Sorafenib Plus Irinotecan Combination in Patients With *RAS*-mutated Metastatic Colorectal Cancer Refractory To Standard Combined Chemotherapies: A Multicenter, Randomized Phase 2 Trial (NEXIRI-2/PRODIGE 27)

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Abstract

No treatment was available for patients with *RAS*-mutated (*RAS*mt) metastatic colorectal cancer (mCRC) refractory to standard chemotherapies at the time of the study. A total of 173 patients with *RAS*mt mCRC were randomized between NEXIRI (IRI + NEX), irinotecan (IRI), and sorafenib (NEX). The 2-month nonprogression disease rate was 52.6% [95% CI: 39%–66%], 21.4% [10%–33%], and 19.3% [9%–30%], respectively. NEXIRI combination can delay progression of RASmt mCRC.

Background: No treatment option was available for patients with *RAS*-mutated (*RAS*mt) metastatic colorectal cancer (mCRC) who progress after standard combined chemotherapies at the time of the study. After promising results in phase II, the aim of the present NEXIRI-2/PRODIGE 27 trial was to assess the 2-month non-progression rate for

Part of this work was presented at the 2016 ASCO-GI and ASCO meetings, and at the 2016 ESMO meeting.

The study was approved by an ethics committee (Comité de Protection des Personnes Sud Mediterranée III, EudraCT 2012-000644-94), institutional review board, and the national regulatory authorities. It was conducted in accordance with the Good Clinical Practices and the Declaration of Helsinki. Written informed consent was obtained from each patient before trial entry.

The dataset supporting the conclusions of this article is available on reasonable request and under specific contract at the Biometrics Unit of the Montpellier Cancer Institute (ICM).

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sorafenib (NEX) plus irinotecan (IRI), that is, NEXIRI, treatment. **Methods:** Patients with *RAS*mt mCRC after failure of oxaliplatin, IRI, fluoropyrimidines, and bevacizumab were randomized between NEXIRI (IRI 120-180 mg/m^2 intravenous, D1 = D15 plus oral NEX 400 mg twice a day) versus IRI (180 mg/m^2) versus NEX. Primary endpoint was the 2-month non-progression rate. Secondary endpoints included progression-free and overall survival (PFS and OS), safety, and germline cyclin D1 (*CCND1*) rs9344 polymorphisms analyses. **Results:** A total of 173 patients were included, 59 in NEXIRI, 57 in IRI, and 57 in NEX arms. The 2-month non-progression rate was 52.6% (95% confidence interval [CI]: 39%−66%), 21.4% (10%−33%), and 19.3% (9%−30%) for NEXIRI, IRI, and NEX. Median PFS was 3.6 (95% CI: 2−4.2), 1.7 (1.7−1.8), and 2 (1.8−2.3) months and the median OS was 7.2 (5.8−9.4), 6.3 (4.8−8), and 5.6 (3.9−7.7) months for NEXIRI, IRI, and NEX, respectively. For NEXIRI rs9344*CCND1* A/A genotype patients, OS was 19.6 months (95% CI: 4.8−not reached). Main grade 3 toxicities included neutropenia, febrile neutropenia, diarrhea, hand-foot syndrome, and hypertension. **Conclusions:** In patients with *RAS*mt mCRC who progressed after standard combined chemotherapies, the results of 2-month non-progression rate and median PFS in the NEXIRI arm were in favor of an increase of the time before progression.

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Introduction

Colorectal cancer (CRC) is the third most common cancer type with more than 1,800,000 new cases and about 883,000 deaths worldwide in 2018 according to the GLOBOCAN estimates.[1] Mortality is driven by the occurrence of metastases, which affect nearly half of patients with CRC. Although some patients with metastatic CRC (mCRC) may be cured by surgery alone, most of them present with non-resectable metastases and are treated with various combinations of cytotoxic agents and/or targeted therapies.[2] The latter include fluorouracil, capecitabine, oxaliplatin, irinotecan (IRI), bevacizumab, aflibercept, cetuximab, and panitumumab.[2] Of note, patients with mCRC and tumors that express activating mutations in the *KRAS* exon 2 gene do not benefit from the use of cetuximab and panitumumab.[3-6] Now, these findings have been extended to less frequent mutations of the *RAS* family (also known as expanded *RAS* analysis) that also predict a lack of response to epidermal growth factor receptor inhibitors.[7] At the time this trial was designed, in 2011, there were no effective therapies for patients with CRC with *RAS*-mutated (*RAS*mt) tumors who had failed standard combined chemotherapies and both regorafenib and trifluridine/tipiracil were not available.

