen patients had breast cancer. Two patients had estrogen receptor [ER+]/progesterone receptor +/human epithelial receptor-2 [HER2]+ breast cancer, five patients had ER+/progesterone receptor+/HER2− breast cancer, and five patients had triple-negative breast cancer. HER2 status was not evaluable in four patients (two patients had ER+/progesterone receptor+, and two patients had ER−/progesterone receptor− breast cancer). The median age was 54.0 (range, 37-74) years, and the median number of prior lines of anticancer therapy was 5 (range, 2-12; Data Supplement, Table S1). At a median follow-up of 14.09 (95% CI, 2.60 to NE) months, the IRC ORR was 31.3% (5 of 16 [95% CI, 11.0 to 58.7]; Tables 1 and 2). All five responses were

TABLE 1. Efficacy Evaluations per the Independent Review Committee in Tumor-Specific Subgroups of the BPC and per Investigator Assessment in the Exploratory and Pediatric Cohorts of RAGNAR

	BPC (n = 114)								
Efficacy End Point	LGG, n = 7	HGG, n = 30	NSCLC, n = 23	Breast, n = 16	Pancreatic, n = 18	HNSCC, n = 15	Salivary Gland, n = 5	Exploratory Cohort (n = 53)	Pediatric Cohort (n = 11)
ORR, No. (% [95% CI])	2 (28.6 [3.7 to 71.0])	3 (10.0 [2.1 to 26.5])	6 (26.1 [10.2 to 48.4])	5 (31.3 [11.0 to 58.7])	10 (55.6 [30.8 to 78.5])	5 (33.3 [11.8 to 61.6])	5 (100 [47.8 to 100])	2 (3.8 [0.5 to 13.0])	1 (9.1 [0.2 to 41.3])
DOR, months, median (95% CI)	NE (NE to NE)	NE (7.00 to NE)	4.62 (2.33 to NE)	6.93 (6.08 to NE)	7.10 (2.76 to NE)	2.89 (2.79 to NE)	13.47 (6.93 to NE)	2.91 (2.79 to NE)	19.75 (NE to NE)
DCR, No. (% [95% CI])	5 (71.4 [29.0 to 96.3])	17 (56.7 [37.4 to 74.5])	17 (73.9 [51.6 to 89.8])	11 (68.8 [41.3 to 89.0])	17 (94.4 [72.7 to 99.9])	13 (86.7 [59.5 to 98.3])	5 (100 [47.8 to 100])	24 (45.3 [31.6 to 59.6])	8 (72.7 [39.0 to 94.0])
CBR, No. (% [95% CI])	3 (42.9 [9.9 to 81.6])	10 (33.3 [17.3 to 52.8])	9 (39.1 [19.7 to 61.5])	6 (37.5 [15.2 to 64.6])	11 (61.1 [35.7 to 82.7])	6 (40.0 [16.3 to 67.7])	5 (100 [47.8 to 100])	9 (17.0 [8.1 to 29.8])	8 (72.7 [39.0 to 94.0])
Best overall response, No. (%)									
Complete response	1 (14.3)	0	1 (4.3)	0	0	0	2 (40.0)	0	0
Partial response	1 (14.3)	3 (10.0)	5 (21.7)	5 (31.3)	10 (55.6)	5 (33.3)	3 (60.0)	2 (3.8)	1 (9.1)
Stable disease	3 (42.9)	14 (46.7)	11 (47.8)	6 (37.5)	7 (38.9)	8 (53.3)	0	22 (41.5)	7 (63.6)
PFS, months, median (95% CI)	NE (2.76 to NE)	3.86 (2.96 to 5.26)	4.11 (2.37 to 6.93)	5.73 (1.22 to 9.56)	7.00 (3.78 to NE)	4.14 (3.98 to 5.42)	15.11 (8.34 to NE)	1.41 (1.35 to 2.73)	29.47 (0.72 to NE)
OS, months, median (95% CI)	NE (5.72 to NE)	6.34 (3.75 to 10.74)	10.45 (4.37 to 14.82)	8.87 (4.86 to 11.76)	19.71 (9.92 to NE)	11.60 (5.55 to NE)	NE (12.71 to NE)	5.32 (3.71 to 10.28)	NE (2.23 to NE)

Abbreviations: BPC, Broad Panel Cohort; CBR, clinical benefit rate; DCR, disease control rate; DOR, duration of response; HGG, high-grade glioma; HNSCC, head and neck squamous cell carcinoma; LGG, low-grade glioma; NE, not evaluable; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

TABLE 2. Overall Response Rate by *FGFR* Gene and Alteration Type per the Independent Review Committee in Tumor-Specific Subgroups of the BPC and per Investigator Assessment in the Exploratory and Pediatric Cohorts of RAGNAR

