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Evolving role of regorafenib for the treatment of advanced cancers

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ABSTRACT

Regorafenib is an oral tyrosine kinase inhibitor (TKI) approved for the treatment of refractory metastatic colorectal cancer (mCRC), advanced gastrointestinal stromal tumors (GIST) previously treated with imatinib and sunitinib, and unresectable hepatocellular carcinoma (HCC) following progression on sorafenib. Regorafenib was initially approved for mCRC based on improved overall survival (OS) in the randomized, placebo-controlled, phase 3 CORRECT trial, which was confirmed in an expanded population of Asian patients in the randomized, placebo-controlled phase 3 CONCUR trial. Approvals in GIST, and more recently in HCC, were based on the results from the randomized, placebo-controlled, phase 3 GRID and RESORCE trials, respectively. In this review, we provide a comprehensive summary of the clinical evidence for approval of regorafenib in mCRC, GIST, and HCC, present emerging evidence of regorafenib activity in other tumor types (namely, gastroesophageal cancer, sarcomas, biliary tract cancer, and glioblastoma), and discuss trials in progress within the context of regorafenib's mechanism of action. We describe recent advances and key lessons learned with regorafenib, including the importance of managing common drug-related toxicities using dose-optimization strategies, the search for biomarkers to predict response to treatment, and highlight some of the unaddressed questions and future directions for regorafenib across tumors.

Introduction

Regorafenib is an oral tyrosine kinase inhibitor (TKI) approved for patients with treatment-refractory metastatic colorectal cancer (mCRC), advanced gastrointestinal stromal tumors (GISTs) after imatinib and sunitinib, and unresectable hepatocellular carcinoma (HCC) following sorafenib [1,2]. Initially, regorafenib was approved for mCRC based on improved overall survival (OS) in the randomized, placebo-controlled, phase 3 CORRECT trial [3], which was confirmed in an expanded population of Asian patients in the randomized, double-blind, placebo-controlled phase 3 CONCUR trial [4]. Approvals in GIST and HCC were based on results from the randomized, placebo-controlled, phase 3 GRID and RESORCE trials, respectively [5,6]. Here, we provide a comprehensive summary of the clinical evidence for regorafenib in mCRC, GIST, and HCC, and present emerging evidence of regorafenib activity in other tumors.

Mechanism of action

Preclinical studies have shown that regorafenib targets kinases involved in tumor angiogenesis (e.g. vascular endothelial growth factor receptors [VEGFRs] 1–3, tyrosine kinase with immunoglobulin-like and epidermal growth factor-like domains 2 [TIE2], fibroblast growth factor receptors [FGFRs] 1–2, and platelet-derived growth factor receptor [PDGFR]), proliferation (e.g. KIT, RAF, RET), the tumor microenvironment, and metastasis (VEGFR2–3, PDGFR) [7–10]. Regorafenib also disrupts tumor immunity by inhibiting colony-stimulating factor-1 receptor (CSF-1R), important for macrophage differentiation and survival, and causes a reduction in tumor-infiltrating macrophages [8,10,11]. Tumor-associated macrophages (TAMs), a major component of tumor-infiltrating leukocytes, promote tumor cell occurrence, development, and migration [12]. The role of TAMs in carcinogenesis is well documented in several tumor types, including colorectal cancer (CRC), gastric cancer, HCC, and sarcoma [12,13].

Regorafenib, a tyrosine and serine–threonine kinase inhibitor, displays different activity to other TKIs, which could explain its activity in tumors refractory to bevacizumab and chemotherapy (mCRC), sorafenib (HCC), and imatinib and sunitinib (GIST). In preclinical models of HCC, sorafenib and regorafenib show differences in anti-tumor activity and exert different effects on protein expression [14]. Data from preclinical GIST models suggest that, compared with imatinib and sunitinib, regorafenib targets a broader range of relevant protein kinases

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Table 1
Efficacy of regorafenib in mCRC.

Study	Patients	Treatment	Overall survival	Progression-free survival	Tumor response
Phase 3 studies (REG 160 mg/day)					
CORRECT [3] NCT01103323 RCT phase 3 N = 760	mCRC progression within 3 mo of standard therapy; ECOG PS 0–1 All received previous anti-VEGF therapy	REG (160 mg/day, n = 500), Days 1–21 of 28-day cycle, vs PBO (n = 253)	OS (primary endpoint): 6.4 vs 5.0 mo (HR = 0.77; $P = 0.0052$)	PFS[a]: 1.9 vs 1.7 mo (HR = 0.49; $P < 0.0001$)	CR[a]: 0% vs 0% PR[a]: 1% vs 0.4% ORR[a]: 1.0% vs 0.4% ($P = 0.19$) DCR ≥ 6 wks[a]: 41% vs 15% ($P < 0.0001$)
CORRECT Japanese post-hoc analysis [18] N = 760	mCRC (Japanese vs non-Japanese subpopulations) progression within 3 mo of standard therapy; ECOG PS 0–1 All received previous anti-VEGF therapy	REG (160 mg/day, Japanese pts n = 67; non-Japanese pts n = 438), Days 1–21 of 28-day cycle, vs PBO (Japanese pts n = 33, non-Japanese pts n = 222)	OS (primary endpoint), Japanese subpopulation: 6.6 vs 7.0 mo (HR = 0.81; 95% CI 0.43–1.51) OS (primary endpoint), non-Japanese subpopulation: 6.2 vs 4.9 mo (HR = 0.77, 95% CI 0.62–0.94)	PFS, Japanese subpopulation[a]: 1.9 vs 1.7 mo (HR = 0.47; 95% CI 0.30–0.74) PFS, non-Japanese subpopulation[a]: 1.9 vs 1.7 mo (HR = 0.50; 95% CI 0.42–0.60)	DCR ≥ 6 wks, Japanese subpopulation[a]: 40% vs 15% DCR ≥ 6 wks, non-Japanese subpopulation[a]: 41% vs 15% ORR, Japanese subpopulation[a]: 2% vs 0% ORR, non-Japanese subpopulation[a]: 1% vs < 1%
CONCUR [4] NCT01584830 RCT, phase 3 N = 204	Previously treated mCRC (Asian population); received ≥ 2 previous treatment lines or intolerant of standard therapy Biologic naïve (REG: 41%/PBO: 38%) Previous anti-VEGF therapy (REG: 24%/PBO: 19%) Previous anti-EGFR therapy (REG: 18%/PBO: 25%)	REG (160 mg/day, n = 136) Days 1–21 of 28-day cycle, vs PBO (n = 68)	OS (primary endpoint): 8.8 vs 6.3 mo (HR = 0.55, $P = 0.00016$)	PFS[a]: 3.2 vs 1.7 mo (HR = 0.31, $P < 0.0001$)	CR[a]: 0% vs 0% PR[a]: 4% vs 0% ORR[a]: 4% vs 0% ($P = 0.045$) DCR ≥ 6 wks[a]: 51% vs 7% ($P < 0.0001$)
CONSIGN [19] NCT01538680 Open-label, single-arm, phase 3b N = 2872	mCRC progression within 3 mo of standard therapy; ECOG PS 0–1	REG (160 mg/day, n = 2872) Days 1–21 of 28-day cycle	NR	PFS[b]: 2.7 mo (95% CI 2.6—2.7)	NA
Real-world studies					
REBECCA [20] NCT02310477 Observational cohort N = 690	Refractory mCRC	REG in real-life clinical practice (n = 654)	OS: 5.6 mo (IQR 2.4–11.4)	PFS[c]: 2.7 mo (IQR 1.6–4.6)	NR
CORRELATE [21] NCT02042144 Observational cohort N = 1037	Previously treated mCRC	REG in real-life clinical practice (n = 1037)	OS: 7.7 mo (95% CI 7.2–8.3)	PFS[c]: 2.9 mo (95% CI 2.8—3.0)	DCR[c]: 26% PR[c]: 4%
RECORA [22] NCT01959269 Observational cohort N = 481	Previously treated mCRC	REG in real-life clinical practice in Germany (n = 464 [safety]; n = 463 [efficacy])	OS: 5.8 mo (95% CI 5.3–6.6)	PFS[c]: 3.1 mo (95% CI 2.8–3.3)	DCR[c]: 26.7%
Japanese post-marketing surveillance study [23] NCT01843400 Observational cohort N = 1301	Previously treated mCRC (Japanese pts)	REG in real-life clinical practice in Japan (n = 1227 [September 2016 cut-off])	OS: 6.9 mo (95% CI 6.4–7.4)	TTF[c]: 2.2 mo (95% CI 2.1–2.3)	NR

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Table 1 (*continued*)