The orally administered multikinase inhibitor sorafenib (NEX) inhibits tumor cell proliferation and tumor angiogenesis. It is a potent inhibitor of the mitogen-activated protein kinase pathway, either through inhibition of cell surface tyrosine kinases (eg, VEGFR-2, VEGFR-3, PDGFR-β, c-KIT, FLT-3, and RET) or through the direct inhibition of the serine-threonine kinases Raf-1 and B-Raf.[8,9] It was anticipated that *RAS* mutations would have no negative impact on NEX-induced Raf inhibition because Raf functions downstream of the RAS protein.

Initial preclinical studies showed antitumor activity of NEX, either alone or combined with IRI in CRC cell lines, including *KRAS*mt.[10,11] We conducted a phase I/II study to define the recommended dose and assess the safety, and preliminary efficacy of the NEX/IRI combination (NEXIRI) in a series of 54 heavily pretreated patients with *KRAS*mt mCRC.[12] Oral NEX 400 mg twice daily plus intravenous IRI 180 mg/m^2 was recommended as the dose for phase 2. The main grade 3 adverse events (AE) were as follows: diarrhea (37%), neutropenia (18%), hand-foot syndrome (13%), and grade 4 neutropenia (17%). Disease control was promising, with a rate of 64.9% (95% confidence interval [CI]: 55%−77%). Median progression-free (PFS) and overall survival (OS) were 3.7 months (95% CI: 3.2−4.7) and 8.7 months (95% CI: 4.8−9.7). Interestingly, the germline cyclin D1 (*CCND1*) rs9344 A/A polymorphism was found as a predictor of disease control.[12]

These results taken together, and regarding the lack of alternative treatment at the time of the study design, we initiated a multicenter randomized phase 2 study to evaluate the NEXIRI combination over the single-agents NEX and irinotecan for patients with mCRC with *(K)RAS*mt tumors who had failed standard treatments at the time.