	BPC (n = 114)														Exploratory Cohort (n = 53)		Pediatric Cohort (n = 11)	
	LGG, n = 7		HGG, n = 30		NSCLC, n = 23		Breast, n = 16		Pancreatic, n = 18		HNSCC, n = 15		Salivary Gland, n = 5					
Genetic Alteration	No.[a]	ORR, No. (%)	No.[a]	ORR, No. (%)	No.[a]	ORR, No. (%)	No.[a]	ORR, No. (%)	No.[a]	ORR, No. (%)	No.[a]	ORR, No. (%)	No.[a]	ORR, No. (%)	No.[a]	ORR, No. (%)	No.	ORR, No. (%)
Patients with any *FGFR* alterations	7	2 (28.6)	30	3 (10.0)	23	6 (26.1)	16	5 (31.3)	18	10 (55.6)	15	5 (33.3)	5	5 (100)	53	2 (3.8)	11	1 (9.1)
FGFR1	5	1 (20.0)	2	1 (50.0)	0	0	2	0	4	2 (50.0)	0	0	1	1 (100)	9	0	7[b]	1 (14.3)
Mutations	4	1 (25.0)	1	0	0	0	0	0	0	0	0	0	0	0	9	0	3	0
Fusions	1	0	1	1 (100)	0	0	2	0	4	2 (50.0)	0	0	1	1 (100)	0	0	3	1 (33.3)
FGFR2	1	1 (100)	1	0	7	2 (28.6)	12	4 (33.3)	14	8 (57.1)	1	1 (100)	5	5 (100)	9	0	1	0
Mutations	0	0	0	0	1	1 (100)	4	1 (25.0)	0	0	1	1 (100)	5	5 (100)	9	0	0	0
Fusions	1	1 (100)	1	0	6	1 (16.7)	8	3 (37.5)	14	8 (57.1)	0	0	1	1 (100)	0	0	1	0
FGFR3	1	0	27	2 (7.4)	16	4 (25.0)	2	1 (50.0)	0	0	14	4 (28.6)	0	0	16	1 (6.3)	3	0
Mutations	0	0	0	0	9	1 (11.1)	2	1 (50.0)	0	0	11	2 (18.2)	0	0	15	1 (6.7)	1	0
Fusions	1	0	27	2 (7.4)	7	3 (42.9)	0	0	0	0	3	2 (66.7)	0	0	0	0	2	0
FGFR4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	20	1 (5.0)	0	0
Mutations	0	0	0	0	0	0	0	0	0	0	0	0	0	0	20	1 (5.0)	0	0
Fusions	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Abbreviations: BPC, Broad Panel Cohort; HGG, high-grade glioma; HNSCC, head and neck squamous cell carcinoma; LGG, low-grade glioma; NSCLC, non–small cell lung cancer; ORR, objective response rate.

[a]No. refers to the total number of patients with a *FGFR* by gene and type alteration.

[b]One duplication not shown in the table.

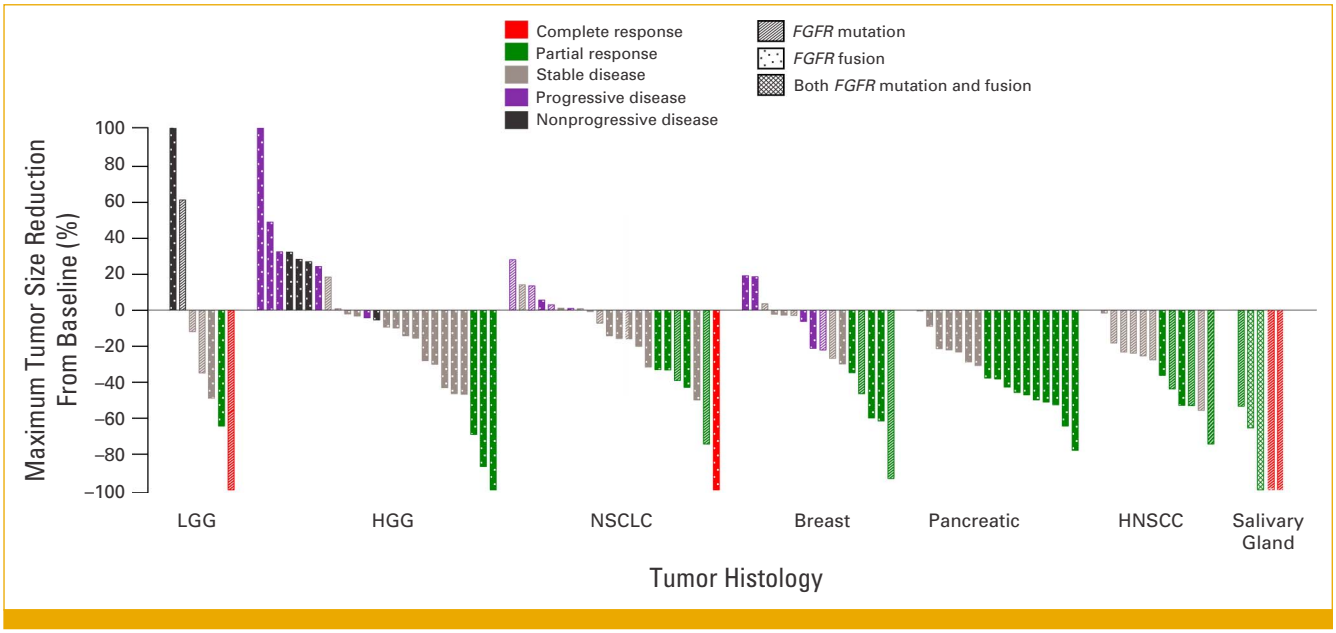

FIG 1. Maximum percent reduction in the size of target lesions from baseline by *FGFR* alterations per the Independent Review Committee in tumor-specific subgroups of the Broad Panel Cohort. For disease evaluations based on RECIST v1.1, maximum percent reduction from baseline is calculated from sum of target lesion diameters. For disease evaluations based on RANO, maximum percent reduction from baseline is calculated from the sum of product of biperpendicular dimensions. The maximal percentage increase of target lesions from baseline >100% is set to 100%. The best overall response is the best response recorded from the start of study treatment to the end of study, before progressive disease and subsequent anticancer therapy (subsequent surgery/procedure, radiotherapy, or systemic therapy), taking into account any requirement for confirmation. HGG, high-grade glioma; HNSCC, head and neck squamous cell carcinoma; LGG, low-grade glioma; NSCLC, non–small cell lung cancer; RANO, Response Assessment In Neuro-Oncology.

