Facts and New Hopes on Selective FGFR Inhibitors in Solid Tumors

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ABSTRACT

Precision oncology relies on the identification of molecular alterations, responsible for tumor initiation and growth, which are suitable targets of specific inhibitors. The development of FGFR inhibitors represents an edifying example of the rapid evolution in the field of targeted oncology, with 10 different FGFR tyrosine kinase inhibitors actually under clinical investigation. In parallel, the discovery of FGFR activating molecular alterations (mainly *FGFR3* mutations and *FGFR2* fusions) across many tumor types, especially urothelial carcinomas and intrahepatic cholangiocarcinomas, widens the selection of patients that might benefit from selective FGFR inhibitors. The ongoing concomitant clinical evaluation of selective FGFR inhibitors in molecularly selected solid tumors brings new hopes for patients with metastatic cancer, for tumors so far excluded from molecularly guided treatments. Matching molecularly selected tumors with selective FGFR inhibitors has indeed led to promising results in phase I and II trials, justifying their registration to be expected in a near future, such as the recent accelerated approval of erdafitinib granted by the FDA for urothelial cancer. Widening our knowledge of the activity, efficacy, and toxicities relative to the selective FGFR tyrosine kinase inhibitors under clinical investigation, according to the exact *FGFR* molecular alteration, will be crucial to determine the optimal therapeutic strategy for patients suffering from FGFR-driven tumors. Similarly, identifying with appropriate molecular diagnostic, every single tumor harboring targetable *FGFR* alterations will be of utmost importance to attain the best outcomes for patients with FGFR-driven cancer.

Introduction

The evolving spectrum of oncogene alterations accompanied by the increasing availability of specific inhibitors both concur to produce previously unachievable clinical results. The recent approval of dabrafenib/trametinib in *BRAF*-mutated cancers and larotrectinib for *NTRK*-rearranged tumors, regardless of tumor histology, is an emblematic example demonstrating the relevancy of molecular diagnosis that, coupled with specific inhibitors, can lead to an impressive improvement of patients' outcome (1, 2).

The development of FGFR1–4 tyrosine kinase inhibitors (TKI) is similarly being concomitantly evaluated in multiple tumor types. Since the identification of FGFR as a relevant player in cancer, abundant efforts have been dedicated toward its efficient inhibition, leading to a nearly simultaneous release of competing drug candidates, by contrast to the slower but classical stepwise investigation of generations of inhibitors (e.g., EGFR and ALK-TKI in lung cancer).

Previous strategies for FGFR inhibition in clinical trials have been reviewed elsewhere (3–5). This review discusses the recent improvements in selective FGFR targeting, coupled with the detection of functionally validated FGFR molecular drivers.

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FGFR Oncogene Family

The role of the FGFR tyrosine kinase family as oncogenic drivers is more heterogeneous than the classical BRAF, ALK, or EGFR ones. Four different *FGFR* genes (1–4) can be affected by mutation, rearrangement, or amplification across multiple tumor types. The location of mutations, mainly affecting *FGFR3* gene, differ from the ones activating the kinase domain of other oncogenes (e.g., *EGFR*, *HER2*, and *BRAF*). Indeed, mutations such as the most common $FGFR3^{R248C/S249C}$ occur in the ligand-binding domain, mimicking a constitutive extracellular signaling. *FGFR*2/3 rearrangements lead to increased signaling by means of protein dimerization promoted by partner genes involved. For *FGFR* amplification, only in the setting of high level gene amplification (i.e., $\geq$16 copies), leading to mRNA and protein overexpression, *FGFR* represents a selective marker of drug efficacy, as in the case of *FGFR2*-amplified breast and gastric cancers (6). Aberrant signaling in FGFR-activated tumors is mediated by the intracellular pathways shared with other oncogenes (i.e., RAS–MAPK and PI3K–AKT–mTOR). These promote the proliferation, survival, and aggressiveness of FGFR-dependent tumor cells (see section "Selective FGFR Inhibitors").

FGFR Molecular Epidemiology

FGFR1 is frequently amplified in squamous non–small cell lung cancer (NSCLC, 20%–25%) and breast cancer (15%; refs. 7, 8) but mutated in 18% of midline gliomas (9). *FGFR2* is mainly activated by gene fusions in intrahepatic cholangiocarcinomas (iCCA, 15%) but by mutations in 10% of endometrial tumors (10, 11). *FGFR3* is affected by mutations in urothelial carcinomas (up to 20% in the metastatic setting; refs. 12, 13); gene fusions (mainly *FGFR3-TACC3*) are present in glioblastomas and gliomas (3%; refs. 14, 15), as well as in bladder cancer (2%–3%; ref. 16).

Although approximately 7% of all cancers harbor an *FGFR* aberration (17), molecular screening to identify patients suitable for treatment with selective FGFR inhibitors is currently seeking for

histotypes in which FGFR inhibition would provide major clinical benefit (i.e., cases with gene fusions and mutations; ref. 18). Indeed, if the majority of alterations are *FGFR* amplifications (66%), the lack of robust efficacy data of FGFR inhibition in *FGFR*-amplified cancers has hampered the interest in this setting. *FGFR* amplification may represent an imperfect biomarker for FGFR-TKI for several reasons. First, *FGFR* gene amplification may not be accompanied by FGFR overexpression; second, amplification may not represent the pivotal event for cancer cells growth and invasion; third, FISH cutoffs for a definition of *FGFR* amplification are still lacking. Definitions of *FGFR* amplification included the threshold of 6 to 10 gene copies per cell, with a variable cutoff between studies (7, 19–21), the ratio *FGFR* gene/centromere probes, ranging from 2 to 3 (22–27), and the notion of gene clusters in populations of tumor cells (23, 24). In addition, *FGFR* amplifications in squamous NSCLC, breast, and gastric malignancies may be accompanied by the concomitant presence of molecular alterations involving cyclins or cyclin-dependent kinases, PI3K signaling, and amplification with high expression of IGF1R, HER2, and EGFR (22, 27), thus questioning the FGFR dependency of those tumor cells.