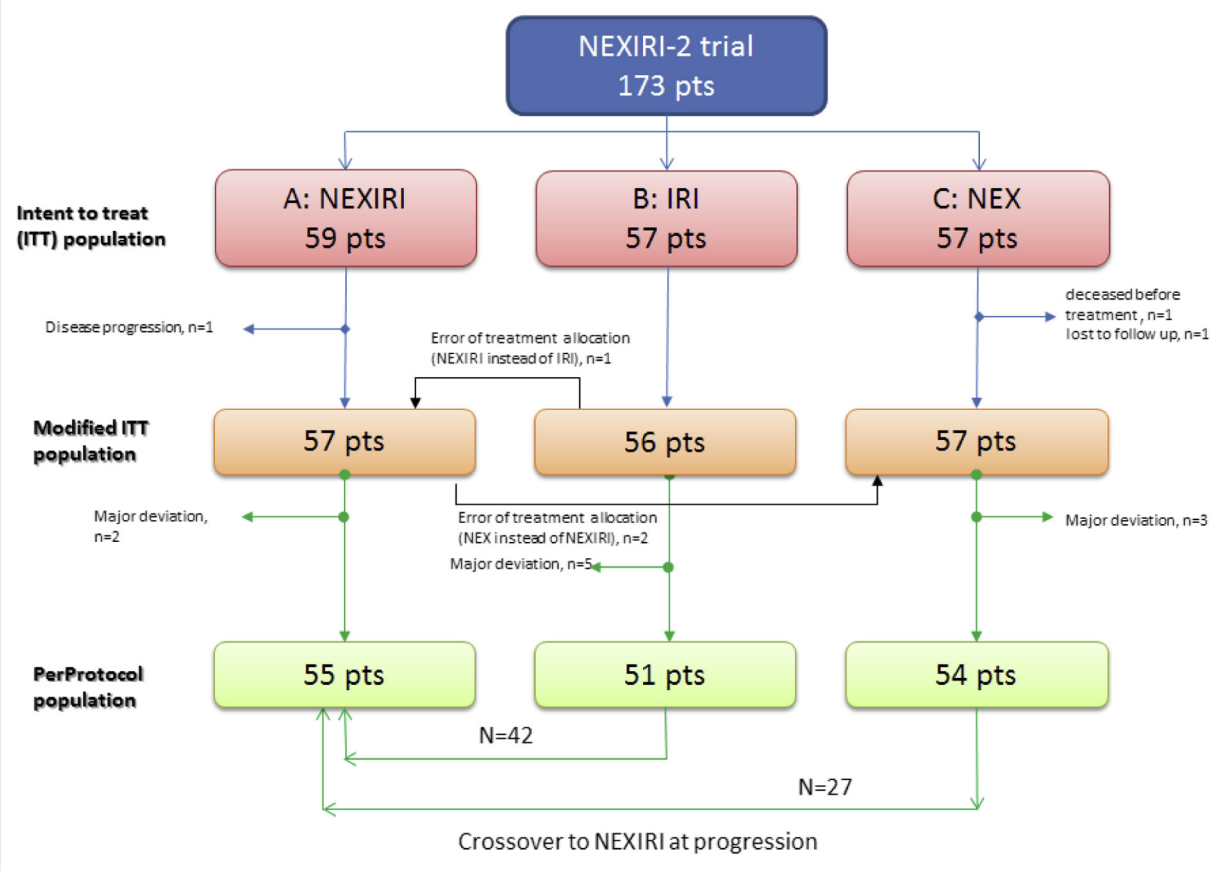
Patients and Methods

The NEXIRI-2/PRODIGE 27 trial was designed to estimate the 2-month non-progression rate for NEXIRI in patients with *(K)RAS*mt mCRC who had progressed under all approved drugs at the time of the study design (2011). IRI and NEX arms served as internal controls, without formal comparison intent. Secondary objectives included disease control and response rates, toxicity, PFS, OS, and quality of life. Exploratory analyses included patient genotyping and tumor immunochemistry for the study of cyclin-D1 polymorphisms and expression compared with the treatment response. The protocol was approved by the local ethics committee and registered on clinical.trials.gov (NCT01715441). The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines.

Patients

Main eligible criteria were histologically confirmed CRC with measurable unresectable metastases and documented progressive disease after failure of all approved drugs (oxaliplatin, IRI, fluoropyrimidines, and bevacizumab) at the time of the study, a KRAS (then extended RAS from November 2013) mutation and a World

Figure 1 Study Flow Chart



Health Organization performance status ≤1, age ≥18 years, life expectancy >3 months, and adequate organ, hematologic and renal functions. Written informed consent was obtained from each patient before trial entry.

Treatment

Randomization was performed (1-to-1-to-1 ratio), with stratification according to the center. In the NEXIRI arm, patients received a 400-mg fixed-dose of oral NEX twice daily, combined with intravenous IRI 120 mg/m^2 over 90 minutes every 2 weeks (cycle 1); doses were increased to 150 mg/m^2 (cycle 2) and 180 mg/m^2 (cycle 3) if patients had no diarrhea > grade 1 and no other toxicity > grade 2. In the IRI-only arm, patients received intravenous IRI 180 mg/m^2 every 2 weeks; in the NEX only arm, they received oral NEX 400 mg twice daily. In the monotherapy arms, a cross-over to NEXIRI was planned at the time of disease progression.

Cyclin D1 Analyses

Germline DNA was extracted from whole blood samples using a QIAamp DNA blood maxi kit (Qiagen, Courtaboeuf, France). The rs9344 (c.723G > A, p. Pro241=) single nucleotide polymorphism (SNP) in the *CCND1* gene that had been demonstrated to be potentially related to treatment responses was analyzed with a method previously described.[13,14] Cyclin D1 protein expression was studied by immunohistochemistry using the rabbit monoclonal antibody EP12 (Dako, Glostrup, Denmark).