PRs and occurred in patients with *FGFR2* (one mutation, three fusions) and *FGFR3* (one mutation) alterations (Figs 1 and 2D; Table 2). The median DOR was 6.93 (95% CI, 6.08 to NE) months (Table 1). Six patients had SD (Figs 1 and 2D; Table 1), including one patient with SD for >4 months. The DCR was 68.8%, and the CBR was 37.5%. The median PFS was 5.73 (95% CI, 1.22 to 9.56) months, and the median OS was 8.87 (95% CI, 4.86 to 11.76) months (Table 1).

Pancreatic cancer. Patients with pancreatic cancer (n = 18) had a median age of 60.5 (range, 34-78) years and a median of 3 (range, 1-9) prior lines of anticancer therapy (Data Supplement, Table S1). All tumors were *KRAS* wild-type. At a median follow-up of 13.83 (95% CI, 5.52 to NE) months, the IRC ORR was 55.6% (10 of 18 [95% CI, 30.8 to 78.5]; Tables 1 and 2). All responses were PRs in patients with either *FGFR1* or *FGFR2* gene fusions (Figs 1 and 2E; Table 2); the median DOR was 7.10 (95% CI, 2.76 to NE) months (Table 1). There were seven patients with SD (Figs 1 and 2E; Table 1), including one patient with SD for >4 months. The DCR was 94.4%, and the CBR was 61.1%. The median PFS and OS were 7.00 (95% CI, 3.78 to NE) months and 19.71 (95% CI, 9.92 to NE) months, respectively (Table 1).

Head and neck cancers. Patients with HNSCC (n = 15) had a median age of 64.0 (range, 27-76) years and a median of 3 (range, 1-8) prior lines of anticancer therapy (Data Supplement, Table S1). The IRC ORR was 33.3% (5 of 15 [95% CI, 11.8 to 61.6]; Tables 1 and 2). All responses were PRs in patients with *FGFR2* (mutation) or *FGFR3* (two mutations, two fusions) alterations (Figs 1 and 2F; Table 2). The median DOR was 2.89 (95% CI, 2.79 to NE) months (Table 1). Eight patients had SD (Figs 1 and 2; Table 1), including one patient with SD for >4 months. The DCR was 86.7%, and the CBR was 40.0%. The median PFS and OS were 4.14 (95% CI, 3.98 to 5.42) months and 11.60 (95% CI, 5.55 to NE) months, respectively (Table 1).

In patients with SGC (n = 5), the median age was 53.0 (range, 41-78) years and the median number of prior lines of anticancer therapy was 1 (range, 1-4; Data Supplement, Table S1). At a median follow-up of 16.79 (95% CI, 11.04 to NE) months, the IRC ORR was 100% (5 of 5 [95% CI, 47.8 to 100]; Table 1 and Fig 2F), including two CRs and three PRs in patients with *FGFR1* (fusion) and *FGFR2* (five mutations, one fusion [one patient had both mutations and fusions]) alterations (Figs 1 and 2F; Tables 1 and 2). The median DOR, median PFS, and median OS were 13.47 (95% CI, 6.93 to NE) months, 15.11 (95% CI, 8.34 to NE) months, and NE (95% CI, 12.71 to NE) months, respectively (Table 1).

Exploratory Cohort

Patients in the Exploratory Cohort (n = 53) had a median age of 62.0 (range, 24-80) years and a median of 3 (range, 1-14) prior lines of anticancer therapy (Data Supplement, Table S1). Patients in the Exploratory Cohort primarily had CCA