Selective FGFR Inhibitors

First-generation FGFR-TKI (e.g., anlotinib, ponatinib, dovitinib, lucitanib, lenvatinib, and nintedanib) operate as multi-target inhibitors, including FGFR among their wide range of hits (VEGFR1/3, KIT, and RET among others). This led to the lack of a profound anti-FGFR inhibition and to the occurrence of deleterious adverse events (e.g., the disappointing results of dovitinib in *FGFR2*-mutated endometrial cancer; ref. 11).

The refinement in the molecular selection of patients with FGFR-driven cancer has been accompanied by the recent development of inhibitors specifically and selectively acting on the tyrosine kinase domain of FGFR family members, counteracting their phosphorylation at nanomolar concentrations (**Table 1**). Namely, this review focuses on erdafitinib (JNJ-42756493; Janssen-Johnson & Johnson), infigratinib (BGJ398; BridgeBio/QED Therapeutics), pemigatinib (INCB054828; Incyte), rogaratinib (BAY1163877; Bayer), derazantinib (ARQ 087; Basilea Pharmaceutica), futibatinib (TAS-120; Tahio), LY2874455 (Eli Lilly), AZD4547 (AstraZeneca), Debio 1347 (Debiopharm Group), and fisogatinib (BLU-554; Blueprint Medicines). These inhibitors are being developed almost simultaneously through clinical trials. Schematically, erdafitinib and rogaratinib have been mainly developed in urothelial cancer, infigratinib and futibatinib in cholangiocarcinoma, and pemigatinib in both tumor types. With regard to the other inhibitors, the initial results from clinical trials are too preliminary to allow direct comparisons between individual drugs and specific tumor types. With the exception of futibatinib all the inhibitors are characterized by a reversible, ATP-competitive binding to FGFR kinase domain. The irreversible, covalent binding of futibatinib is likely to account for its activity in patients with *FGFR2*-rearranged cholangiocarcinoma after progression to reversible FGFR-TKI (see section "Resistance to FGFR Inhibitors"). Of note, due to its promising clinical activity and efficacy (see section "Urothelial Cancer"), FDA has recently granted accelerated approval to erdafitinib for urothelial carcinomas harboring *FGFR2–3* alterations (28).

In addition to the mentioned TKI, FGFR3-directed mAbs have also been developed, with promising signs of activity of vofatmab (B-701) combined with docetaxel in pretreated urothelial tumors (29), a setting in which the association of vofatmab and pembrolizumab is also envisaged (NCT03123055).

Clinical Evidence

Activity data in early studies

The initial evidence of the activity and safety profile of selective FGFR inhibitors from phase I studies are summarized in Supplementary Table S1. In the dose-escalating phases, pretreated patients for whom no further standard therapies could be recommended were included, regardless of tumor type and molecular status, in line with an "all-comers" way. For all those selective inhibitors, almost no responses were observed in patients without any *FGFR* molecular alteration (erdafitinib, refs. 30–32; infigratinib, ref. 24; derazantinib, ref. 33; LY2874455, ref. 25; AZD4547, refs. 26, 27, 34, 35; pemigatinib, ref. 36; and rogaratinib, ref. 37).

In contrast, in the phase I dose-finding study of Debio 1374, patient enrollment was molecularly oriented toward the selection of diseases harboring *FGFR1–3* alterations regardless of tumor type (38). Of the 58 patients exposed to increasing doses of the drug, 6 experienced partial responses (PR) and 16 stable diseases (SD), providing evidence of Debio 1374 activity in molecularly selected patients across histologies (**Table 2**), with a predilection for *FGFR* mutations or fusions (38). Importantly, 9 of 43 centrally rescreened cases turned out to be negative after local screening for FGFR activations, underlying the importance of a reliable molecular diagnostic process to select accurately the patient population (38).

Altogether, these early-phase studies highlighted the importance of an accurate molecular selection of patients in targeted therapy trials,

Table 1. Selective FGFR inhibitors in clinical development.

Drug	Targets	Inhibition type	Dose adopted in ongoing trials	Phase of ongoing trials
Erdafitinib (JNJ-42756493)	FGFR1–4	Reversible	8 mg daily[a]	III
Infigratinib (BGJ398)	FGFR1–3	Reversible	125 mg daily 3-week on/1-week off	III
Pemigatinib (INCB054828)	FGFR1–3	Reversible	13.5 mg daily	III
Rogaratinib (BAY1163877)	FGFR1–3	Reversible	800 mg twice daily	III
Futibatinib (TAS-120)	FGFR1–4	Irreversible	20 mg daily	II
Derazantinib (ARQ 087)	FGFR1–4	Reversible	300 mg daily	II
LY2874455	FGFR1-4	Reversible	16 mg twice daily	I
AZD4547	FGFR1–3	Reversible	80 mg twice daily	II
Debio 1347 (CH5183284)	FGFR1–3	Reversible	80 mg daily	II
Fisogatinib (BLU-554)	FGFR4	Irreversible	600 mg daily	I extension

[a]To be escalated to 9 mg daily at day 14 if plasma phosphate levels < 5.5 mg/dL (pharmacodynamically guided dose escalation).