Statistical Considerations

The primary endpoint was the 2-month non-progression rate (RECIST v1.1). A single-stage Fleming design with $\alpha = 5\%$ (unilateral) and $\beta = 10\%$ was planned: H0: $p \leq p0$ with p0=50% and H1: $p \geq p1$ with p1=70% (based on an exact binomial approach). It was necessary to include a total of 159 patients, 53 in each arm. A chest-abdomen-pelvis computed tomography (CT) scan was performed every 8 weeks. Tumor responses were confirmed 4 weeks after initial reporting. All CT scans were reviewed by an independent radiologist panel. Toxicities and quality of life were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30. Analyses were performed in per-protocol and intention-to-treat (ITT) populations. Survival durations were defined from the date of randomization and estimates calculated using the Kaplan-Meier method. *P* values were 2-sided and significance was set at $P < .05$. All statistical analyses were performed using STATA.11 software (College Station, TX).

Table 1 Baseline Characteristics of Patients

	NEXIRI n = 59	IRI n = 57	NEX n = 57
Age (y)			
Median (range)	63.0 (35–81)	62.0 (35–77)	60.0 (31–82)
Gender	35/24	31/26	34/23
Male/Female			
WHO Performance Status, n (%)			
0	26 (44.8)	18 (32.1)	21 (36.8)
1	32 (55.2)	37 (66.1)	35 (61.4)
2	0	1 (1.8)	1 (1.8)
Missing	*1*	*1*	*0*
Primary tumor localization, n (%)			
Left colon	34 (57.6)	23 (59.6)	26 (66.7)
Right colon	25 (42.4)	23 (40.4)	19 (33.3)
Metastases, n (%)			
Synchronous	40 (67.8)	36 (63.2)	40 (70.2)
Metastatic sites, n (%)			
Liver	48 (81.4)	43 (75.4)	43 (75.4)
Lung	23 (39.0)	19 (33.3)	19 (33.3)
Nodes	6 (10.2)	5 (8.8)	8 (14.0)
Others	7 (11.9)	8 (14.1)	10 (17.5)
Liver-limited disease	27 (45.8)	30 (53.6)	25 (43.9)
Number of metastatic sites			
1	31 (52.5)	34 (59.6)	33 (57.9)
>1	28 (47.5)	23 (40.4)	24 (42.1)
Previous surgery for primary, n (%)	49 (86.0)	50 (89.3)	48 (84.2)
Previous chemotherapy			
Adjuvant, n (%)	29 (49.2)	29 (50.9)	27 (47.4)
Palliative, n (%)	55 (93.2)	51 (89.5)	52 (91.2)
Number of palliative chemotherapy lines, n (%)			
1	8 (14.5)	8 (15.7)	4 (7.7)
2	28 (50.9)	19 (37.3)	23 (44.2)
3	8 (14.5)	12 (23.5)	12 (23.1)
≥4	9 (16.3)	12 (23.5)	13 (25.0)
Chemotherapy received, n (%)			
Fluorouracil	59 (100.0)	57 (100)	57 (100)
Oxaliplatin	59 (100.0)	57 (100)	57 (100)
Irinotecan	58 (98.3)	57 (100)	57 (100)
Bevacizumab	55 (93.2)	52 (91.2)	55 (96.5)
Ras mutation location, n			
Kras	50	51	51
Exon 2	49	50	49
Exon 3	0	1	2
Exon 4	1	0	0
NRAS	2	1	0
Exon 2	1	1	0
Exon 3	1	0	0
Location not done	7	5	6

Abbreviations: IRI = irinotecan; NEXIRI = NEX + IRI; NEX = sorafenib; WHO = World Health Organization.

Table 2 Two-month Non-progression Rate (Modified Intent-to-Treat Analysis) by Treatment Arm

	NEXIRI N = 57	IRI N = 56	NEX N = 57
2-mo response status			
Nonevaluable	6	4	8
Progressive disease (PD)	21	40	38
Stable disease	28	11	11
Partial response	2	1	0
2-mo non-PD status (ie, success to treatment)	30	12	11
2-month non-PD rate, %	52.6	21.4	19.3
95% confidence interval, %	39.7–65.6	10.7–32.2	9.1–29.6

Nonevaluable patients were analyzed as treatment failures.
Abbreviations: IRI = irinotecan; NEXIRI = NEX + IRI; NEX = sorafenib.