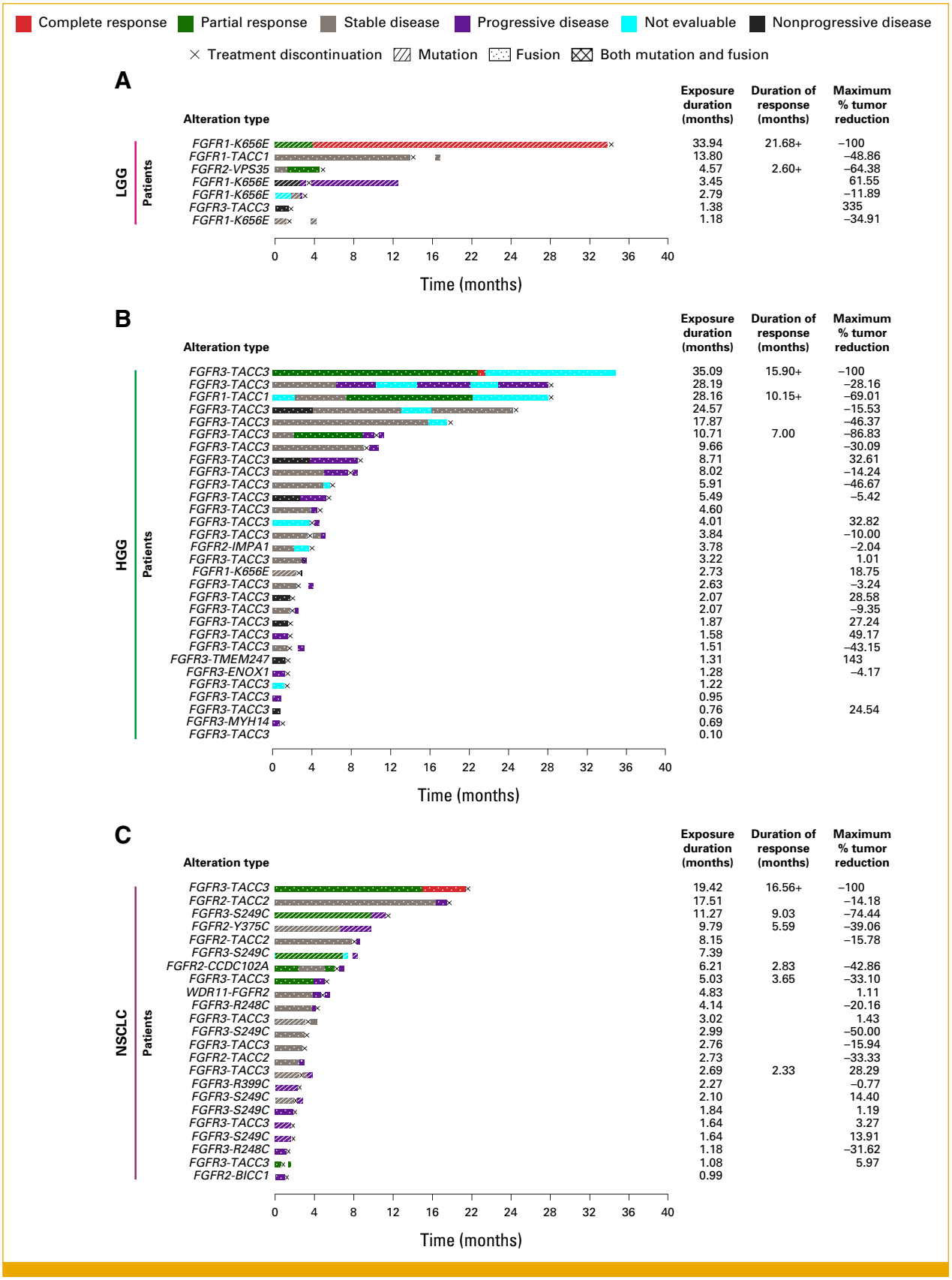

FIG 2. Swim lane plot for treatment duration and duration of response by *FGFR* alterations per the Independent Review Committee in tumor-specific subgroups of the Broad Panel Cohort. + indicates that the duration of response for a patient is censored. The maximum % tumor reduction is the best % change in the size of target lesions recorded from the start of study treatment until the end of the study, (continued on following page)

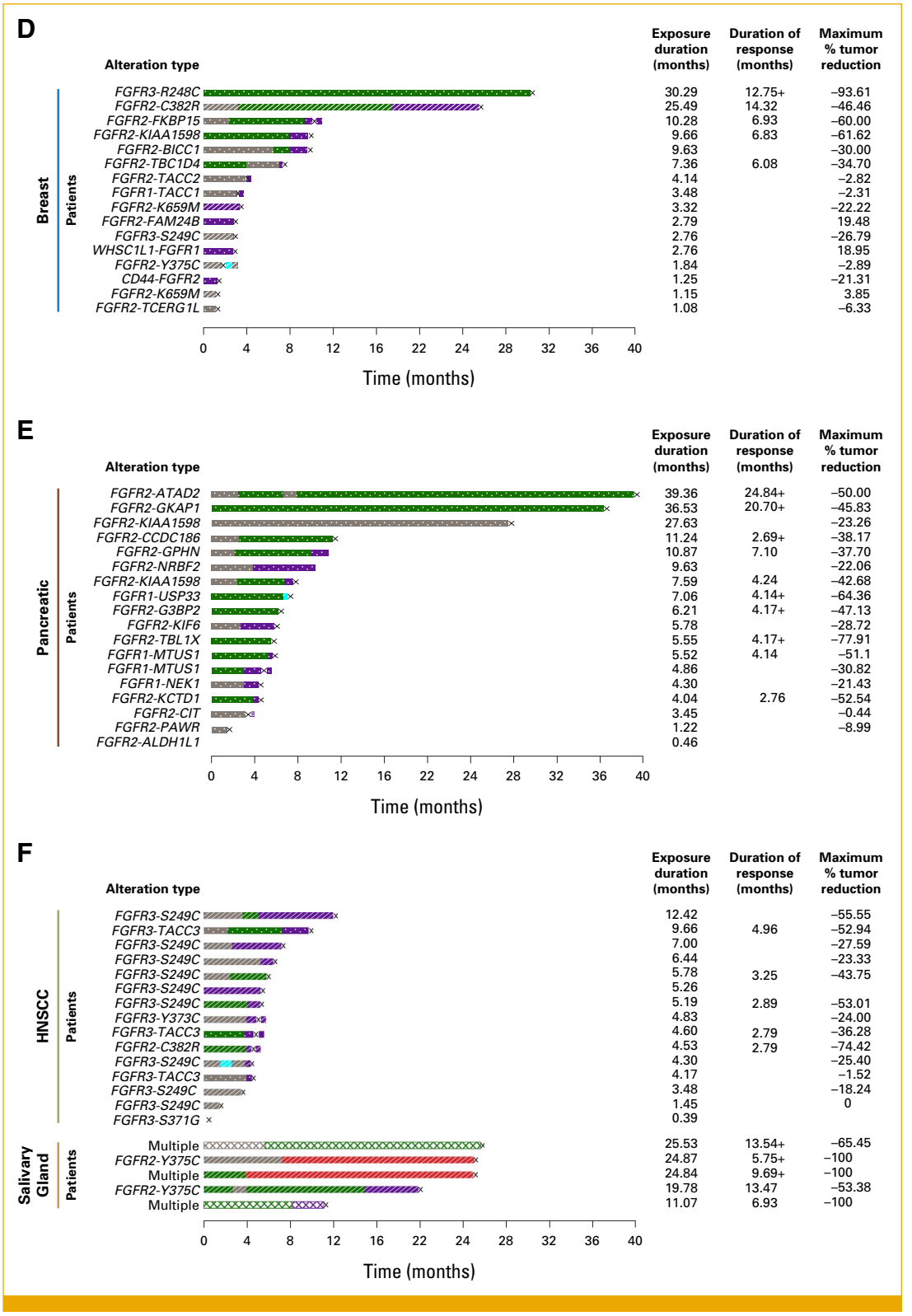

FIG 2. (Continued). before progressive disease and subsequent anticancer therapy (subsequent surgery/procedure, radiotherapy, or systemic therapy), taking into account any requirement for confirmation. HGG, high-grade glioma; HNSCC, head and neck squamous cell carcinoma; LGG, low-grade glioma; NSCLC, non–small cell lung cancer.