Study	Patients	Treatment	Overall survival	Progression-free survival	Tumor response
Combination studies (REG 160 mg/day)					
REG + FOLFIRI [34] NCT01298570 RCT, phase 2 N = 181	mCRC progression on first-line oxaliplatin and 5-FU or capecitabine (with or without prior biologic); ECOG PS 0–1	REG (160 mg/day, Days 4–10 and Days 18–24 of 28-day cycle) + FOLFIRI (irinotecan + 5-FU + leucovorin, Days 1–2 and 15–16 of every 28-day cycle) (n = 120) vs PBO + FOLFIRI (n = 61)	HR for OS: 1.01 (95% CI: 0.71–1.44)	PFS (primary endpoint)[c]: 6.1 vs 5.3 mo (HR = 0.73; P = 0.06)	RR (ITT)[c]: 29% vs 20% (P = 0.21) RR[c]: 34% vs 21% (P = 0.07) DCR: 82% vs 74% (P = 0.23)
REG + mFOLFOX6 (CORDIAL) [33] NCT01289821 Open-label, phase 2 N = 54	mCRC without prior systemic anticancer therapy for metastatic disease	mFOLFOX6, Days 1–15; REG (160 mg/day) on Days 4–10 and 18–24 of each 28-day cycle (n = 54)	Not reached	PFS[a]: 8.5 mo (95% CI 7.4–11.3 mo) PFS, control (FOLFOX/FOLFIRI)[a]: 8.0/8.5 mo	Primary analysis set (n = 41) CR[d]: 0% PR[d]: 43.9% SD[d]: 41.5% PD[d]: 12.2% DCR[d] (with SD ≥ 7 wks): 85.4% ORR (primary endpoint)[d]: 43.9%
Dose optimization studies (alternative starting dose)					
ReDOS [30] NCT02368886 RCT, phase 2 N = 123	Previously treated mCRC	REG (80 mg up to 160 mg/day, n = 54, Arm A) Days 1–21 of 28-day cycle plus pre-emptive/reactive clobetasol REG (standard 160 mg/day dose, n = 62, Arm B) Days 1–21 of 28-day cycle plus pre-emptive/reactive clobetasol	OS (Arm A vs Arm B): 9.8 vs 6.0 mo, HR = 0.72; P = 0.12	PFS (Arm A vs Arm B)[c]: 2.8 vs 2.0 mo, HR = 0.84; P = 0.38	NR
REGOCC-12 [31] UMIN000018968 Single-arm, phase 2 N = 60	Japanese pts with mCRC who progressed on standard chemotherapy	REG (120 mg/day dose) Days 1–21 of 28-day cycle, followed by dose escalation to 160 mg/day (Cycle 2 onwards)	NR	PFS[c]: 2.3 mo (95% CI 1.8–2.8)	DCR at ≥ 6 wks (primary endpoint)[c]: 36.7% SD ≥ 6 mo[c]: 7%
REARRANGE [32] NCT02835924 RCT, phase 2 N = 299	Previously treated mCRC	Arm A: REG 160 mg/day, 3 wk on/1 wk off Arm B: REG 120 mg/day, 3w on/1w off first cycle; 160 mg/day at second cycle Arm C: REG 160 mg/day, 1 wk on/1 wk off first cycle; 160 mg/day, 3 wk on/1 wk off second cycle	OS (Arm A vs Arm B vs Arm C): 7.4 vs 8.6 mo vs 7.1 mo; P = 0.7152	PFS (Arm A vs Arm B vs Arm C)[c]: 1.9 vs 2.0 mo vs 2.0 mo; P = 0.3871	NR

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Table 1 (*continued*)

Study	Patients	Treatment	Overall survival	Progression-free survival	Tumor response
Other (REG 160 mg/day)					
REVERCE [29] UMIN000011294 RCT, phase 2 N = 101	Previously treated mCRC	REG (160 mg/day) 3 wk on, 1 wk off followed by cetuximab + irinotecan (R–C, n = 51) Cetuximab + irinotecan, followed by REG (160 mg/day) 3 wk on/ 1 wk off (C–R, n = 50)	OS (primary endpoint) R–C: 17.4 mo OS (primary endpoint) C–R: 11.6 mo HR = 0.61 (95% CI 0.39–0.96), P = 0.029	PFS (sequential treatment)[a]: 9.0 (R–C) vs 7.1 mo (C–R); HR = 0.55; P = 0.015	ORR (treatment 1)[a]: 4% (REG in R–C) vs 20% (cetuximab in C–R) DCR (treatment 1)[a]: 46% (REG in R–C) vs 78% (cetuximab in C–R) ORR (treatment 2)[a]: 28% (cetuximab in R–C) vs 0% (REG in C–R) DCR (treatment 2)[a]: 77% (cetuximab in R–C) vs 31% (REG in C–R)
REFRAME [123] NCT01875380 Single-arm, open-label, phase 2 N = 47	mCRC Frail/unfit pts not eligible for polychemotherapy; ECOG PS ≤ 2 Dependence in activities of daily living due to comorbidities; ≥ 3 comorbidities; ≥ 1 geriatric feature	REG (160 mg/day, n = 47) Days 1–21 of 28-day cycle	OS: 16.0 mo (95% CI 7.8–24)	PFS[a]: 5.6 mo (95% CI 2.7–8.4) 6-mo PFS (primary endpoint)[a]: 45% (95% CI 30–60)	ORR[a]: 6.4% CR[a]: 2.1% PR[a]: 4.3% SD[a]: 45% PD[a]: 28% DCR[a]: 51%
NCT02465502 [28] Single-arm, open-label, phase 2b N = 59	Antiangiogenic-naïve and chemotherapy-refractory advanced CRC	REG (160 mg/day, n = 59) Days 1–21 of 28-day cycle	OS: 7.4 mo (95% CI 5.3–8.9) 8-wk OS: 98% (95% CI 88.6–99.8)	PFS[a]: 3.5 mo (95% CI 1.8–3.6) 8-wk PFS (primary endpoint)[a]: 53% (95% CI 39.1–64.3)	DCR[e]: 51% (RECIST) ORR[e] (RECIST): 2% Metabolic response rate (EORTC): 41% CR/CMR[e]: 0% PR/PMR[e]: 2% SD/SMD[e]: 14% PD/PMD[e]: 20%

5-FU, fluorouracil; ^{18}F-PET, fludeoxyglucose-positron emission tomography; CI, confidence interval; CMR, complete metabolic response; CR, complete response; C–R, cetuximab–regorafenib; CT, computed tomography; CTX, cetuximab; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EORTC, European Organisation for Research and Treatment of Cancer; FOLFIRI, folinic acid–fluorouracil–irinotecan; FOLFOX/mFOLFOX6, folinic acid–fluorouracil–oxaliplatin; HR, hazard ratio; ITT, intent-to-treat; IQR, interquartile range; mCRC, metastatic colorectal cancer; mo, months; NA, not assessed; NR, not reported; ORR, objective response rate; OS, overall survival; PBO, placebo; PD, progressive disease; PFS, progression-free survival; PMD, progressive metabolic disease; PMR, partial metabolic response; PR, partial response; PS, performance status; pts, patients; R–C, regorafenib–cetuximab; RCT, randomized controlled trial; RECIST, Response Evaluation Criteria in Solid Tumors; REG, regorafenib; RR, response rate; SD, stable disease; SMD, stable metabolic disease; TTF, time-to-treatment failure; VEGF, vascular endothelial growth factor; wk, week.

[a] Radiologically evaluated using RECIST 1.1.

[b] Investigator assessed using radiologic and/or clinical tumor assessment according to local standards.

[c] Assessment criteria/method of assessment not reported.

[d] Centrally assessed using RECIST 1.1.

[e] Tumor response radiologically evaluated using RECIST 1.1 and tumor metabolic response by ^{18}F-PET/CT using EORTC criteria.

Table 2
Efficacy of REG in TKI-refractory GIST.

Study	Patients	Treatment	Overall survival	Progression-free survival	Tumor response
Phase 3 studies					
GRID [5,124] NCT01271712 RCT, phase 3 N = 199	Metastatic/unresectable GIST Failure of prior imatinib and sunitinib; ECOG PS 0–1	REG (160 mg/day, n = 133) Days 1–21 of 28-day cycle vs PBO (n = 66)	OS: not reached vs not reached (HR = 0.77; P = 0.199) OS [after correction from crossover]: 17.4 vs 11.1 mo (HR = 0.59; 95% CI 0.42–0.82)	PFS (primary endpoint)[a]: 4.8 vs 0.9 mo (HR = 0.27; P < 0.0001)	CR[a]: 0% vs 0% PR[a]: 4.5% vs 1.5% ORR[a]: 4.5% vs 1.5% SD[a]: 71% vs 33% DCR (CR, PR, and SD ≥ 12 wks)[a]: 53% vs 9%
GRID, Japanese subgroup analysis [95] N = 17	Japanese pts with metastatic/ unresectable GIST Failure of prior imatinib and sunitinib; ECOG PS 0–1	REG (160 mg/day, n = 12) Days 1–21 of 28-day cycle, vs PBO (n = 5)	OS: no difference between groups; HR = 0.42; P = 0.182	PFS (primary endpoint)[b]: 7.1 vs 0.9 mo (HR = 0.08; P = 0.0002)	CR[b]: 0% vs 0% PR[b]: 0% vs 20% SD[b]: 92% vs 0% DCR (CR, PR, and SD ≥ 12 wks)[b]: 58% vs 20% (P = 0.081)
Phase 2 studies					
NCT01068769 [15] Single-arm, open-label, phase 2 N = 34	Metastatic/unresectable GIST after failure of prior imatinib and sunitinib; ECOG PS 0–1	REG (160 mg/day, n = 33) Days 1–21 of 28-day cycle	OS: not reached (after 11 mo follow-up)	PFS[b]: 10 mo (95% CI 8.3–14.9 mo)	CBR (CR, PR, and SD ≥ 16 wks; primary endpoint)[b]: 75% (95% CI 61–91%) PR[b]: 12% SD[b]: 67%
NCT01068769 [41] Single-arm, open-label, phase 2, long-term follow-up N = 33	Metastatic/unresectable GIST after failure of prior imatinib and sunitinib	REG (160 mg/day, n = 33) Days 1–21 of 28-day cycle	OS, all pts: 25 mo (95% CI 13.2–39.1) (after 41 mo follow-up), with no difference between genotypes (P = 0.77)	PFS, all pts[b]: 13.2 mo (95% CI 9.2–18.3 mo) PFS, *KIT* exon 11 mutation: 13.4 mo PFS, SDH-deficient GIST: 10 mo PFS, *KIT* exon 9 mutation: 5.7 mo PFS, WT, non-SDH-deficient: 1.6 mo (difference between genotypes, P < 0.0001)	CBR (CR, PR, and SD ≥ 16 wks; primary endpoint), all pts[b]: 76% (95% CI 58–89%) CBR, *KIT* exon 11 mutation: 79% (95% CI 54–94%) CBR, *KIT* exon 9: 67% (95% CI 9–99%) CBR, SDH deficient: 100% (95% CI 54–100%) Unknown genotype: 67% (95% CI 9–99%)
NCT02606097 [125] Single-arm, open-label, phase 2 N = 18	Pts with GIST with exon 17 mutations	REG (160 mg/day, n = 15) Days 1–21 of 28-day cycle	OS: not reached (after 10.9 mo follow-up)	PFS[c]: 22.1 vs 5.5 mo (historical cohort who did not receive REG) (P = 0.0001) PFS (pts with SD at enrollment vs PD)[c]: not reached vs 12.9 mo (P = 0.015)	CBR (CR, PR, and SD at 16 wks; primary endpoint)[b]: 93% PR[b]: 40% SD[b]: 53%
Dose optimization studies (alternative starting dose)					
NCT02889328 [109] Single-arm, open-label, phase 2 N = 25	Metastatic/unresectable GIST after failure of prior imatinib and sunitinib	REG (100 mg/day, n = 25), every 4 wks (28 days)	OS: not reached (after 8.6 mo median follow-up) 1-year OS rate: 64.5%	PFS [b]: 7.3 mo (95% CI 5.9–8.6 mo)	DCR (CR, PR, and SD ≥ 12 wks; primary endpoint)[b]: 64% PR: 8% SD: 64% PD: 24%