Table 2. Activity and efficacy data of selective FGFR inhibitors in urothelial tumors.

Reference	Patients treated	Objective responses	SDs	mPFS (mo) (95% CI)	mDOR (mo) (95% CI)	mOS (mo) (95% CI)
Erdafitinib phase I patients with UC Balheda and colleagues, Clin Cancer Res 2019 (31) NCT01703481	27 $FGFR^{pos}$ (17 $FGFR3^{mut}$, 11 $FGFR^{fused}$, 1 $FGFR^{mut+fused}$) of 30 UC	12/30 (40%) among all UC 12/26 (46%) among $FGFR^{pos}$	$FGFR^{pos}$: 4/26 (15%)	$FGFR^{mut/fused}$: 5.1	5.6	—
Erdafitinib phase II Loriot and colleagues, ASCO GU 2018 (13) NCT02365597	$FGFR^{mut/fused}$ A: 10 mg intermittent: 33 B: 6 mg daily: 78	A: 8 (24%) B: 27 (35%)	A: 16 (49%) B: 30 (39%)	A: 4 B: 5.1	A: 12.6 B: 4.9	1-year survival: A: 31% B: 32%
Erdafitinib phase II 8 mg daily[a] Loriot and colleagues, New Engl J Med 2019 (39) NCT02365597	99 $FGFR^{pos}$ 74 (75%) $FGFR3^{mut}$ 25 (25%) $FGFR2/3^{fused}$	40 (40%)	39 (39%)	5.5 (4.2–6)	5.6 (4.2–7.2)	13.8 (9.8-NR)
Infigratinib phase I expansion cohort Pal and colleagues, Cancer Discov 2018 (40) NCT01004224	67 $FGFR3^{pos}$	17 (25%)	26 (39%)	3.7 (3.1–5.4)	—	7.7 (5.6–11.6)
Pemigatinib phase II Necchi and colleagues, ESMO 2018 (41) NCT02872714	Cohort A: $FGFR3^{mut/fused}$: 61 Cohort B: other FGFR/FGF driver: 42	A: 13 (21%) B: 1 (2%) $FGF10^{ampli}$	A: 22 (36%) B: 10 (24%)	A: 4.1 (3.0–5.6) B: 2.0 (1.9–2.1)	A: 6.2 (4.2–8.4)	—
Rogaratinib phase I expansion cohort Schuler and colleagues, Lancet Oncol 2019 (37) NCT01976741	52 high FGFR1-3 mRNA[b] (48 high FGFR3; among these, 16 $FGFR3^{mut}$ and 2 $FGFR3^{fused}$)	12 (24%) 7 without *FGFR* genetic alterations	25 (49%)	100 days (57–143)	—	—
Futibatinib phase I patients with UC Meric-Bernstam and colleagues, AACR 2019 (71) NCT02052778	20 FGF/FGFR altered UC	3 (15%)	9 (45%)	—	—	—

Abbreviations: 95% CI, 95% confidence interval; mDOR, median duration of response; mo, months; mOS, median OS; mPFS, median PFS; NR, not reached; UC, urothelial carcinomas.
[a]Dose pharmacodynamically escalated to 9 mg daily if target phosphate levels < 5.5 mg/dL after 14 days of treatment.
[b]RNAscope and NanoString analysis on fresh or archival specimens.

revealing *FGFR* mutations and fusions as strong predictors of FGFR-TKI clinical activity, compared with *FGFR* amplification.

Histology-oriented trials

Expansion cohorts of phase I and II trials of selective FGFR inhibitors included specific histologies with mandatory *FGFR* molecular selection. As in early-stage studies, patients enrolled were mainly heavily pretreated (≥third line in about 50% of the cases).

Urothelial cancer

Five FGFR-TKI (erdafitinib, infigratinib, pemigatinib, rogaratinib, and futibatinib) showed activity in patients with urothelial carcinomas (**Table 2**). After the promising results of the phase I expansion cohort (31), the phase II study of erdafitinib included 99 patients with FGFR-altered urothelial carcinomas (74 with *FGFR3* mutations and 25 with a *FGFR2* or *3* fusion, evaluated in a central laboratory) treated at the "selected regimen" of 8 mg daily. Responses and SD occurred in 40% and 39% of the cases, respectively; of interest, 49% of patients harboring *FGFR*-mutated tumors achieved disease response, compared with 16% among the FGFR-fusion group. A median progression-free survival (PFS) of 5.5 months lead to a remarkable median overall survival of 13.8 months, taking into account the pretreatment setting of these patients with urothelial carcinomas (39). These data therefore prompted the FDA-accelerated approval of erdafitinib for urothelial carcinomas (28).

With the limitation of a reduced number of patients treated, slightly inferior results of activity and efficacy were observed for infigratinib [objective response rate (ORR) 25%, median PFS 3.7 months] and pemigatinib (ORR 21%, median PFS 4.1 months) in *FGFR3*-altered cases (40, 41). Similar activity results were observed with rogaratinib in patients selected with high expression of FGFR1–3 mRNA (37).

The best results in terms of activity and efficacy have been observed when the detection of specific FGFR alterations, such as *FGFR3* mutations and *FGFR2* or *3* fusions (39), was required to receive targeted treatment. Inclusion of less defined *FGFR* abnormalities (FGFR-positive or -altered tumors) led to inferior results (**Table 2**).