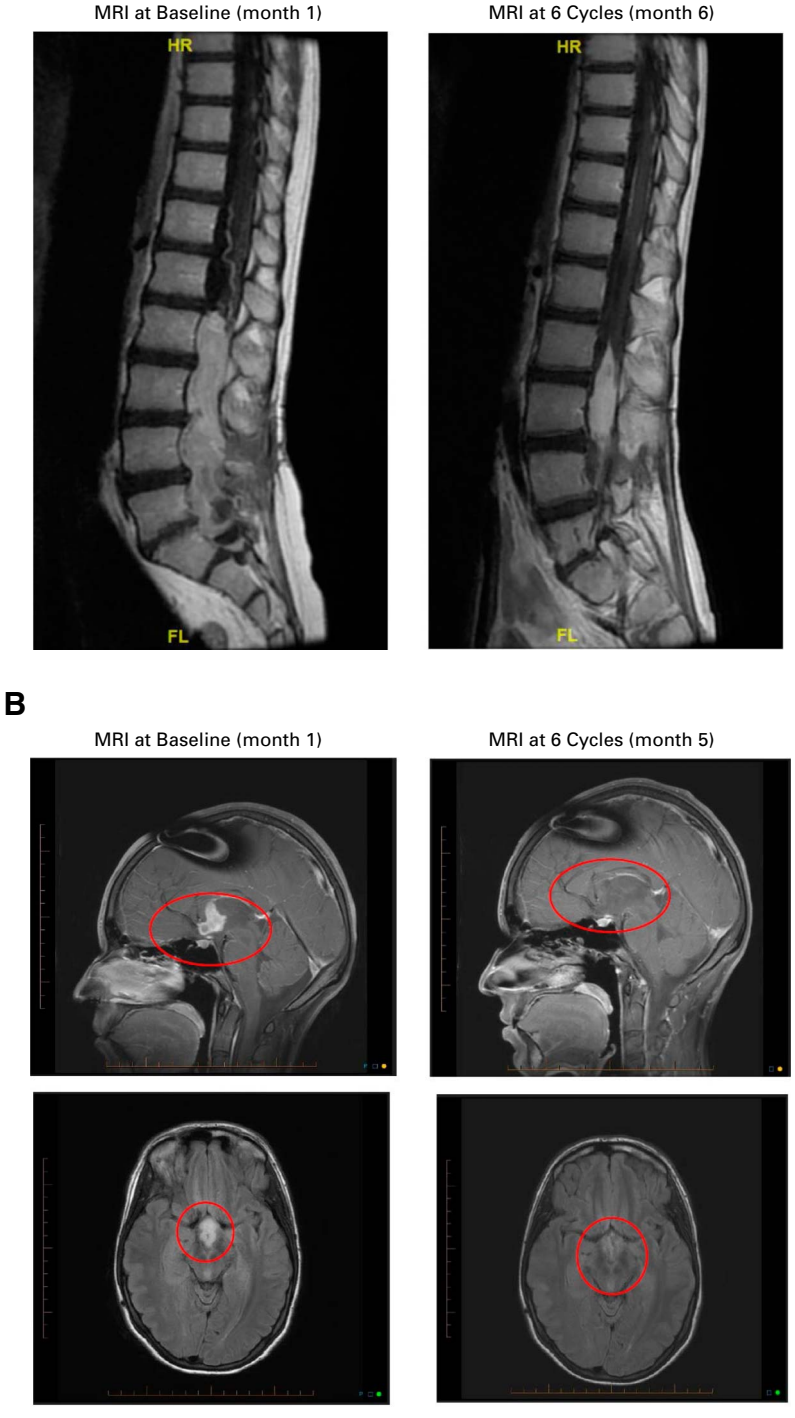

FIG 3. (A) Case study of a 26-year-old patient with dysembryoplastic neuroepithelial tumor and a *FGFR1-K656E* mutation who achieved a complete response for 21.68 months and (B) case study of a 13-year-old patient with anaplastic pilocytic astrocytoma and a *FGFR1-TACC1* fusion who achieved a partial response of 19.75 months. MRI, magnetic resonance imaging.

(n = 10), breast cancer (n = 7), endometrial cancer (n = 6), HNSCC (n = 5), ovarian cancer (n = 4), or soft tissue sarcoma (n = 4). Additional tumor types are reported in Supplementary Results. Per eligibility criteria, patients had *FGFR* alterations only in nontarget mutations in *FGFR1* (n = 9; 17.0%), *FGFR2* (n = 9; 17.0%), *FGFR3* (n = 16; 30.2%),

and *FGFR4* (n = 20, 37.7%; Table 2). *FGFR* alterations by tumor type are detailed in the Data Supplement (Table S2).