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; GIST, gastrointestinal stromal tumors; HR, hazard ratio; mo, months; OS, overall survival; PBO, placebo; PD, progressive disease; PFS, progression-free survival; PR, partial response; PS, performance status; pts, patients; REG, regorafenib; RCT, randomized controlled trial; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SDH, succinate dehydrogenase; TKI, tyrosine kinase inhibitor; wk, week; WT, wild-type.

[a] Radiologically evaluated according to central blinded review using (modified) RECIST 1.1.

[b] (Centrally) assessed using (modified) RECIST 1.1.

[c] Assessment criteria/method of assessment not reported.

Table 3
Efficacy of REG in advanced HCC.

Study	Patients	Treatment	Overall survival	Progression-free survival	Time to progression	Tumor response
Phase 3 studies						
RESORCE [6] NCT01774344 RCT, phase 3 N = 573	HCC with progression on sorafenib Child–Pugh A liver function BCLC stage B/C No prior systemic treatment	REG (160 mg/day, n = 374) vs PBO (n = 194) Days 1–21 of 28-day cycle	OS (primary endpoint): 10.6 vs 7.8 mo (HR = 0.62; $P < 0.0001$) [48]	PFS[a]: 3.1 vs 1.5 mo (HR = 0.46; $P < 0.0001$) PFS[b]: 3.4 vs 1.5 mo (HR = 0.43; $P < 0.0001$)	TTP[a]: 3.2 vs 1.5 mo (HR = 0.44; $P < 0.0001$) TTP[b]: 3.9 vs 1.5 mo (HR = 0.41; $P < 0.0001$)	CR[a]: 1% vs 0% PR[a]: 10% vs 4% SD[a]: 54% vs 32% PD[a]: 23% vs 56% ORR[a]: 11% vs 4% ($P = 0.0047$) DCR (SD ≥ 6 wks)[a]: 65% vs 36% ($P < 0.0001$) CR[b]: 0% vs 0% PR[b]: 7% vs 3% SD[b]: 59% vs 32% PD[b]: 22% vs 57% ORR[b]: 7% vs 3% ($P = 0.02$) DCR[b]: 66% vs 35% ($P < 0.0001$)
Phase 2 studies						
NCT01003015 [126] Single-arm, open-label, phase 2 N = 36	Intermediate/advanced HCC with progression on sorafenib BCLC stage B/C Child–Pugh A	REG (160 mg/day, n = 36) Days 1–21 of 28-day cycle	OS: 13.8 mo (95% CI 9.3–18.3)	NR	TTP[a]: 4.3 mo (95% CI 2.9–13.1)	PR[a]: 3% SD[a]: 69% PD[a]: 14% ORR[a]: 3% DCR (SD ≥ 6 wks)[a]: 72%

BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; DCR, disease control rate; HCC, hepatocellular carcinoma; HR, hazard ratio; mo, months; NR, not reported; OS, overall survival; ORR, objective response rate; PBO, placebo; PD, progressive disease; PFS, progression-free survival; PR, partial response; REG, regorafenib; RCT, randomized controlled trial; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TTP, time to progression; wk, week.

[a] Radiologically evaluated using modified RECIST.

[b] Radiologically evaluated using RECIST 1.1.

and displays affinity for several *KIT/PDGFRA* mutants resistant to both agents [7,10]. Regorafenib also exhibits activity in non-*KIT* and non-*PDGFRA*-mutated GISTs that are activated by different pathways in a clinical setting where other TKIs have failed [15]. Therefore, regorafenib's broad kinase inhibition, along with its immune-modulating effects, may explain its established and emerging clinical activity across tumor types.

Established activity of regorafenib in CRC, GIST, and HCC

The clinical benefit of regorafenib has been established in randomized trials and observational studies in mCRC (Table 1), in phase 2/3 trials in advanced GIST (Table 2), and in phase 2/3 trials in advanced HCC (Table 3).

mCRC

The mainstay of mCRC treatment is combination chemotherapy with an antiepithelial growth factor receptor (EGFR)-targeted monoclonal antibody or an antiangiogenic agent (i.e. bevacizumab), taking *RAS/BRAF* status and primary tumor location into consideration [16,17]. The clinical value of antiangiogenic therapy supported investigation of regorafenib in mCRC. Regorafenib's approval in mCRC (CORRECT) was based on significantly improved OS versus placebo (median OS: 6.4 vs 5.0 months; hazard ratio [HR] = 0.77; $P = 0.0052$) in heavily pretreated patients (73% received ≥ 3 prior anticancer therapies) [3]. Results were later confirmed in CONCUR in a broader population of Asian patients (median OS: 8.8 vs 6.3 months; HR = 0.55; $P = 0.00016$) [4]. Importantly, regorafenib was effective across all clinically relevant subgroups in both studies, independent of *KRAS* mutation status, age, and time from diagnosis of metastatic disease [3,4]. Regorafenib also showed similar survival benefits (vs placebo) in the Japanese (n = 100) versus non-Japanese subpopulation (n = 660) of CORRECT (HR = 0.81; 95% confidence interval [CI] 0.43–1.51) [18]. More recently, the safety and efficacy of regorafenib was confirmed in the large, prospective, single-arm, phase 3b CONSIGN expanded safety study of patients with mCRC [19], and in a broader population of patients in real-world practice [20–23].

Phase 3 trials and observational cohort studies demonstrated that most patient mCRC subgroups had improved survival with regorafenib and about 20% achieved an extended progression-free survival (PFS) benefit > 4 months [24–26]. Although there are currently no genetic or protein biomarkers to predict response to regorafenib in mCRC, evidence suggests that previous exposure to targeted therapy is associated with poorer outcome [4]. Notably, in CORRECT, all patients received prior bevacizumab and 52% received prior anti-EGFR therapy versus 41% and 35%, respectively, in CONCUR, which may contribute to the greater OS benefit in CONCUR [3,4,27]. More recently, a single-arm, phase 2b study evaluating regorafenib in antiangiogenic-naïve patients with chemotherapy-refractory, advanced CRC reported a median PFS and OS of 3.5 and 7.4 months, respectively [28], consistent with CONCUR, but comparing favorably with CORRECT. In the randomized, phase 2 REVERCE study, previously treated patients with mCRC receiving regorafenib followed by cetuximab (plus irinotecan) had better survival outcomes versus cetuximab followed by regorafenib, supporting the rationale for introducing regorafenib earlier in the treatment sequence [29]. Dose optimization may also have an impact on treatment duration, with no adverse impact on outcome; in the phase 2 ReDOS study, more patients in the dose-escalation arm initiated Cycle 3 compared with the standard regimen, and OS was 9.8 versus 6.0 months (HR = 0.72; $P = 0.12$), respectively [30]. Other dose-optimization studies, REGOCC-12 and REARRANGE (Table 1) [31,32], are discussed further in the *Dose-optimization strategies* section.

Phase 2 clinical trials in mCRC investigating regorafenib combined with chemotherapy have produced mixed results. In the second-line setting, the addition of regorafenib to folinic acid–fluorouracil–irinotecan (FOLFIRI) resulted in a modest PFS improvement versus FOLFIRI alone, while regorafenib in combination with folinic acid–fluorouracil–oxaliplatin (mFOLFOX6) in first line did not improve objective response rate over historical controls, although some patients remained on treatment for an extended period of time (> 1 year) [33,34].

Since the approval of regorafenib for the treatment of mCRC in the third-line setting, other agents have emerged in the refractory setting, increasing the number of treatment options available to patients [17]. For patients in third line or later, the oral nucleoside analogue trifluridine/tipiracil hydrochloride (TAS-102) is another recommended treatment option with supportive evidence for activity from phase 3 and real-world studies [17,35,36]. Sequencing of these two agents is an important consideration, which is briefly covered in the *Treatment sequence* section of this article. DNA mismatch repair (MMR)/microsatellite status has become an important biomarker in mCRC, with immunotherapy demonstrating activity in microsatellite instability-high (MSI-H)/MMR deficient (dMMR) tumors; current treatment options include nivolumab, nivolumab plus ipilimumab, and pembrolizumab [17,36]. Finding successful treatment strategies for MMR proficient or microsatellite stable mCRC is an ongoing challenge, with a number of trials in progress, including regorafenib in combination with nivolumab, which has recently showed encouraging results [37].