Cholangiocarcinoma

Infigratinib, pemigatinib, derazantinib, futibatinib, and erdafitinib were investigated in patients with cholangiocarcinoma (**Table 3**). Disease responses were almost exclusively observed in *FGFR2*-rearranged tumors, with ORR reaching 21% (derazantinib; ref. 42), 30% (infigratinib; refs. 43, 44), 40% (pemigatinib and futibatinib; refs. 45–47), with the outlier 67% for erdafitinib in the Asian trial [with 100% of Disease Control Rate (DCR)] requiring however validation with a wider patient population (only 9 patients evaluated; ref. 48). Even more marked than for urothelial carcinomas, tumor shrinkage was obtained in the large majority of patients with cholangiocarcinoma. While benefiting from FGFR-TKI, those cases did not always reach the threshold for PR, which is taken into account when evaluating drug activity in cholangiocarcinoma using RECIST criteria.

In the *FGFR2*-rearranged population, an extremely large variety of *FGFR2* fusion partners were identified: beside *BICC1* (30% of the cases), 30 additional partner genes were detected (45, 47). Of note, among this group of advanced cholangiocarcinoma, pemigatinib achieved the longest median PFS of 9.2 months (45).

The phase I trial of the covalent inhibitor futibatinib in patients with cholangiocarcinoma allowed the enrollment of patients who had already progressed on a reversible FGFR inhibitor. Notably, 4 of 13 patients (3 *FGFR2*-rearranged and 1 *FGFR2*-amplified) previously exposed to reversible inhibitors achieved a PR, supporting the utility of futibatinib in overcoming drug-specific resistance (see section "Ongoing Trials," for second-line FGFR-TKI), owing likely to its covalent binding (see section "Resistance to FGFR Inhibitors;" refs. 46, 47).

Globally, the most relevant results were observed when the molecular screening focused on *FGFR2* rearrangements, toward which current trials are now being addressed (see section "Ongoing Trials").

Other tumor types

AZD4547 phase II trials have been dedicated to cancers known to harbor *FGFR* gene abnormalities, namely squamous NSCLC, breast, and gastric tumors (refs. 6, 20–23, 26, 49; Supplementary Table S2). Nevertheless, when selecting for *FGFR* amplification (the most frequent *FGFR* alteration present in the cited malignancies), ORR rarely exceeded 10% across the reports, as seen also in *FGFR1*-amplified squamous NSCLC treated in the dedicated expansion cohort of infigratinib phase I study (ref. 24; Supplementary Table S2). These disappointing results confirmed the weakness of *FGFR* amplification as a biomarker for FGFR inhibitors sensitivity. As elegantly pointed out by Pearson and colleagues in their translational work, AZD4547 activity relies on the level of *FGFR* amplification (6).

Rogaratinib revealed promising efficacy data in patients with head and neck cancer overexpressing FGFR1–3 at the mRNA level but will require a larger number of patients and a longer follow-up for validation (50). In NSCLC nevertheless, only 2 responses out of 36 evaluable patients with high FGFR1–3 mRNA were observed, suggesting that more precise biomarkers are required (ref. 51; Supplementary Table S2).

FGFR4 is emerging as a potential target in hepatocellular carcinoma (HCC), through FGF19 overexpression (30% of HCC; refs. 52, 53). In the phase I trial of the highly selective FGFR4 inhibitor fisogatinib no responses were observed among the 29 HCC cases not tested or negative for FGF19 IHC. Six of 38 (16%) IHC-positive patients experienced disease response and additional 20 patients (53%) remained stable, achieving a median PFS of 3.7 months (ref. 54; Supplementary Table S2).

Altogether, these histology-oriented trials validated the mandatory aspect of *FGFR* molecular selection of patients and the urgent need for a better definition of the *FGFR* amplification or overexpression status in cases without mutation of fusion.

Safety and toxicity

The spectrum of adverse events accompanying selective FGFR inhibitors is thought to be due to their specific mechanism of action, counteracting the physiologic role of the FGF/FGFR axis. **Table 4** reports the incidence of the most frequent events occurring in FGFR-TKI clinical trials but, considering the limited number of patients exposed, updated results will be required to characterize inhibitor-specific toxicities.

The most commonly observed toxicities included hyper-phosphoremia, fatigue, alopecia, dry skin and mouth with stomatitis, hand–foot syndrome (**Fig. 1**), diarrhea, and other gastrointestinal events (nausea, vomiting, abdominal pain, and constipation; **Table 4**). In particular, FGFR inhibition disrupts phosphate homeostasis physiologically maintained by FGF23 (secreted from the bone and acting on the kidney), whose high levels induced by FGFR-TKI administration lead to hyper-phosphoremia (55).

Table 3. Activity and efficacy data of selective FGFR inhibitors in cholangiocarcinoma.