The investigator-assessed ORR was 3.8% (2 of 53 [95% CI, 0.5 to 13.0]; Table 1). Both responses were PRs: one patient with breast cancer and *FGFR3* mutation and one patient with carcinoma of unknown primary location and *FGFR4* mutation (Table 2); both were variants of unknown significance. There were 22 patients with SD, including seven patients with SD for >4 months. The DCR was 45.3%, and the CBR was 17.0%. The median DOR, PFS, and OS were 2.91 (95% CI, 2.79 to NE) months, 1.41 (95% CI, 1.35 to 2.73) months, and 5.32 (95% CI, 3.71 to 10.28) months, respectively (Table 1).

Pediatric Cohort

Patients in the Pediatric Cohort (n = 11) had LGG (n = 6), HGG (n = 3), soft tissue sarcoma (n = 1), or temporal neurocytoma (n = 1). Patients had a median age of 13 (range, 6-16) years and a median of 1 (range, 0-5) prior line of anticancer therapy; one patient with LGG had no prior therapy (Data Supplement, Table S1). *FGFR* alterations observed included fusions (n = 6; 54.5%), mutations (n = 4; 36.4%), and duplications (n = 1; 9.1%) in *FGFR1* (n = 7; 63.6%), *FGFR2* (n = 1; 9.1%), and *FGFR3* (n = 3; 27.3%; Table 2 and Data Supplement, Table S3). Two patients who had LGG (n = 1) and HGG (n = 1) were also enrolled in the BPC.

With a median follow-up of 9.69 (95% CI, 4.17 to 13.90) months, the investigator-assessed ORR was 9.1% (1 of 11 [95% CI, 0.2 to 41.3]; Table 1). One patient with HGG and *FGFR1* fusion achieved a PR lasting 19.75 months (Fig 3B and Table 2). Six patients with LGG and one patient with HGG had SD for >4 months: three had *FGFR1* mutations, one had *FGFR1* duplication, two had *FGFR1* fusions, and one had *FGFR2* fusion (Table 2). The DCR and CBR were both 72.7% (Table 1). The median PFS was 29.47 (95% CI, 0.72 to NE) months. Median OS was not reached (95% CI, 2.23 months to NE), with 9 of 11 (81.8%) patients censored for OS and 2 (18.2%) deaths.

Safety

Most patients had ≥1 TRAE. The most common TRAEs across cohorts were hyperphosphatemia, diarrhea, stomatitis, and dry mouth. The most frequent TRAEs leading to drug discontinuation across the cohorts were stomatitis (n = 3), dry mouth (n = 2), dry eye (n = 2), and palmar-plantar erythrodysesthesia syndrome (n = 2). There were no TRAEs leading to death.

The Pediatric Cohort experienced lower frequencies of stomatitis (27.3%; 3 of 11) and dry mouth (18.2%; 2 of 11); no central serous retinopathy events occurred (Table 3). Patients in the Pediatric Cohort also had grade 2 tibia fracture (n = 1; dose not modified). Grade ≥3 TRAEs occurred in 5 of 11 (45.5%) pediatric patients: dehydration (n = 1), epiphysiolysis (n = 1; erdafitinib discontinuation), peripheral neuropathy (n = 1), bone pain and hyperphosphatemia (n = 1), and leukopenia and neutropenia (n = 1). Serious TRAEs occurred in 4 of 11 (36.4%) pediatric patients: dehydration, epiphysiolysis, peripheral neuropathy, and tibia fracture. Adverse events of special interest were observed in all pediatric patients (Supplementary Results).

DISCUSSION

Adult and pediatric patients with advanced, unresectable, or metastatic solid tumors who have exhausted standard-of-care therapy have limited treatment options and a high unmet need for novel therapies. Furthermore, the toxicity of anticancer therapies for later lines is considerable, leading to deterioration in quality of life and general well-being.

In the phase II RAGNAR study, treatment with the pan-*FGFR* tyrosine kinase inhibitor erdafitinib was associated with clinically meaningful and durable histology-agnostic activity across prespecified study cohorts. In the BPC of patients with target *FGFR* alterations and *FGFR* gene fusion with intact kinase domain, DOR varied across tumor types but was generally encouraging and ranged from 2.89 months (HNSCC) to 13.47 months (SGC). The clinical activity in the Exploratory Cohort of patients with only nontarget *FGFR* mutations was limited compared with that in the BPC, thereby validating the proposed biomarker panel for patient selection demonstrated in the BPC. These findings suggest that FGFR inhibition may be a treatment option for patients with tumors that harbor *FGFR* alterations with validated oncogenicity. In pediatric patients enrolled based on molecular eligibility criteria, the predominant tumor types were gliomas (LGG and HGG); efficacy with erdafitinib was generally limited, with one responder and seven patients with SD for >4 months.

Our findings are encouraging and compare favorably with the efficacy of later lines of therapy for multiple tumor types in a FGFR-unselected patient population. In patients with gliomas, erdafitinib showed clinical efficacy per IRC (HGG: 10% ORR, 6.3 months median OS; LGG, 28.6% ORR, median OS not reached), with the DOR ranging from 7.0 to 15.9 months in patients with HGG and a CR lasting 21.68 months in a patient with LGG. Lomustine and bevacizumab are second-line therapies for glioblastoma that have shown a median OS of approximately 9 months and ORRs of 13.9% and 28.2%, respectively, with responses typically lasting 4-6 months.[9,10] Although lower ORR was observed with erdafitinib for patients with HGG than LGG, which may be attributable to a more challenging response assessment based on Response Assessment In Neuro-Oncology criteria and the infiltrative nature of the cancer, seven of the 30 patients with HGG had SD for >4 months. In NSCLC, erdafitinib demonstrated an ORR of 26.1% and a median OS of 10.4 months. Second-line ramucirumab plus docetaxel showed an ORR of 23% and a median OS of 10.5 months in patients with NSCLC.[11] In breast cancer,