GIST

Imatinib followed by sunitinib are standard systemic therapies for unresectable or metastatic GIST [38,39]; however, most patients develop resistance within a few years [5,40]. In GRID, regorafenib showed a statistically significant improvement in PFS versus placebo (4.8 vs 0.9 months; HR = 0.27; $P < 0.0001$) in advanced GIST following imatinib and sunitinib. These benefits were observed across all subgroups, including treatment line, duration of previous imatinib/sunitinib therapy, age, and Eastern Cooperative Oncology Group performance status (ECOG PS) [5]. PFS benefit was observed in patients with the two most common primary *KIT* mutations, exon 11 (HR = 0.21; 95% CI 0.10–0.46) and exon 9 (HR = 0.24; 95% CI 0.07–0.88) [5]. Another smaller phase 2 study (NCT01068769) suggested a benefit in patients with exon 17 mutations (a subtype of GIST resistant to imatinib and sunitinib) based on a matched historical control comparison [41]. These results are clinically important in GIST because primary/secondary *KIT* mutations are commonly associated with resistance to standard TKIs [40]. Long-term follow-up over a median of 41 months also revealed durable benefit of regorafenib in *KIT/PDGFRA* wild-type GIST and high expression of proteins involved in angiogenesis, including VEGF; therefore, potent VEGF inhibition may provide an important disease control mechanism [15,41].

Since cancer stem cells play a role in targeted drug resistance, using an alternating regimen of imatinib and regorafenib with short drug-free intervals may permit tumor stem cells to re-enter the cell cycle and become susceptible to therapy again, potentially overcoming resistance [42]. Furthermore, targeting resistant mutations earlier may lead to improved outcomes. A phase 2, randomized trial (ALT GIST) is underway to determine whether alternating imatinib and regorafenib improves disease control in advanced GIST versus first-line imatinib alone [42]. Ongoing studies of regorafenib in GIST are listed in Table 5.

Despite the success of imatinib, sunitinib, and regorafenib in the first-, second-, and third-line settings, respectively, most patients eventually develop resistance [43]. Owing to the frequency and diversity of resistance mutations in GIST, efforts are being made to find agents with different mechanisms of action or to use combination therapy approaches to overcome resistance without adding toxicity – examples include avapritinib (a KIT/PDGFRα inhibitor, recently FDA approved [44]), dabrafenib (a BRAF inhibitor), and a MEK inhibitor in combination with imatinib [43].

HCC

Regorafenib was the first agent to show survival benefits in patients with HCC progressing on sorafenib in the phase 3 RESORCE trial [6],

Table 4
Activity of REG in other cancers.

Study	Patients	Treatment	Overall survival	Progression-free survival	Tumor response
Gastric/esophageal cancer					
INTEGRATE [57] RCT, phase 2 N = 152	Metastatic/recurrent GC; ECOG PS 0–1 Refractory to ≤ 2 lines of chemotherapy	REG (160 mg/day, n = 100) Days 1–21 of 28-day cycle vs PBO (n = 52)	OS: 5.8 vs 4.5 mo (HR = 0.74; $P = 0.147$)	PFS (primary endpoint)[a]: 2.6 vs 0.9 mo (HR = 0.40; $P < 0.001$)	ORR/PR[b]: 3% vs 2%
NCT01913639 [60] Single-arm, open-label, phase 2 N = 36	Previously untreated metastatic EGAC No prior chemotherapy for metastatic disease	REG (160 mg/day) Days 4–10 and Days 18–24 of 28-day cycle) + mFOLFOX6 every 14 days (n = 36)	OS: not reached (after 12.4 mo follow-up)	PFS[c]: 7 mo (95% CI 4.5–11.5) 6-mo PFS (primary endpoint)[c]: 53%	PR[b]: 54% SD[b]: 24% PD[b]: 21%
REPEAT [59] EudraCT: 2014-005433-31, phase 1 N = 14	Metastatic EGAC failure on ≥ 1 prior treatment line (including fluoropyrimidine/platinum-based chemotherapy)	REG (80, 120, 160 mg/day) Days 1–21 of 28-day cycle + paclitaxel (80 mg/m^2 IV) Days 1, 8, and 15 (n = 14)	OS: 8.5 mo	PFS[b]: 4.2 mo	PR[b]: 8% (1/13) SD[b]: 92% (12/13) PD[b]: 8% (1/13)
Sarcomas					
REGOSARC [65] NCT01900743 RCT, phase 2 N = 182 Nonadipocytic sarcoma cohorts (updated analysis): N = 139 [67]	Advanced STS Prior doxorubicin/other anthracycline treatment; ECOG PS 0–1	REG (160 mg/day) Days 1–21 of 28-day cycle vs PBO (+BSC) Liposarcoma cohort: REG (n = 20); PBO (n = 23) Leiomyosarcoma: REG (n = 28); PBO (n = 28) Synovial sarcoma: REG (n = 13); PBO (n = 14) Other sarcomas: REG (n = 29); PBO (n = 27) Updated analysis (nonadipocytic cohorts): Leiomyosarcoma: REG (n = 28); PBO (n = 28) Synovial sarcoma: REG (n = 13); PBO (n = 14) Other nonadipocytic cohort: REG (n = 29); PBO (n = 27)	Liposarcoma: No difference REG vs PBO (HR = 1.57; $P = 0.21$) Leiomyosarcoma: No difference REG vs PBO (HR = 0.50; $P = 0.056$) Synovial sarcoma: No difference REG vs PBO (HR = 0.87; $P = 0.79$) Other sarcoma: No difference REG vs PBO (HR = 0.75; $P = 0.37$) Pooled analysis (nonadipocytic sarcomas): 13.4 vs 9.0 mo (HR = 0.67; $P = 0.059$) Updated analysis (nonadipocytic cohorts): Leiomyosarcoma: 13.2 vs 9.1 mo (HR = 0.76; $P = 0.36$) Synovial sarcoma: 13.4 vs 6.7 mo (HR = 0.81; $P = 0.61$) Other sarcoma: 12.1 vs 9.5 mo (HR = 0.82; $P = 0.49$) Overall: 12.8 vs 9.1 mo (HR = 0.78; $P = 0.18$)	PFS (primary endpoint)[d]: Liposarcoma: 1.1 vs 1.7 mo (HR = 0.89; $P = 0.70$) Leiomyosarcoma: 3.7 vs 1.8 mo (HR = 0.46; $P = 0.0045$) Synovial sarcoma: 5.6 vs 1.0 mo (HR = 0.10; $P < 0.0001$) Other sarcoma: 2.9 vs 1.0 mo (HR = 0.46; $P = 0.0061$) Pooled analysis (nonadipocytic sarcomas): 4.0 vs 1.0 mo (HR = 0.36; $P < 0.0001$) Updated analysis (nonadipocytic cohorts): Leiomyosarcoma: 3.7 vs 1.8 mo (HR = 0.60; $P = 0.06$) Synovial sarcoma: 3.8 vs 1.0 mo (HR = 0.10; $P \leq 0.0001$) Other sarcoma: 2.9 vs 1.0 mo (HR = 0.57; $P = 0.04$) Overall: 3.7 vs 1.0 mo (HR = 0.50; $P \leq 0.0001$)	Tumor response[b] Liposarcoma PR: 0% vs 0% Liposarcoma SD: 45% vs 57% Liposarcoma PD: 55% vs 43% Leiomyosarcoma PR: 0% vs 4% Leiomyosarcoma SD: 86% vs 54% Leiomyosarcoma PD: 11% vs 39% Synovial sarcoma PR: 8% vs 0% Synovial sarcoma SD: 77% vs 22% Synovial sarcoma PD: 15% vs 76% Other sarcomas PR: 11% vs 0% Other sarcoma SD: 67% vs 34% Other sarcoma PD: 22% vs 64% Updated analysis (nonadipocytic cohorts): Leiomyosarcoma CR: 0% vs 0% Leiomyosarcoma PR: 0% vs 4% Leiomyosarcoma SD: 86% vs 54% Leiomyosarcoma PD: 11% vs 39% Synovial sarcoma CR: 0% vs 0% Synovial sarcoma PR: 8% vs 0% Synovial sarcoma SD: 77% vs 29% Synovial sarcoma PD: 15% vs 64% Other sarcoma: CR: 0% vs 0% Other sarcoma PR: 10% vs 0% Other sarcoma SD: 62% vs 30% Other sarcoma PD: 21% vs 59% Overall CR: 0% vs 0% Overall PR: 6% vs 1% Overall SD: 74% vs 39% Overall PD: 16% vs 52%

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Table 4 (*continued*)