Reference	Patients treated	Objective responses	SDs	mPFS (mo) (95% CI)	mDOR (mo) (95% CI)	mDDC (mo) (95% CI)	mOS (mo) (95% CI)
Infigratinib phase II Javle and colleagues, J Clin Oncol 2018 [a] (43) NCT02150967	61 $FGFR^{pos}$: 48 $FGFR2^{fused}$ 8 $FGFR2^{mut}$ 8 $FGFR1\text{-}3^{ampl}$	9 (15%) All in $FGFR2^{fused}$ (19%)	37 (61%) 31 (65%)	5.8 (4.3–7.6)	5.1 (3.9–7.4)	7.5 (5.6–7.6)	—
Infigratinib phase II Javle and colleagues, ESMO 2018[b] (44) NCT02150967	71 $FGFR2^{fused}$	22 (31%)	41 (58%)	6.8 (5.3–7.6)	5.4 (3.7–7.4)		12.5 (9.9–16.6)
Erdafitinib phase I patients with CCA Balheda and colleagues, Clin Cancer Res 2019 (31) NCT01703481	11 $FGFR^{pos}$: 8 $FGFR^{fused}$ 3 $FGFR^{mut}$	3/11 (27%)	3/11 (27%)	≈5	11.4		
Derazantinib phase II Mazzaferro and colleagues, Br J Cancer 2018 (42) NCT03230318	29 $FGFR2^{fused}$	6 (21%)	18 (62%)	5.7 (4.0–9.2)	4.6 (2.3–8.9)	5.8 (5.3–8.4)	Not reached (mFU 20 mo)
Pemigatinib phase II Hollebecque and colleagues, ESMO 2018 (45) NCT02924376	Cohort A: $FGFR2^{fused}$: 47 Cohort B: Other FGF/FGFR driver: 22 Cohort C: No FGF/FGFR: 18	A: 19 (40%) B: 0 C: 0	A: 21 (45%) B: 10 (45%) C: 4 (22%)	A: 9.2 (6.44–NE) B: 2.1 (1.2–6.80) C: 1.7 (1.4–1.8)	A: NE (6.9–NE)		A: 15.8 B: 6.8 C: 4
Futibatinib phase I CCA data (1) Tran and colleagues, ESMO Asia 2018 (46) (2) Meric-Bernstam and colleagues, ESMO GI 2018 (47) NCT02052778	45 $FGFR^{pos}$ (41 iCCC): 8 $FGFR2^{fused}$ 13 (29%) FGFR-TKI pretreated	$FGFR2^{fused}$: 7/24 (25%) $FGFR2fusion^{neg}$: 3/17 (18%) All in $FGFR2^{"rearranged"}$ 4/13 (31%) in FGFR-TKI pretreated (3 fused, 1 ampli)	$FGFR2^{fused}$: 15 (54%) $FGFR2fusion^{neg}$: 10 (59%)	$FGFR2^{fused}$: 7.4 (4.8–NC)[c] $FGFR2fusion^{neg}$: 6.8 (1.9–NC)[c]	—	—	—
Erdafitinib phase IIa Asian Park and colleagues, ASCO 2019 (48) NCT02699606	34: 15 $FGFR2^{fused}$, 9 $FGFR2^{mut}$, 7 $FGFR3^{mut}$, $FGFR1^{mut}$ out of 157 molecularly evaluable	7/15 (47%) $FGFR^{fused}$: 6/9 (67%)	5/15 (33%) $FGFR^{fused}$: 3/9 (33%)	5.59 (1.91–12.65) $FGFR^{fused}$: 12.65 (3.15–19.38)	7.06 (3.6–12.2) $FGFR^{fused}$: 7.29 (3.9–12.2)	—	—

Abbreviations: 95% CI, 95% confidence interval; CCA, cholangiocarcinoma; mDDC, median duration of disease control; mDOR, median duration of response; mFU, median follow-up; mo, months; mOS, median OS; mPFS, median PFS; NE, not evaluable.

[a]Protocol was then modified to limit enrollment only to cases harboring *FGFR2* fusions.

[b]This update includes patients with cholangiocarcinoma with *FGFR2* fusions already presented in the published study in the upper line.

[c]Median treatment time.

Table 4. Toxicity rates across trials with selective FGFR inhibitors.

		Toxicity																	
		All toxicities		HyperPh		HypoPh		Stomatitis		Diarrhea		Digestive tract events		Nail events		Hand–foot syndrome		Ocular events	
Drug and disease Reference	Patients number	Any G	G ≥ 3	Any G	G ≥ 3	Any G	G ≥ 3	Any G	G ≥ 3	Any G	G ≥ 3	Any G	G ≥ 3	Any G	G ≥ 3	Any G	G ≥ 3	Any G	G ≥ 3
Erdafitinib UC Loriot and colleagues, New Engl J Med 2019 (39)	99	100%	46%	77%	2%	NR	NR	58%	10%	51%	4%	30–40%	1%	18%	2%	23%	5%	19%	3%
Infigratinib CCA Javle and colleagues, J Clin Oncol 2018 (44)	61	92%	41%	72%	16%	11%	5%	29%	7%	15%	3%	18%	1%	18%	—	21%	5%	21%	—
Pemigatinib CCA/UC Hollebecque/Necchi and colleagues, ESMO 2018 (41, 46)	89/108	93%	NR	31%	1%	10%	6%	34%	7%	43%	3%	35%	3%	NR		NR		13%	1%
Rogaratinib UC Joerger and colleagues, ASCO 2018 (42)	51	NR		45%	—	NR		NR		61%	4%	29%	2%	NR		NR		NR	
Derazantinib CCA Mazzaferro and colleagues, Br J Cancer 2018 (43)	29	93%	28%	76%	10%	NR		7%	3%	21%	—	45%	3%	NR		NR		41%	7%
AZD4547 NCI-MATCH Arm W Chae and colleagues, ASCO 2018 (21)	49	80%	49%	NR		NR	2%	22%	14%	20%	—	24%	2%	NR		NR	6%	NR	2%

Note: Futibatinib, LY2874455, Debio 1347, and fisogatinib only phase I dose-finding data available. Studies with the largest patient population were chosen for each inhibitor. Digestive tract events: constipation, nausea, vomiting, abdominal pain, and dyspepsia and ocular events: dry eye, vision blurred, conjunctivitis, visual acuity reduced, photophobia, corneal erosion, blepharitis, and serous retinal detachment.
Abbreviations: CCA, cholangiocarcinoma; G, grade; HyperPh, hyperphosphatemia; HypoPh, hypophosphatemia; NR, not reported; UC, urothelial carcinomas.