TABLE 3. Safety Summary for Tumor-Specific Subgroups of the BPC and for the Exploratory and Pediatric Cohorts of RAGNAR

Adverse Event	BPC, No. (%)						Exploratory Cohort (n = 53), No. (%)	Pediatric Cohort (n = 11), No. (%)
	Gliomas (LGG + HGG), n = 37	NSCLC, n = 23	Breast, n = 16	Pancreatic, n = 18	Head and Neck (HNSCC + salivary gland), n = 20	Total, n = 114		
Any TEAEs	36 (97.3)	23 (100)	16 (100)	18 (100)	20 (100)	113 (99.1)	53 (100)	11 (100)
Any TRAEs[a]	36 (97.3)	21 (91.3)	16 (100)	18 (100)	19 (95.0)	110 (96.5)	51 (96.2)	11 (100)
TRAEs[a] with ≥10% in any cohort								
Hyperphosphatemia	27 (73.0)	15 (65.2)	11 (68.8)	10 (55.6)	17 (85.0)	80 (70.2)	42 (79.2)	7 (65.6)
Dry skin	18 (48.6)	7 (30.4)	6 (37.5)	12 (66.7)	7 (35.0)	50 (43.9)	9 (17.0)	1 (9.1)
Diarrhea	16 (43.2)	13 (56.5)	10 (62.5)	11 (61.1)	13 (65.0)	63 (55.3)	23 (43.4)	4 (36.4)
Dry mouth	15 (40.5)	10 (43.5)	10 (62.5)	13 (72.2)	8 (40.0)	56 (49.1)	24 (45.3)	2 (18.2)
Dry eye	11 (29.7)	5 (21.7)	3 (18.8)	4 (22.2)	5 (25.0)	28 (24.6)	9 (17.0)	1 (9.1)
Nail discoloration	10 (27.0)	3 (13.0)	3 (18.8)	2 (11.1)	0	18 (15.8)	8 (15.1)	3 (27.3)
Fatigue	10 (27.0)	3 (13.0)	3 (18.8)	6 (33.3)	6 (30.0)	28 (24.6)	10 (18.9)	0
Paronychia	10 (27.0)	2 (8.7)	2 (12.5)	6 (33.3)	3 (15.0)	23 (20.2)	5 (9.4)	2 (18.2)
Nail disorder	9 (24.3)	8 (34.8)	2 (12.5)	4 (22.2)	4 (20.0)	27 (23.7)	3 (5.7)	1 (9.1)
PPE syndrome	9 (24.3)	7 (30.4)	7 (43.8)	7 (38.9)	5 (25.0)	35 (30.7)	5 (9.4)	0
Stomatitis	9 (24.3)	13 (56.5)	13 (81.3)	13 (72.2)	15 (75.0)	63 (55.3)	21 (39.6)	3 (27.3)
Alopecia	8 (21.6)	2 (8.7)	4 (25.0)	1 (5.6)	1 (5.0)	16 (14.0)	6 (11.3)	2 (18.2)
Decreased appetite	8 (21.6)	4 (17.4)	3 (18.8)	1 (5.6)	5 (25.0)	21 (18.4)	14 (26.4)	2 (18.2)
Dysgeusia	8 (21.6)	5 (21.7)	2 (12.5)	3 (16.7)	2 (10.0)	20 (17.5)	5 (9.4)	0
Increased ALT	8 (21.6)	6 (26.1)	2 (12.5)	4 (22.2)	5 (25.0)	20 (17.5)	12 (22.6)	4 (36.4)
Asthenia	6 (16.2)	1 (4.3)	4 (25.0)	0	1 (5.0)	12 (10.5)	5 (9.4)	1 (9.1)
Constipation	6 (16.2)	4 (17.4)	2 (12.5)	1 (5.6)	1 (5.0)	14 (12.3)	5 (9.4)	1 (9.1)
Increased AST	6 (16.2)	3 (13.0)	3 (18.8)	3 (16.7)	5 (25.0)	20 (17.5)	9 (17.0)	3 (27.3)
Onycholysis	6 (16.2)	2 (8.7)	4 (25.0)	3 (16.7)	4 (20.0)	19 (16.7)	7 (13.2)	3 (27.3)
Nausea	5 (13.5)	1 (4.3)	2 (12.5)	2 (11.1)	6 (30.0)	16 (14.0)	6 (11.3)	2 (18.2)
Pain in extremity	3 (8.1)	2 (8.7)	3 (18.8)	2 (11.1)	1 (5.0)	11 (9.6)	2 (3.8)	2 (18.2)
Nail ridging	3 (8.1)	1 (4.3)	0	2 (11.1)	0	6 (5.3)	0	2 (18.2)
Decreased weight	2 (5.4)	1 (4.3)	2 (12.5)	1 (5.6)	4 (20.0)	10 (8.8)	6 (11.3)	2 (18.2)
Vomiting	2 (5.4)	1 (4.3)	3 (18.8)	1 (5.6)	3 (15.0)	10 (8.8)	8 (15.1)	0
Vision blurred	0	1 (4.3)	3 (18.8)	0	1 (5.0)	12 (10.5)	2 (3.8)	0
Grade ≥3 TEAEs	27 (73.0)	14 (60.9)	10 (62.5)	12 (66.7)	14 (70.0)	77 (67.5)	39 (73.6)	8 (72.7)
Grade ≥3 TRAEs[a]	19 (51.4)	9 (39.1)	7 (43.8)	9 (50.0)	9 (45.0)	53 (46.4)	24 (45.3)	5 (45.5)
TEAEs leading to dose interruption	26 (70.3)	18 (78.3)	10 (62.5)	15 (83.3)	14 (70.0)	83 (72.8)	29 (54.7)	8 (72.7)
TRAEs[a] leading to dose interruption	20 (54.1)	15 (65.2)	10 (62.5)	13 (72.2)	12 (60.0)	70 (61.4)	21 (39.6)	4 (36.4)
TEAEs leading to dose reduction	21 (56.8)	13 (56.5)	11 (68.8)	14 (77.8)	15 (75.0)	74 (64.9)	19 (35.8)	7 (63.6)
TRAEs[a] leading to dose reduction	19 (51.4)	13 (56.5)	11 (68.8)	14 (77.8)	15 (75.0)	72 (63.1)	18 (34.0)	6 (54.5)
TEAEs leading to treatment discontinuation	8 (21.6)	2 (8.7)	0	2 (11.1)	3 (15.0)	15 (13.2)	7 (13.2)	1 (9.1)
TRAEs[a] leading to treatment discontinuation	7 (18.9)	1 (4.3)	0	1 (5.6)	2 (10.0)	11 (9.6)	7 (13.2)	1 (9.1)