Study	Patients	Treatment	Overall survival	Progression-free survival	Tumor response
SARC024 [68–70] NCT02048371 Randomized, cross-over, phase 2 N = 30 (Ewing's sarcoma, single-arm) N = 48 (liposarcoma, randomized, PBO-controlled) N = 42 (metastatic osteosarcoma, randomized, PBO-controlled)	Advanced/metastatic Ewing's sarcoma, liposarcoma, osteosarcoma, and related tumors of soft tissue and bone; progression within 6 mo; ECOG PS 0–2; at least one line of therapy	REG (160 mg/day, Ewing's sarcoma [n = 30]) Days 1–21 of 28-day cycle REG (160 mg/day, liposarcoma [n = NR]) Days 1–21 of 28-day cycle, vs PBO (n = NR) REG (160 mg/day, osteosarcoma [n = 22]) Days 1–21 of a 28-day cycle vs PBO (n = 20)	OS (Ewing's sarcoma): not reached OS (liposarcoma, REG vs PBO): not reached (95% CI 4.2 not reached) vs 8.1 mo (95% CI 2.9 not reached), $P = 0.13$ OS (osteosarcoma, REG vs PBO): 11.1 mo (95% CI 4.7–26.7) vs 13.4 mo (95% CI 8.5–38.1), $P = 0.62$	8-wk PFS (primary endpoint Ewing's sarcoma)[b]: 73% (95% CI 57–89%) Median PFS (Ewing's sarcoma)[b]: 3.6 mo (95% CI 2.8–3.8 mo) Median PFS (liposarcoma, REG vs PBO)[c]: 1.9 mo (95% CI 0.9–3.7) vs 2.1 (95% CI 1.6–3.1); HR = 0.87; $P = 0.68$ Median PFS (osteosarcoma, REG vs PBO)[c]: 3.6 mo (95% CI 2.0–7.6) vs 1.7 (95% CI 1.2–1.8); HR = 0.42; $P = 0.017$	Ewing's sarcoma RR[b]: 10% Ewing's sarcoma PR[b]: 10% Ewing's sarcoma SD[b]: 60% Ewing's sarcoma PD[b]: 23% Liposarcoma CR (REG vs PBO) [c]: 0% vs 0% Liposarcoma PR (REG vs PBO) [c]: 0% vs 1 patient Osteosarcoma PR (REG vs PBO)[b]: 13.6% vs 0%
REGOBONE [72] NCT02389244 Randomized, phase 2, PBO-controlled N = 43 (metastatic osteosarcoma)	Metastatic osteosarcoma, age ≥ 10 years, 1–2 prior systemic regimens for metastatic disease; ECOG PS 0–1	REG (160 mg/day, n = 26) Days 1–21 of 28-day cycle vs PBO (n = 12)	OS (REG vs PBO): 11.3 (95% CI 5.9–23.9) vs 5.9 mo (95% CI 1.3–16.4)	PFS rate (primary endpoint, REG vs PBO at 24 wks)[d]: 35% (95% CI 17–52) vs 0% PFS (REG vs PBO)[d]: 16.4 wks (95% CI 8.0–27.3) vs 4.1 wks (95% CI 3.0–5.7)	8-wk CR (REG vs PBO): 0% vs 0% 8-wk PR (REG vs PBO): 8% vs 0% 8-wk SD (REG vs PBO): 58% vs 0% 8-wk PD (REG vs PBO): 35% vs 100%
Biliary tract cancers					
NCT02115542 [77] Multi-institutional, open-label, phase 2 N = 39	Advanced biliary cancer, ≥ 1 prior systemic therapy	REG (160 mg/day, n = 32 [evaluable for efficacy]/39 [received ≥ 1 dose]) Days 1–21 of 28-day cycle	OS (primary endpoint): 8.8 mo (95% CI 3.9–14.2) 6-mo OS: 50.9% 12-mo OS: 35% 18-mo OS: 35%	PFS[c]: 4.1 mo (95% CI 2.5–5.8)	PR[b]: 9.4% SD[b] 53.1% DCR[b]: 62.5%
NCT02053376 [78] Single-arm, open-label, phase 2 N = 43	Advanced or metastatic biliary carcinoma/ cholangiocarcinoma; failed on systemic chemotherapy	REG (160 mg/day, n = 34 [dose reduced to 120 mg/day in the majority]) Days 1–21 of 28-day cycle	OS: 31.8 wks (90% CI 23.3–74.3)	PFS (primary endpoint)[b]: 15.6 wks (90% CI 12.9–24.7)	ORR[b]: 11% SD[b]: 44% DCR[b]: 56%
REACHIN [79] NCT02162914 Randomized, double-blind, PBO-controlled, multicenter, phase 2 N = 66	Locally advanced (nonresectable) and metastatic biliary tract cancer progressing after standard chemotherapies	REG (160 mg/day) Days 1–21 of 28-day cycle (n = 33) vs PBO + BSC (n = 33)	OS: 5.3 vs 5.1 mo (HR = 0.76; $P = 0.31$)	PFS (primary endpoint)[c]: 3.0 vs 1.5 mo (HR = 0.49; $P = 0.005$)	CR[b]: 0% vs 0% PR[b]: 0% vs 0% SD[b]: 70% vs 33% PD[b]: 24% vs 64% DCR[b]: 70% vs 33% ($P = 0.002$)
BREGO [80] NCT02386397 Single-arm, open-label, phase 1b N = 22	Advanced biliary tract cancer	REG (80 mg/day [n = 6], 120 mg/day [n = 3], 160 mg/day [n = 13], Days 1–14) and IV gemcitabine 900 mg/m^2 followed with oxaliplatin 80 mg/m^2 IV, Days 1 and 8	NR	NR	NR

(*continued on next page*)

Table 4 (*continued*)

Study	Patients	Treatment	Overall survival	Progression-free survival	Tumor response
Glioblastoma					
REGOMA [86] NCT02926222 RCT, phase 2 N = 119	Relapsed glioblastoma; ECOG PS 0–1 (Karnofsky performance score ≥ 70)	REG (160 mg/day, n = 59) Days 1–21 of 28-day cycle vs lomustine (110 mg/m^2 every 6 wks, n = 60)	OS (primary endpoint): 7.4 vs 5.6 mo (HR = 0.50; P = 0.0009)	PFS[c]: 2.0 vs 1.9 mo; 6-mo PFS[c]: 16.9% vs 8.3% (HR = 0.65; P = 0.022)	CR[c]: 2% vs 2% PR[c]: 3% vs 2% ORR[c]: 5% vs 3% SD[c]: 39% vs 17% DCR[c]: 44% vs 20% (P = 0.006) PD[c]: 56% vs 75%

BSC, best supportive care; CI, confidence interval; CR, complete response; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; EGAC, esophagogastric adenocarcinoma; FOLFOX/mFOLFOX6, folinic acid–fluorouracil–oxaliplatin; GC, gastric cancer; HR, hazard ratio; IV, intravenous; mo, months; NA, not available; NR, not reported; ORR, objective response rate; OS, overall survival; PBO, placebo; PFS, progression-free survival; PD, progressive disease; PR, partial response; PS, performance status; RANO, Revised Assessment in Neuro-Oncology; RCT, randomized controlled trial; RECIST, Response Evaluation Criteria in Solid Tumors; REG, regorafenib; RR, response rate; SD, stable disease STS, soft tissue sarcoma; wk, week.

[a] Radiologically assessed according to central blinded review using RECIST 1.1.

[b] Radiologically evaluated using RECIST 1.1.

[c] Assessment criteria/method of assessment not reported.

[d] Centrally assessed using RECIST 1.1.

[e] Evaluated using RANO criteria.

following several failed phase 3 trials [45–47]. Regorafenib significantly improved OS versus placebo (median OS: 10.6 vs 7.8 months, respectively; HR = 0.62; P < 0.0001 [updated OS analysis]) [48], reduced the risk of progression or death, prolonged median time-to-progression (TTP), and improved disease control rate (DCR; all P < 0.0001 vs placebo) [6]. Benefits were maintained across all stratified subgroups, including age, ECOG PS (0/1), Child–Pugh score (A5/A6), alpha-fetoprotein level (< 400/ ≥ 400 ng/mL), presence of extrahepatic disease and/or macrovascular invasion, hepatitis B or C, or history of alcohol use. No patient receiving regorafenib or placebo achieved complete response, while 7% versus 3% achieved partial response by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, respectively. The proportion of patients with stable disease for ≥ 6 weeks was 59% versus 32% (regorafenib vs placebo; RECIST v1.1). By comparison, as per modified RECIST (mRECIST), 11% of regorafenib-treated patients achieved an objective response rate (1% complete response; 10% partial response) and 54% achieved stable disease. Notably, PFS and TTP outcomes were similar when assessed by RECIST v1.1 or mRECIST. Exploratory subgroup analyses of RESORCE showed a consistent OS benefit for regorafenib, irrespective of prior sorafenib dose (including duration of sorafenib and median OS by last sorafenib dose [800 vs < 800 mg/day]) [49], as well as pattern of progression under sorafenib, a factor identified as predictive of outcome [49,50]. An exploratory analysis of RESORCE revealed a median OS of 26.0 months (regorafenib) versus 19.2 months (placebo) from time of sorafenib initiation [51]. Differences in protein expression between regorafenib and sorafenib, including downregulation of proteins involved in angiogenesis, metabolism, cell cycle regulation, and apoptosis following exposure to sorafenib (but not regorafenib), may explain the anti-tumor effects of regorafenib in sorafenib-refractory patients [7,14]. An exploratory analysis of predictive biomarkers suggested an association between expression patterns of plasma proteins and microRNAs and OS in patients with HCC following regorafenib in RESORCE, and showed that regorafenib treatment benefit for OS and TTP was independent of alpha-fetoprotein and c-Met levels [52].

Since the approval of regorafenib in 2017, the treatment landscape for advanced HCC has changed dramatically, with a number of new systemic therapies now approved [53], including the TKIs lenvatinib and cabozantinib in the first- and second-line setting, respectively, and the anti-VEGF agent ramucirumab (AFP ≥ 400 ng/mL only) in the second-line setting. The immuno-oncology drugs nivolumab and pembrolizumab individually received accelerated FDA approval based on early phase trials in sorafenib-refractory patients, but have failed to significantly improve OS in phase 3 trials. Potentially practice changing immuno-oncology combinations are on the horizon, including atezolizumab plus bevacizumab in the first-line setting following the positive results of the phase 3 IMbrave150 trial [53,54]. Further understanding of the comparative effectiveness and safety of these therapies alone and in combination, as well as appropriate patient selection, is necessary to develop evidence-based treatment approaches for patients with advanced HCC.

Emerging evidence of regorafenib activity in other tumor types

Several recent clinical trials have demonstrated that regorafenib is active in other tumor types including gastric cancer (GC), sarcomas (other than GIST), biliary tract cancers, and glioblastoma (Table 4).