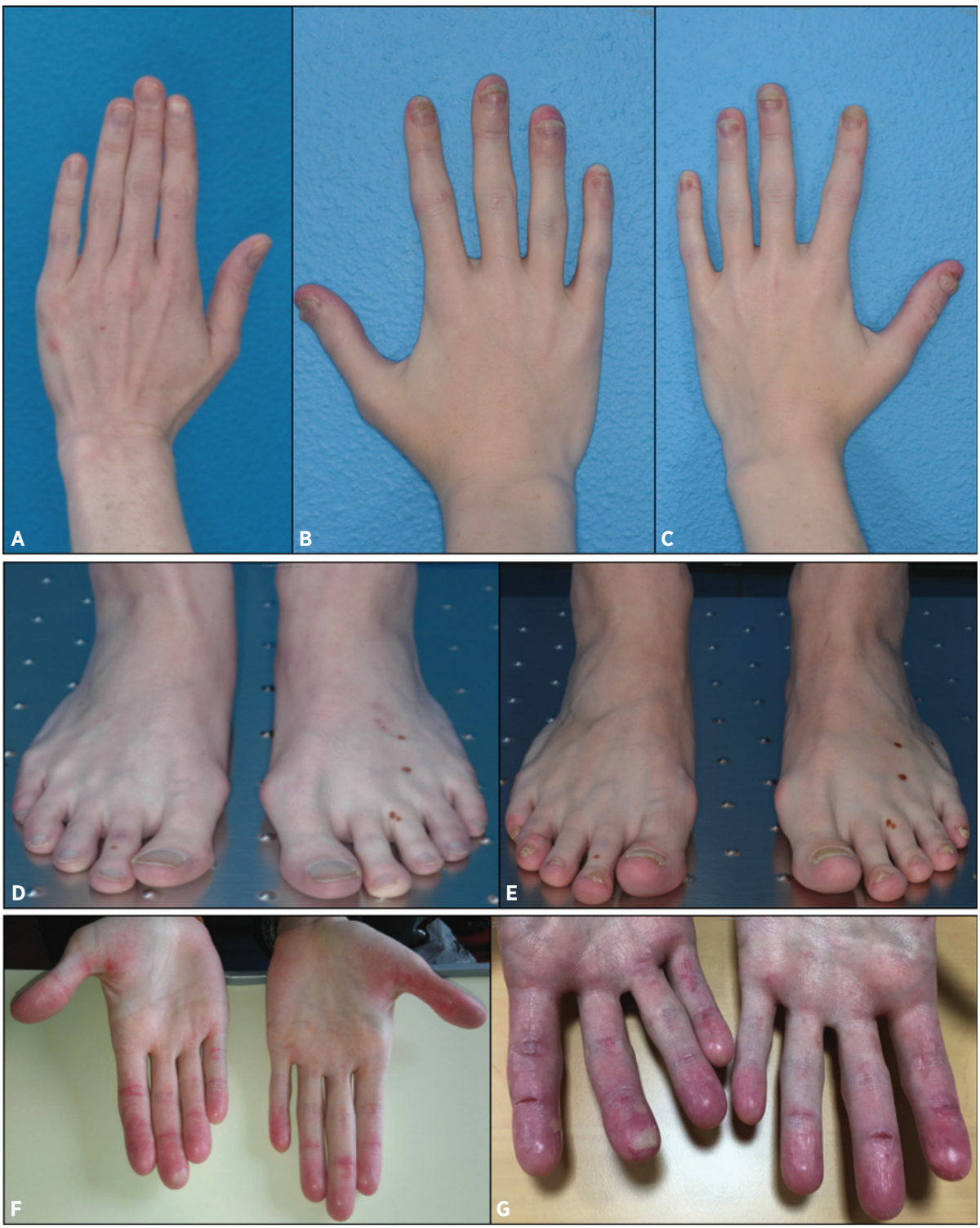

Figure 1.
Nail toxicity and hand–foot syndrome in a patient treated with erdafitinib. **A** and **D**, Baseline. **B**, **C**, and **E**, Onychodystrophy appearing few weeks from treatment beginning and persisting over time (more than 1 year). **F** and **G,** Progressive worsening of hand–foot syndrome.

Biological abnormalities, namely aspartate aminotransferase, alanine aminotransferase, and lipase increase, were often detected. Adverse events affecting nails (onychodystrophy and nail loss) and eyes (dryness and central serous retinopathy) were frequently reported (**Table 4**). Globally, limiting toxicities were represented by fatigue, stomatitis, and nail events (**Fig. 1**; ref. 56). In the clinical trials, toxicity was managed by dose interruption or reduction and supportive therapies (e.g., low-phosphate diet and administration of phosphate binders such as sevelamer for hyperphosphoremia) but rarely led to treatment discontinuation.