(continued on following page)

TABLE 3. Safety Summary for Tumor-Specific Subgroups of the BPC and for the Exploratory and Pediatric Cohorts of RAGNAR (continued)

Adverse Event	BPC, No. (%)						Exploratory Cohort (n = 53), No. (%)	Pediatric Cohort (n = 11), No. (%)
	Gliomas (LGG + HGG), n = 37	NSCLC, n = 23	Breast, n = 16	Pancreatic, n = 18	Head and Neck (HNSCC + salivary gland), n = 20	Total, n = 114		
Serious TEAEs	16 (43.2)	6 (26.1)	6 (37.5)	5 (27.8)	8 (40.0)	41 (36.0)	26 (49.1)	8 (72.7)
Serious TRAEs[a]	6 (16.2)	2 (8.7)	2 (12.5)	0	3 (15.0)	13 (11.4)	6 (11.3)	4 (36.4)
TEAEs[b] leading to death	1 (2.7)	1 (4.3)	0	0	1 (5.0)	3 (2.6)	1 (1.9)	1 (9.1)
TRAEs[a] leading to death	0	0	0	0	0	0	0	0

Abbreviations: BPC, Broad Panel Cohort; HGG, high-grade glioma; HNSCC, head and neck squamous cell carcinoma; LGG, low-grade glioma; NSCLC, non–small cell lung cancer; PPE, palmar-plantar erythrodysesthesia; TEAE, treatment- emergent adverse event; TRAE, treatment-related adverse event.

[a]TEAEs were considered related to erdafitinib by study investigators.

[b]TEAEs leading to death in the BPC were COVID-19 disease (HGG), sepsis (HNSCC), and cardiac arrest (NSCLC); TEAEs leading to death in the Pediatric and the Exploratory Cohorts were hypoxia and respiratory failure, respectively.

erdafitinib achieved an ORR of 31.3% and a median OS of 8.9 months. For breast cancer, capecitabine as third-line therapy resulted in an ORR of 18.5% with a median OS of 306 days.[12] For patients with *KRAS* wild-type pancreatic cancer, erdafitinib achieved an ORR of 55.6% and a median OS of 19.7 months. Second-line treatment with gemcitabine produced an ORR of 10% and a median OS of 3.7 months.[13] Although there were only five patients with SGC included in RAGNAR, the efficacy observed with erdafitinib was particularly encouraging: 100% ORR and median OS not reached. Oxaliplatin plus capecitabine is a second-line treatment for SGC and achieved an ORR of 19% and a median OS of 9.7 months.[14] Although the prognosis of *FGFR*-altered tumors has been shown to be similar to that of non–*FGFR*-altered tumors,[15] the observed clinical activity with erdafitinib in FGFR-selected patients highlights the rationale to use novel and targeted therapies in this molecularly defined patient population.

Safety findings in adult patients across the tumor-specific subgroups of the BPC and the Exploratory Cohort were consistent with the known safety profile of erdafitinib.[5] In the Pediatric Cohort, objective responses were limited (ORR 9.1%; 1 of 11), with one patient achieving a PR and seven patients achieving SD lasting >4 months. Most patients in the Pediatric Cohort experienced events related to growth and development (eg, epiphysiolysis and bone fracture) compared with adult patients. Although available data are limited, the safety profile of erdafitinib in the pediatric population is generally consistent with that reported for other FGFR inhibitors administered in oncologic and nononcologic settings.[16,17] Similarly, erdafitinib's clinical activity aligns with findings from other studies investigating FGFR inhibitors in similar pediatric populations, including erdafitinib in the NCI-COG Pediatric MATCH (APEC1621B) study[18] and futibatinib in the AcSé-ESMART trial.[19] However, direct comparisons are challenging given differences in patient characteristics, molecular eligibility criteria, and small sample sizes. Finally, considering the limitations of RAGNAR's single-arm design and differences in response assessment across cohorts (ie, IRC in the BPC and by investigator in the Exploratory and Pediatric Cohorts), these findings support erdafitinib activity in patients selected based on prespecified *FGFR* alterations but do not establish predictive biomarker performance or treatment selection benefit.

In conclusion, overall efficacy findings from RAGNAR support the potential clinical benefit of erdafitinib in patients with advanced solid tumors harboring susceptible oncogenic *FGFR* alterations. The antitumor activity of erdafitinib observed in the Exploratory Cohort was limited compared with that observed in the BPC. Improved understanding of tumor-specific biology may help guide FGFR-targeted treatment decisions.

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