Gastroesophageal cancer

In preclinical models of GC, regorafenib inhibited angiogenesis and tumor proliferation and had proapoptotic effects [55,56], coinciding with clinical investigations in patients with refractory, advanced gastroesophageal cancer (aGEC) (phase 2 INTEGRATE) [57], which is ongoing in a broader population of patients with aGEC (phase 3 INTEGRATE II) [58]. In the randomized, placebo-controlled, phase 2 INTEGRATE trial, regorafenib showed a significant improvement in PFS (primary endpoint) versus placebo (2.6 vs 0.9 months; HR = 0.40; P < 0.001) and a numerical improvement in OS (median OS: 5.8 vs 4.5 months; HR = 0.74; P = 0.15)

[57]; the PFS impact was greater in South Korea than the combined population of Australia, New Zealand, and Canada (PFS: HR = 0.12 vs 0.61; interaction $P = 0.001$). INTEGRATE II is enrolling patients from Australia, Canada, New Zealand, the USA, Japan, Taiwan, and the Republic of Korea, and is designed to assess OS in the overall study population and an Asian subpopulation [58]. Studies evaluating regorafenib combined with chemotherapy in other settings have produced varied results. A phase 1, dose-escalation study in pretreated patients with metastatic esophageal/GC showed promising effects on survival with regorafenib combined with paclitaxel [59], while a phase 2 study of regorafenib combined with FOLFOX failed to meet the prespecified endpoint of 6-month PFS [60].

Several other novel targeted therapies have been evaluated in clinical studies, but only trastuzumab and ramucirumab (± paclitaxel) have demonstrated an OS benefit in the first- and second-line setting, respectively [61,62]. While PD-1 inhibitors, alone or in combination with other targeted agents, have demonstrated to be highly active against MSI-H GCs, other molecular targets under investigation in GC, including EGFR, FGFR2, and MET, have had mixed results.

Sarcomas (other than GIST)

The role of angiogenesis in the tumorigenesis of soft-tissue sarcoma (STS) and bone sarcomas is well documented [63], and several targeted therapies, including the multikinase inhibitor pazopanib, are now recommended in guidelines as second-line treatment for certain STS subtypes [38,64]. To ensure a detailed assessment of regorafenib activity for select sarcoma subtypes, trial designs accounted for the histologic diversity and extreme rarity of these tumors. In the randomized, placebo-controlled, phase 2 REGOSARC study [65], multiple histologic cohorts were run in parallel, enabling comprehensive, independent, evaluation of regorafenib in certain STS subtypes and cross-trial comparisons with other agents [66]. In REGOSARC, regorafenib significantly prolonged PFS in patients with non-adipocytic STS (e.g. leiomyosarcoma, synovial sarcoma, and other sarcomas) relative to placebo (median PFS: 4.0 vs 1.0 month; HR = 0.36; $P < 0.0001$ [pooled analysis]), but failed to improve PFS in liposarcoma (HR = 0.89; $P = 0.70$) [65]. Liposarcomas are highly heterogeneous and, currently, the underlying carcinogenic mechanisms and role of proangiogenic and antiangiogenic factors are poorly understood. In REGOSARC, 70 patients initially receiving placebo crossed over to regorafenib; thus, regorafenib's effect on OS cannot be ascertained, although pooled data for nonadipocytic STS showed a trend towards improved OS with regorafenib (HR = 0.67; $P = 0.06$) [65]. The updated analysis of REGOSARC confirmed the PFS benefit of regorafenib over longer term follow-up (median: 32.4 months) in refractory nonadipocytic sarcomas (HR = 0.50; $P < 0.0001$), again reporting a statistically nonsignificant difference in OS (HR = 0.78; $P = 0.18$) due to the high rate of patient crossover from placebo to regorafenib post progression [67].

Results of the phase 2 crossover SARC024 study were consistent with REGOSARC, showing no PFS benefit from regorafenib in patients with treatment-refractory liposarcoma (HR = 0.87 vs placebo; $P = 0.68$) [68]. However, the study showed that regorafenib may have activity in patients with advanced Ewing's sarcoma (a form of bone sarcoma) and metastatic osteosarcoma. The median PFS for patients with Ewing's sarcoma was 3.6 months and 73% were progression-free at 8 weeks [69], while in the osteosarcoma cohort, the median PFS was significantly improved with regorafenib versus placebo (3.6 months vs 1.7 months, HR = 0.42; $P = 0.017$) [70].

Using a similar trial design to REGOSARC, the randomized, phase 2, placebo-controlled REGOBONE study is investigating regorafenib in adult patients with different subtypes of metastatic bone sarcomas; namely Ewing's sarcoma, chondrosarcomas, osteosarcomas, and chordoma [71]. Early results of the metastatic osteosarcoma cohort in REGOBONE have showed promising efficacy with regorafenib [72]. Median PFS was 16.4 weeks (95% CI 8.0–27.3) for regorafenib versus 4.1 weeks (95% CI 3.0–5.7) for placebo, with a 24-week PFS rate of 35% versus 0%, respectively. The median OS was 11.3 months (95% CI 5.9–23.9) for regorafenib versus 5.9 months (95% CI 1.3–16.4) for placebo. Enrollment has been completed for chondrosarcoma and is continuing for the Ewing's sarcoma and chordoma cohorts.

The histology and molecular heterogeneity of sarcomas has created a challenging and complex treatment environment where chemotherapy still plays a key role. However, several targeted agents are now recommended in the treatment guidelines, including olaratumab (anti-PDGFRA) in combination with doxorubicin as a first-line therapy for advanced STS [64], and the TKI pazopanib for nonadipocytic STS [38,64]. Regorafenib is now listed as a treatment options for refractory nonadipocytic STS and osteosarcoma in the ESMO and NCCN guidelines [38,64,73]. A number of novel agents are in clinical development and have shown promise, including immuno-oncology agents [74].

Biliary tract cancer

Preclinical studies have shown that regorafenib inhibits FGFR2, which together with PDGFR, plays a key role in maintaining the tumor microenvironment in CRC, HCC, and other tumor types [7,8,10]. A proportion of intrahepatic cholangiocarcinomas (CCAs) are FGFR2 fusion-driven, suggesting that FGFR kinase inhibition may be effective [75]. Additionally, in preclinical models of CCAs, regorafenib inhibited mucosa-associated lymphoid tissue protein 1 (MALT1)-mediated NF-κB activation via suppression of the Raf/ERK/Elk-1/MALT1 pathway, inhibiting human CCA cell growth and inducing apoptosis [76]. MALT1 plays an important role in aberrant activation of the NF-κB and Raf/ERK/Elk-1 pathways, and represents a novel therapeutic target for regorafenib in CCA/biliary tract carcinoma.

Regorafenib has shown survival benefit in patients with chemotherapy-refractory advanced and metastatic biliary adenocarcinoma in two single-arm, open-label, phase 2 studies [77,78]. In the multi-institutional study (NCT02115542) with 32 patients evaluable for efficacy, the 6-, 12-, and 18-month OS rates were 51%, 35%, and 35%, respectively [77]. Based on the primary endpoint (6-month OS), regorafenib was deemed to have good activity if 43.8% of evaluable patients survived ≥ 6 months ($\alpha = 0.10$, 86% power). The median PFS and OS of evaluable patients was 4.1 months (95% CI 2.5–5.8) and 8.8 months (95% CI 3.9–14.2), respectively. A best response of partial response or stable disease was observed in 9.4% and 53.1% of patients, respectively, giving a DCR of 62.5%. In the other study (NCT02053376), the median PFS was 15.6 weeks (90% CI 12.9–24.7), where a median PFS of ≥ 3.5 months was defined as evidence of regorafenib activity ($\alpha = 0.10$, 83% power). Median OS was 31.8 weeks (90% CI 23.3–74.3), with a survival rate of 40% at 12 months and 32% at 18 months [78]; the DCR was 56%.

In REACHIN, a randomized, double-blind, placebo-controlled, phase 2 trial, regorafenib improved median PFS versus placebo (3.0 vs 1.5 months, HR = 0.49; $P = 0.05$), and showed evidence of disease control (DCR: 70%) in patients with advanced (nonresectable) metastatic biliary tumors following progression on standard chemotherapies [79].

The single-arm, open-label, phase 1b/2R BREGO trial proposed an alternative regimen of regorafenib combined with modified gemcitabine–oxaliplatin in first line for patients with metastatic or locally advanced biliary tract cancer. The safety of this combination was acceptable in this population, with efficacy results expected in 2019 [80].

Patients with advanced biliary tract cancer typically have poor prognosis and limited treatment options, with chemotherapy being the treatment of choice, and no established treatment options when patients reach second line [81,82]. In addition to regorafenib, a number of other targeted agents are being evaluated in clinical trials, including drugs targeting *FGFR* aberrations and *IDH* mutations [83], as well as immuno-oncology agents (including pembrolizumab), which is a treatment option for patients with unresectable or metastatic MSI-H/dMMR biliary tract tumors [81,83].

Glioblastoma

Regorafenib has shown antiangiogenic effects in a ratGS9L glioblastoma model [7]; similar to other tumor types, glioblastomas have

high expression of proangiogenic factors, triggering the activation of multiple signaling pathways in the tumor microenvironment, including VEGFR, FGFR, and PDGFR [84,85].

In the randomized, open-label, phase 2 REGOMA trial, regorafenib significantly improved OS (median OS: 7.4 vs 5.6 months; HR = 0.50; $P = 0.0009$) and PFS (6-month PFS: 16.9% vs 8.3%; HR = 0.65; $P = 0.022$) compared with the active comparator, lomustine, in patients with advanced glioblastoma with disease progression post surgery, followed by radiotherapy and temozolomide chemotherapy, with evidence of superior DCR (44% vs 20%; $P = 0.006$) [86]. Regorafenib is also being evaluated in an open-label, randomized, phase 2/3 multi-arm platform trial (GBM AGILE) in newly diagnosed and recurrent glioblastoma [87].