Ongoing Trials

Supplementary Table S3 resumes the ongoing trials evaluating selective FGFR inhibitors in molecularly selected populations, in single-arm or randomized trials, either as monotherapy or in combination with other agents (cytotoxic treatments, targeted therapies, and immune checkpoint inhibitors). Information gathered in Supplementary Table S3 has been obtained from clinicaltrials.gov (checked last time on June 2019) and abstracts presented in international meetings. Of note, phase III clinical trials are currently ongoing to compare selective FGFR-TKI with standard-of-care chemotherapy or immunotherapy, both in second- and first-line setting in urothelial carcinomas and cholangiocarcinoma. Considering the recently established efficacy of immune checkpoint inhibitors in urothelial carcinomas, potential synergies are being envisaged. Anti-PD-1/PD-L1 antibodies are indeed associated with erdafitinib (NCT03473743, pretreated patients) or rogaratinib (first-line).

Resistance to FGFR Inhibitors

Clinical data on molecular mechanisms of resistance to specific FGFR inhibitors are limited thus far. Preclinical work has mostly been dedicated toward FGFR-amplified models and mainly defines the potential involvement of bypass tracks activation in both primary and acquired resistance (57–60). However, on-target mechanisms (e.g., the onset of *FGFR* mutations) can also confer acquired resistance to FGFR-TKI in patients. Of note, in several experiences the longitudinal evaluation of circulating tumor DNA (ctDNA) of patients receiving FGFR inhibitors was able to catch the multiplicity of *FGFR* mutations occurring in the tyrosine kinase domain at disease progression.

Goyal and colleagues analyzed longitudinal blood samples and tumor biopsies at progression of 3 patients with *FGFR2*-rearranged cholangiocarcinoma receiving infigratinib (61). Blood and biopsy sequencing revealed the acquisition of multiple resistant mutations in the *FGFR2* kinase domain (N549H/K, V564F, E565A, L617V, K641R, and K659M), among which the gatekeeper V564F was shared by the 3 patients. Conversely, a limited number of *FGFR2* mutations were detected in tumor tissue samples, thus corroborating the utility of liquid biopsies to capture the heterogeneity of resistance mechanisms (62). A broader autopsy analysis, besides confirming the presence of *FGFR2* mutations, allowed the detection of a *PTEN* deletion and a *PI3KCA*-activating mutation (Q546R) suggesting the potential involvement of the PI3K/AKT pathway in FGFR resistance (63). In their related *in vitro* studies, the authors defined the functional role of each *FGFR2* mutation observed in clinical samples and provided evidence that LY2874455 is an active inhibitor across a range of secondary mutations (61). This is in line with the biochemical and pharmacologic study provided by Wu and colleagues, determining LY2874455 as an active FGFR inhibitor in presence of gatekeeper mutations (i.e., $FGFR1^{V561M}$, $FGFR2^{V564F}$, $FGFR3^{V555M}$, and $FGFR4^{V550L}$; refs. 64, 65). Crystallographic studies of LY2874455 interaction with FGFR revealed that the inhibitor positions away from the gatekeeper residues, avoiding the steric clash precluding drug binding usually induced by gatekeeper mutations (64).

Goyal and colleagues later demonstrated futibatinib efficacy in 4 patients with *FGFR2*-rearranged iCCA after acquired resistance to infigratinib or Debio 1347. Using preclinical models, the authors demonstrated the futibatinib activity against multiple *FGFR2* mutations conferring resistance to the two others FGFR-TKI (M537I, N549K/H, E565A, L617V, K659M, H682L, and K714R; ref. 66). Differently from LY2874455, futibatinib lacks activity against FGFR2 gatekeeper–mutant V564F, due to a steric clash. Futibatinib-irreversible interaction with the ATP-binding pocket is the basis for its activity in the occurrence of the cited mutations that shift FGFR2 tyrosine kinase domain conformation in a constitutively active state, only targetable by a covalent inhibitor (66, 67).

Similar detection of polyclonal *FGFR* mutations in ctDNA at progression, mainly in patients with *FGFR2*-rearanged cholangiocarcinoma and in patients with *FGFR3*-mutated urothelial carcinomas receiving infigratinib or erdafitinib were reported in other studies (12, 40, 68). Remarkably, futibatinib is thus far the only inhibitor able to resensitize in the clinic tumors resistance to reversible FGFR inhibitors, likely owing to its covalent binding. The following emergence of $FGFR2^{N549K}$, $FGFR2^{V652L}$, and $FGFR2^{V564F/L}$ mutations at progression on futibatinib nevertheless testifies the complexity of the mutations arising in *FGFR* kinase domain, responsible for resistance to differential inhibitors (69).

Conclusion

Since the initial targeting of FGFR with multi-target inhibitors evaluated in clinical trials lacking a strict molecular selection, meaningful improvements have been provided in this field. Specific FGFR inhibition represents a concrete reality in the field of precision medicine, thanks to the refinement of *FGFR* targetable alterations (i.e., fusions and mutations) and to the availability of selective inhibitors. Waiting for definitive results from randomized phase III trials, the benefit driven from FGFR inhibitors has been acknowledged for urothelial cancer (28) and it is expected to be fully proven for cholangiocarcinoma in a near future.

FGFR activations should be screened across a multitude of malignancies (17), with a particular mention for brain tumors given the frequency of these aberrations (9, 15), the initial signs of activity of selective inhibitors (30), the availability of specific clinical trials (NCT01975701; Supplementary Table S3), and the urgent need for effective treatment options. The narrowing of molecular selection, allowing only tumors harboring functionally validated *FGFR* activations to be included into clinical trial, has provided the better results and accelerated the approval of erdafitinib in urothelial carcinomas (28, 39). On the other hand, the recent widening of molecular next-generation sequencing (NGS) diagnostics in the clinical setting, should speed up the implementation of *FGFR* molecular screening on a daily basis, leading to treatment with selective FGFR inhibitors as a common clinical practice (39).