Despite the therapeutic rationale for angiogenic therapies in glioblastoma, multiple studies with antiangiogenic therapies (including bevacizumab) have failed to demonstrate an OS benefit [84,86]. Regorafenib's broad activity beyond angiogenesis serves as a rationale for its efficacy in recurrent glioblastoma where other therapies are less effective [86]. In addition, new targeted therapies are continually emerging, with immunotherapies (immune checkpoint inhibitors, tumor vaccines, and chimeric antigen receptor T-cell therapy) are emerging as promising new clinical strategies [88].

Safety of regorafenib across tumor types

Safety data from studies of regorafenib in mCRC, GIST, and HCC, in addition to emerging evidence in other tumors, are summarized in Supplementary Table A1. In CORRECT, the most frequent any-grade drug-related adverse events (AEs) in the regorafenib group were fatigue (47%), hand–foot skin reaction (HFSR; 47%), diarrhea (34%), and anorexia (30%); the most common grade ≥ 3 drug-related AEs were HFSR (17%), fatigue (10%), diarrhea (7%), hypertension (7%), and rash or desquamation (6%) [3]. Regorafenib-related AEs reported in CONCUR and mCRC observational studies have generally been consistent with those reported in CORRECT [3,4,19–23] and are typical of TKIs [89–91]. However, differences were noted in the incidence of AEs between the non-Asian and Asian populations of CORRECT and CONCUR. As reported for other TKIs [92–94], the occurrence of any-grade drug-related HFSR was more common in Asian patients in CONCUR than in the predominately non-Asian population in CORRECT (74% vs 47%, respectively); however, the incidence of grade ≥ 3 drug-related HFSR was similar between the two study populations (16% vs 17%). Similarly, of the Japanese patients in CORRECT who received regorafenib, the incidence of any-grade and grade ≥ 3 drug-related HFSR was 80% and 28%, respectively, versus 42% and 15% in the non-Japanese population [3,4,18]. Regorafenib-associated liver function AEs also occurred more frequently among Asian patients in both trials [3,4,18].

In GRID, the most frequent drug-related AEs of any grade in the regorafenib group were HFSR (56%), hypertension (49%), diarrhea (40%), fatigue (39%), and oral mucositis (38%); the most common grade ≥ 3 drug-related AEs were hypertension (23%), HFSR (20%), diarrhea (5%), fatigue, and maculopapular rash (each 2%) [5]. As in CORRECT and CONCUR, HFSR occurred more frequently in Japanese regorafenib-treated patients in GRID. The incidence of any-grade drug-related HFSR was 92% versus 56%, respectively, in the Japanese versus overall population, although rates of grade ≥ 3 drug-related HFSR were similar [5,95]. The reason for differences in the frequency of all-grade HFSR between Asian and non-Asian populations receiving regorafenib is unclear.

In RESORCE, the most common any-grade drug-related AEs were HFSR (52%), diarrhea (33%), fatigue (29%), anorexia (24%), and hypertension (23%); clinically relevant grade ≥ 3 drug-related toxicities included hypertension (13%), HFSR (13%), hyperbilirubinemia (7%), fatigue (6%), and increased aspartate aminotransferase (5%) [6]. The incidence of grade ≥ 3 drug-related HFSR with regorafenib was lower in RESORCE (13%) than CORRECT (17%), CONCUR (16%), and GRID (20%) [3–5]. Of note, unlike studies in mCRC and GIST (the latter included patients who received two prior TKIs [imatinib and sunitinib]), all patients enrolled in RESORCE had received, and tolerated, sorafenib, which because of the overlapping AE profiles, may account for the lower incidence of grade ≥ 3 drug-related HFSR in this population. Rates of liver-related AEs and liver failure were not higher in the RESORCE HCC population than CORRECT and GRID [3,5,6]. Two deaths due to liver failure, both occurring in the placebo group, were considered drug related [6]. Another important consideration is that patients with mCRC have generally had other treatments including surgery, radiotherapy, and adjuvant therapies prior to treatment for metastatic disease than patients with GIST and HCC, which may account for differences in the nature, incidence, and severity of AEs (and tolerance to regorafenib) observed between trials.

To date, no new safety concerns have arisen from studies in other cancer types, including gastric cancer [57], STS/bone sarcoma [65,68,69,72], biliary tract cancer [77,78,80], or glioblastoma [86], with the nature, incidence, and severity of AEs (including skin toxicities) consistent with those described in the label [1,2]. In INTEGRATE, there was a lower incidence of grade 3/4 HFSR and fatigue versus CORRECT, possibly due to racial differences affecting drug absorption/pharmacokinetics or improved management of regorafenib-related toxicities [57].

Challenges and key lessons

Since the approval of regorafenib, its efficacy and safety has been explored in a number of clinical trials and real-world studies, providing a wealth of experience and important lessons on its optimal use in clinical practice. It is important to understand that survival benefit with regorafenib is achieved through disease control rather than tumor shrinkage, and that proactive management of AEs, dose optimization, and treating patients while they are clinically fit are important for patients to remain on treatment [3,36]. Historically, dose adjustment with regorafenib has been reactive, but more recently, the benefit of proactive first-cycle dose optimization, such as the ReDOS strategy, have become apparent [30]. Some of these key lessons are outlined in more detail in this section.

HFSR and outcomes

One of the most common toxicities associated with TKIs, including regorafenib, is HFSR [96–101]. A published meta-analysis of regorafenib trials observed a clinically significant variation in all-grade regorafenib-related HFSR incidence across studied tumor types, with higher rates in patients with GIST (60%) versus HCC (50%) and mCRC (47%) [102]. Well-established guidelines exist for the prevention and management of HFSR (including recommendations about treatment and dose modifications), which have been covered extensively in several other reviews [98,103]. Importantly, regorafenib-related HFSR generally occurs within Cycles 1–2 and are therefore managed proactively with dose modifications without treatment discontinuation [1,3–6]. To this end, dose modifications were used to manage all AEs in CORRECT and CONCUR, including HFSR, in 67% and 71% of regorafenib-treated patients, respectively. However, in CORRECT and CONCUR, the overall rate of discontinuation was relatively low (17% and 14%, respectively), and only 1% and < 1% of patients, respectively, permanently discontinued regorafenib following HFSR [3,4,104].

Post hoc exploratory analyses of CORRECT and RESORCE indicate that patients with treatment-related HFSR had greater regorafenib benefit than those without; notably, a significant OS benefit was observed when HFSR occurred during the first treatment cycle, supporting continued treatment with dose adjustment [104,105]. Similar outcomes have been reported for regorafenib in the real-world REBECCA study [20], in the Japanese mCRC post-marketing surveillance study [23], and for the TKIs sorafenib and sunitinib in HCC and renal cell carcinoma [99–101]. Recently, early HFSR following sorafenib treatment in HCC has been associated with improved treatment response [106]. Importantly, because these events are observed retrospectively, this approach does not inform the pretreatment selection of patients most likely to benefit from regorafenib, and identification of baseline predictive biomarkers is ongoing [107] (see *Markers of regorafenib activity*).

Dose-optimization strategies

Although the clinical benefit of regorafenib has been demonstrated across multiple tumor types, proactive measures are required to prevent and manage regorafenib-related toxicities to allow patients to remain on treatment. The most common toxicities tend to occur within the first two treatment cycles, are noncumulative, and often decrease over time [3,103,108]. In the phase 3 trials, despite dose modifications to manage AEs, regorafenib was still associated with OS benefit. In real-world studies, overall treatment effectiveness in patients initiated on a lower regorafenib dose, therefore requiring fewer doses reductions to manage AEs, remained similar to that observed in clinical trials [20–23]. The potential benefit of starting regorafenib at a lower dose in Cycle 1 is being investigated in three phase 2 dose-adaptation trials, ReDOS, REGOCC-12, and REARRANGE [30–32]. ReDOS was a randomized study (N = 123) designed to evaluate weekly dose escalation in Cycle 1 (from 80 mg to 160 mg/day) versus standard 160 mg/day dosing [30]. The primary endpoint was reached, with a higher proportion of patients completing two treatment cycles and initiating a third in the dose-escalation arm versus the standard dose arm (43% vs 26%, respectively; $P = 0.043$). The median OS was 9.8 months in the dose-escalation arm versus 6.0 months in the standard arm ($P = 0.12$), and the median PFS was 2.8 months versus 2.0 months ($P = 0.38$), respectively. In addition, a weekly dose-escalation strategy was associated with a lower incidence of AEs and improved patient quality of life after Week 2 of Cycle 1, compared with standard dosing [30]. In REGOCC-12, a single-arm Japanese study of 60 patients, regorafenib was administered at 120 mg/day with an option to increase to 160 mg/day [31]. The DCR (primary endpoint) was 37%, and 7% of patients had stable disease lasting ≥ 6 months. Grade ≥ 3 AEs were observed in 55% of patients receiving regorafenib in REGOCC-12, versus 80% (Japanese) and 51% (non-Japanese) receiving regorafenib in CORRECT [18]. The randomized, phase 2 REARRANGE study (N = 299) compared dosing approaches for regorafenib during Cycle 1 in patients with refractory mCRC [32]. Although the study failed to meet its primary endpoint of improving tolerability through a reduced regorafenib dose of 120 mg/day (3 weeks on/1 week off) or an intermittent 160 mg/day dose (1 week on/1 week off), it showed a numerical improvement in relevant AEs including fatigue, HFSR, and hypertension, without jeopardizing efficacy [32]. The results from these studies suggest that a flexible first-cycle dose-optimization approach may help some patients with mCRC to manage toxicity and stay on treatment.

Although the dose-escalation strategy is limited to mCRC, it is worth noting that a lower continuous dose of regorafenib (100 mg/day) has been explored in a phase 2 study in 25 patients with GIST, demonstrating comparable efficacy to the standard intermittent dose and a favorable safety profile [109].

Treatment sequence

Regorafenib is currently approved in third-line mCRC and second-line HCC [1,2]. Current mCRC clinical guidelines recommend that patients with *RAS* wild-type mCRC receive cetuximab followed by regorafenib later in the treatment sequence [16,17]. However, results of REVERCE suggest that regorafenib followed by cetuximab may hold greater survival benefit in some patients compared with vice versa, and therefore warrants further investigation [29]. The guidelines also do not provide recommendations on whether to use regorafenib or TAS-102 (another third-line agent in mCRC) first; however, TAS-102 could represent a good option after regorafenib because data suggest it is equally effective before and after regorafenib treatment [110,111]. To date, the totality of evidence suggests that regorafenib is more effective in clinically fit patients, and in HCC, underlying liver disease and deterioration of liver function increase the urgency of further systemic treatment intervention following progression on first-line systemic therapy [6]. While regorafenib's approval in HCC resulted in a continuum of first- and second-line treatment (sorafenib–regorafenib), patients with liver-confined disease should be offered regorafenib or another systemic treatment option while they have preserved liver function, providing an opportunity to receive a treatment sequence proven to extend survival and improve long-term outcomes.

Predictive markers of regorafenib activity

Regorafenib extends OS primarily through disease stabilization rather than tumor shrinkage. The low numbers of complete responses among patients receiving regorafenib may relate to its antiangiogenic mechanism of action, leading to central tumor necrosis or reduced arterial enhancement rather than a reduction in tumor volume [6,112]; therefore, RECIST [113,114], which assess tumor response via changes in tumor size, may not be the best criteria to measure the anti-tumor activity of agents such as regorafenib. While mRECIST may overcome some limitations in HCC by assessing tumor necrosis, proper validation is awaited and more appropriate measures for assessing response to TKIs with antiangiogenic function are required [112]. As aforementioned, TTP in RESORCE did not differ between RECIST v1.1 and mRECIST, highlighting the need to develop better tools to capture treatment benefit. However, recent studies suggest that imaging techniques may predict response to regorafenib, and this represents an area of active research [107,115–117]. Some studies have shown that small changes in tumor density and size or early cavitation of lung metastases could predict response to regorafenib [115–117]. A post hoc analysis of CORRECT (RadioCORRECT) showed that cavitation in pulmonary metastases, seen with contrast-enhanced computed tomography, was associated with absence of progression at Week 8 in regorafenib-treated patients with mCRC [117].

Currently, there are no validated molecular biomarkers available to predict outcome with regorafenib treatment. Attempts to identify predictive biomarkers have been largely unsuccessful, potentially due to its multi-targeted mechanism of action. Biomarker analyses from the phase 3 CORRECT and RESORCE trials in CRC and HCC, respectively, have failed to identify single biomarker targets at the genetic, miRNA, or protein level, and there has been some speculation that identifying molecular signatures may be a more successful approach [52,118]. While the multi-targeted mechanism of action of regorafenib may make it difficult to identify biomarkers, and in turn define appropriate patient selection, our increased understanding of the molecular mechanisms of the different tumor types may help inform why regorafenib works and potentially help guide its use. For example, regorafenib's broad spectrum kinase inhibition may explain why it is active in tumors that have become resistant to other VEGF inhibitors [119].

Upcoming studies and future directions

Beyond the approved uses of regorafenib in mCRC, GIST, and HCC following failure of standard therapies, there is a growing body of evidence demonstrating regorafenib's efficacy in other tumor types. Clinical development of regorafenib in various malignant tumors, including sarcomas and advanced biliary cancer, is ongoing [42,71,80,120] (Table 5). The phase 3 INTEGRATE II study will assess OS (primary endpoint), PFS, response rate, and the safety/pharmacokinetics of regorafenib in patients with refractory aGEC [58]. The identification of clinical or biological markers would help individualize treatment protocols and identify those most likely to benefit from regorafenib, representing an important goal for future clinical development. New approaches are also being tested to refine and optimize regorafenib dosing for certain patient groups to improve tolerability, while maintaining efficacy.

While immuno-oncology represents a growing field in cancer therapy, recent results of a much anticipated phase 3 trial (IMblaze370) evaluating atezolizumab (anti-programmed death-ligand 1 antibody [anti-PD-L1]) plus cobimetinib (a MEK inhibitor) versus atezolizumab failed to improve OS over regorafenib alone (median OS: 8.9 [atezolizumab plus cobimetinib] vs 8.5 months [regorafenib]; HR = 1.00; $P = 0.99$) [121]. Most CRC tumors are largely non-inflamed, with low-level T-cell infiltration [122], and may require priming for immuno-oncology agents to be effective. The results of IMblaze370 suggest that MEK inhibition may be insufficient as a primer.

Table 5
Ongoing studies of REG.

Study	Study design	Patients (estimated enrollment)	Treatment	Primary endpoint	Secondary endpoints	Status	Estimated primary completion date
GIST							
REGISTRI [120] GEIS/IGS study NCT02638766	Single-arm, non-randomized, multicenter, phase 2	Unresectable and/ or metastatic *KIT/ PDGFR* WT-GIST (n = 39)	REG (160 mg/day), Days 1–21 of 28-day cycle	DCR (relative to historical control, imatinib)	PFS, OS, tumor response (Choi criteria), correlation with translational research, early metabolic response, and safety (NCI-CTCAE 4.03)	Recruiting	November 2020
ALT GIST [42] NCT02365441	Randomized, open-label, phase 2	Confirmed metastatic GIST, no prior TKI treatment for metastatic disease (n = 240)	Arm A: Imatinib (400 mg/day) continuously Arm B: Alternating 28-day cycle of imatinib (400 mg/day) for 21–25 days; wash-out period for 3–7 days; REG (160 mg/day) 3 wk on/1 wk off	PFS at 24 mo	ORR (at 16 wk), CBR (at 16 wk), CR, TTF, AEs, OS	Recruiting	December 2019
Gastroesophageal cancer							
INTEGRATE II [58] NCT02773524	Randomized, double-blind, PBO-controlled phase 3	Refractory aGEC failure/intolerance to two lines of prior anticancer therapy (n = 350)	REG (160 mg/day) Days 1–21 of 28-day cycle vs PBO (+BSC)	OS	PFS, response rate, quality of life, safety, prognostic/predictive biomarkers, PK	Recruiting	May 2020
Sarcomas							
REGOBONE [71] NCT02389244	Randomized, double-blind, PBO-controlled, multicenter, phase 2	Metastatic bone sarcomas: osteosarcoma, Ewing's sarcoma of bone, chondrosarcomas, chordomas (n = 132)	REG (160 mg/day) Days 1–21 of 28-day cycle, vs PBO (+BSC)	PFS (per RECIST 1.1)	ORR, 6-mo DCR, OS, duration of response, 3- and 6 mo PFS, TTP, growth modulation index, safety (NCI-CTCAE v4.0), pain assessment (chordomas), PFS (Choi criteria for chordomas)	Recruiting	September 2019
Biliary tract cancer							
BREGO [127] NCT02386397	Multicenter, randomized, phase 1b/2R	Metastatic adenocarcinoma of biliary tract; no prior chemotherapy for advanced disease; ECOG PS 0–1 (n = 63)	REG (80, 120, and 160 mg/day on Days 1–14, with fixed doses of gemcitabine (900 mg/m^2 over 30 min IV – oxaliplatin (80 mg/m^2 over 120 min IV) on Days 1 and 8 followed by 2 wk rest	Limiting toxicity (phase 1b)	NR (safety and efficacy evaluated in phase 2R)	Recruiting	November 2018
Glioblastoma							
GBM AGILE [87]	Randomized, multi-arm, platform trial (phase 2/3)	Newly diagnosed or recurrent GBM KPS ≥ 60% (newly diagnosed) or ≥ 70% (recurrent) confirmed within 14 days of randomization	Newly diagnosed GBM: XRT 60 Gy for 6 wks plus TMZ 75 mg/m^2 daily for 6 weeks, then REG (160 mg/day) Days 1–21 of 28-day cycle vs maintenance therapy Recurrent GBM: REG (160 mg/day) Days 1–21 of 28-day cycle vs lomustine 110 mg/m^2/day Day 1 of 42-day cycle (maximum 6 cycles)	OS	PFS, tumor response, duration of response	Recruiting	December 2022

AE, adverse event; aGEC, advanced gastroesophageal cancer; BSC, best supportive care; CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; GBM, glioblastoma multiforme; GIST, gastrointestinal stromal tumors; Gy, gray; KPS, Karnofsky Performance Status; mCRC, metastatic colorectal cancer; min, minutes; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, objective response rate; OS, overall survival; PBO, placebo; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; pts, patients; RECIST, Response Evaluation Criteria in Solid Tumors; TEAEs, treatment-emergent adverse events; TKI, tyrosine kinase inhibitor; TMZ, temozolomide; TTP, time to progression; VEGF, vascular endothelial growth factor; wk, weeks; WT, wild-type; XRT, radiotherapy.

Broader inhibition with a TKI, such as regorafenib, may be a better option. To this end, early clinical data have shown that regorafenib has encouraging anti-tumor activity in combination with anti-PD-1 therapy in patients with advanced gastric cancer and CRC [37]; therefore, novel immuno-oncology combinations with regorafenib represent an exciting avenue for further research.

Conclusion

In conclusion, regorafenib is an effective, orally active TKI with a mechanism of action that enables it to exhibit broad activity in various cancers including hard-to-treat tumor types that have become resistant to standard therapies. Trials continue to provide insight on the potential role of regorafenib in these emerging indications and help to provide answers to outstanding questions surrounding patient selection, dose-optimization, sequencing, and safety.

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Appendix A. Supplementary material

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