Phase I trial of Debio 1347 serve as an example of the importance of an accurate molecular diagnostics, with 21% of the cases, initially considered as *FGFR* altered according to local assessment, but turning out to lack *FGFR* aberration, therefore undermining the global results of the study (38). These discrepancies may

be explained by intratumoral heterogeneity, sampling errors, or technical issues. Among the latter, analysis algorithms evolution during the trial could induce differences in annotating complex fusions and the different accuracy in detecting gene amplifications between FISH and NGS have been evoked by study investigators (38).

Molecular screening should identify cases harboring *FGFR* alterations with known functional significance. In addition, peculiar attention should be paid toward potential passenger events, especially in the case of hypermutated tumors, or benign germline polymorphisms not filtered from the somatic data.

In contrast to fusions and mutations, *FGFR* amplification, frequent in squamous NSCLC, breast, and gastric cancers, is yet to be defined as a reliable biomarker for response to FGFR inhibitors. A careful selection of patients whose tumors harbor biologically meaningful levels of FGFR amplifications (i.e., cases truly relying on FGFR for tumor growth), would potentially help to detect the cases suitable for specific FGFR inhibition (18). In this sense, the refinement of diagnostics approaches and of thresholds for defining significant levels of *FGFR* amplification should be accompanied by analysis of mRNA and/or protein quantification.

Conducting randomized phase III trials in specific histologies with *FGFR* aberration may be challenging, given the gap between the number of patients required for those studies and the relative rarity of precise molecular-altered tumor types. In this sense, phase II basket trials may provide sufficient evidence for activity and efficacy of specific FGFR-TKI with a limited number of patients included for each tumor type (70). Nevertheless, the differential signals of activity of FGFR inhibitors against diverse FGFR activations (i.e., mutations vs. fusions), as well as in different tumor types (**Tables 2** and **3**; Supplementary Table S2), should be mentioned. Each TKI may indeed retain specific activity toward precise targets, influenced in addition by the cellular context in which they arise.

Goyal and colleagues provided the clinical evidence that, guided by biopsies and ctDNA, the sequencing of FGFR inhibitors can prolong the duration of benefit from FGFR inhibition in patients with FGFR-positive cancer (61, 66, 69). Thus far, futibatinib is the only inhibitor to have shown the potential of overcoming resistance to other, reversible FGFR-TKI in patients with *FGFR2*-rearranged cholangiocarcinoma (46, 47). As futibatinib, LY2874455 has been proven to be active *in vitro* against FGFR mutants engendering resistance to other inhibitors (61, 64). Nevertheless, futibatinib development is ongoing (**Table 3**; Supplementary Table S3), LY2874455 lacks recent updates (Supplementary Table S3). A clear functional understanding of the activity of each of the 10 specific FGFR inhibitors against all activating alterations and acquired resistance mechanisms will be key to define the optimal treatment strategies with sequential FGFR-TKI to overcome resistance, likely to be accompanied by a combination approach in the case of bypass activation.

The current estimations of PFS and duration of response reported for selective FGFR inhibitors (**Tables 2** and **3**), still encouraging, are not yet overlapping to the prolonged disease control achieved with other targeted agents in different histologies (e.g., lung cancer and melanoma). Potentially due to an intrinsic aggressiveness of FGFR-driven malignancies, these suboptimal outcomes will be hopefully extended by a wider comprehension of drug resistance and the overcoming strategies. In addition, the molecularly driven tumors for which resistance mechanisms to TKI have already been widely studied (i.e., EGFR- and ALK-positive lung cancers) are characterized by the acquisition of single mutational events responsible for resistance, likely easing the efficacy of sequential inhibitors administration. In contrast, the initial reports regarding *FGFR2*-rearranged cancers (cholangiocarcinoma mainly) prove the development of multiple, polyclonal mutations arising from single tumors. In this sense, covering a multitude of diverse resistance mutations, with differential sensitivity to novel FGFR TKI, may turn out to be arduous. On the other hand, the upfront administration of more potent and widely active FGFR-TKI (once clearly identified) may prevent or delay the onset of polyclonal mutations responsible for disease progression. Ideally, the development of selective FGFR-TKI could retrace the generations of EGFR and ALK inhibitors in NSCLC, with drugs progressively more potent, active on a wide spectrum of resistance mutations and more specific. In this regard, the synthesis of new compounds should be accompanied by the design of optimized clinical trials.

In conclusion, specific FGFR inhibition is a relevant chapter in the field of precision medicine. The design of ongoing trials involving selective anti-FGFR drugs, as well as the recent approval of erdafitinib, will hopefully lead to a wide clinical availability. In this sense, it is essential to implement appropriate molecular screening tests for detecting *FGFR* alterations (mutations and fusions) or other means of activation (amplification accompanied by overexpression of the target) starting from tumors suitable for FGFR-targeted treatments (i.e., urothelial carcinomas and cholangiocarcinomas). Initiating basket clinical trials agnostic of tumor origin would hopefully fasten FGFR-TKI approvals for patients with *FGFR*-mutated/rearranged/overexpressed cancer (2).

Disclosure of Potential Conflicts of Interest

A. Hollebecque is an employee/paid consultant for Incyte and Debiopharm. Y. Loriot is an employee/paid consultant for Janssen, Astellas, Roche, AstraZeneca, MSD, Bristol-Myers Squibb, and Seattle Genetics. No potential conflicts of interest were disclosed by the other authors.

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