Results

Patients

From September 2012 to July 2014, 173 patients from 17 centers were randomized and represented in the ITT population. A total of 59 patients were allocated to the NEXIRI arm, 57 to the IRI arm, and 57 to the NEX arm (Figure 1). At the time of tumor progression, 69 patients crossed-over to NEXIRI, including 42 of 69 and 27 of 69 patients from the IRI and NEX arms, respectively. The modified ITT population (n = 170) included patients who actually received at least 1 cycle of their allocated treatment. The per-protocol population (n = 160) included the modified ITT population without major deviations (n = 10). The 3 treatment arms were comparable for demographic and baseline characteristics (Table 1).

Treatment

Patients received a median number of treatment cycles of 3 (1–9), 2 (1–7), and 2 (1–8) in the NEXIRI, IRI, and NEX arms, respectively. Patients who crossed-over to NEXIRI received a median number of treatment cycles of 2 (1–8). More than 50% of patients underwent at least 1 dose-reduction at the time they received NEX alone or in combination. Dose-reductions were also observed with IRI, either in the NEXIRI (38 [76%]) or IRI (11 [19.6%]) arms. The median IRI relative dose-intensity was 101.8% (51%–108%) in the IRI arm and 76.3% (48%–103%) in NEXIRI. The median NEX relative dose-intensity was 74.6% (21%–118%) in the NEXIRI arm and 77.7% (26%-101%) in the NEX arm. Patients who crossed-over to NEXIRI had a median IRI relative dose-intensity of 70.0% (35%–104%) and a NEX relative dose-intensity of 66.3% (7%–112%).

Tumor Response

Based on a central review, the 2-month non-progression rate was 30 (52.6%, 95% CI: 39%–66%) of 57, 12 (21.4%, 95% CI: 10%–33%) of 56, and 11 (19.3%, 95% CI: 9%–30%) of 57 in the NEXIRI, IRI, and NEX arms, respectively. Disease control was reported in 30 (50.9%; 95% CI: 38%–64%) of 57 patients, including 2 partial responses in NEXIRI, in 13 (23.2%; 95% CI: 12%–34%) of 56 patients, including 1 partial response in the IRI arm, and in 11 (19.3%; 95% CI: 9%–30%) of 57 patients in the NEX arm. Interestingly, disease control was reported in 29 (42.0%; 95% CI: 30%–54%) of 69 patients, including 1 partial response in patients who crossed-over to NEXIRI at the time of their first tumor progression (Table 2).

PFS and OS

Median follow-up was 17.5 months (95% CI: 14–22). Median PFS was 3.6 months (95% CI: 2.2–4.9), 1.9 months (95% CI: 1.7–2.1), and 2.1 months (95% CI: 1.9–2.5) in the NEXIRI, IRI, and NEX arms, respectively (Figure 2). In the ITT population, median OS was 7.2 months (95% CI: 6–9), 6.3 months (95% CI: 5–8), and 5.6 months (95% CI: 4–8) in the NEXIRI, IRI, and NEX arms, respectively. OS of patients treated with NEXIRI as first intent or after crossover (7.9 months [95% CI: 7.1–8.7]) were similar.

Safety

Focusing on NEXIRI, the most frequently reported AEs (all grades) per patient (modified ITT population, n = 57) were as follows: diarrhea (93%), fatigue (71%), anemia (70%), appetite loss (53%), vomiting (46%), hand-foot skin reaction (42%), neutropenia (44%), stomatitis (33%), and rash (30%). Maximal severe (grades 3 and 4) AEs per patient were found in 48 (84.2%) of 57, 33 (58.9%) of 56, and 48 (84.2%) of 57 patients in the NEXIRI, IRI, and NEX arms, respectively (Table 3). One death was considered possibly related to the study treatment in the NEX arm (pulmonary embolism).

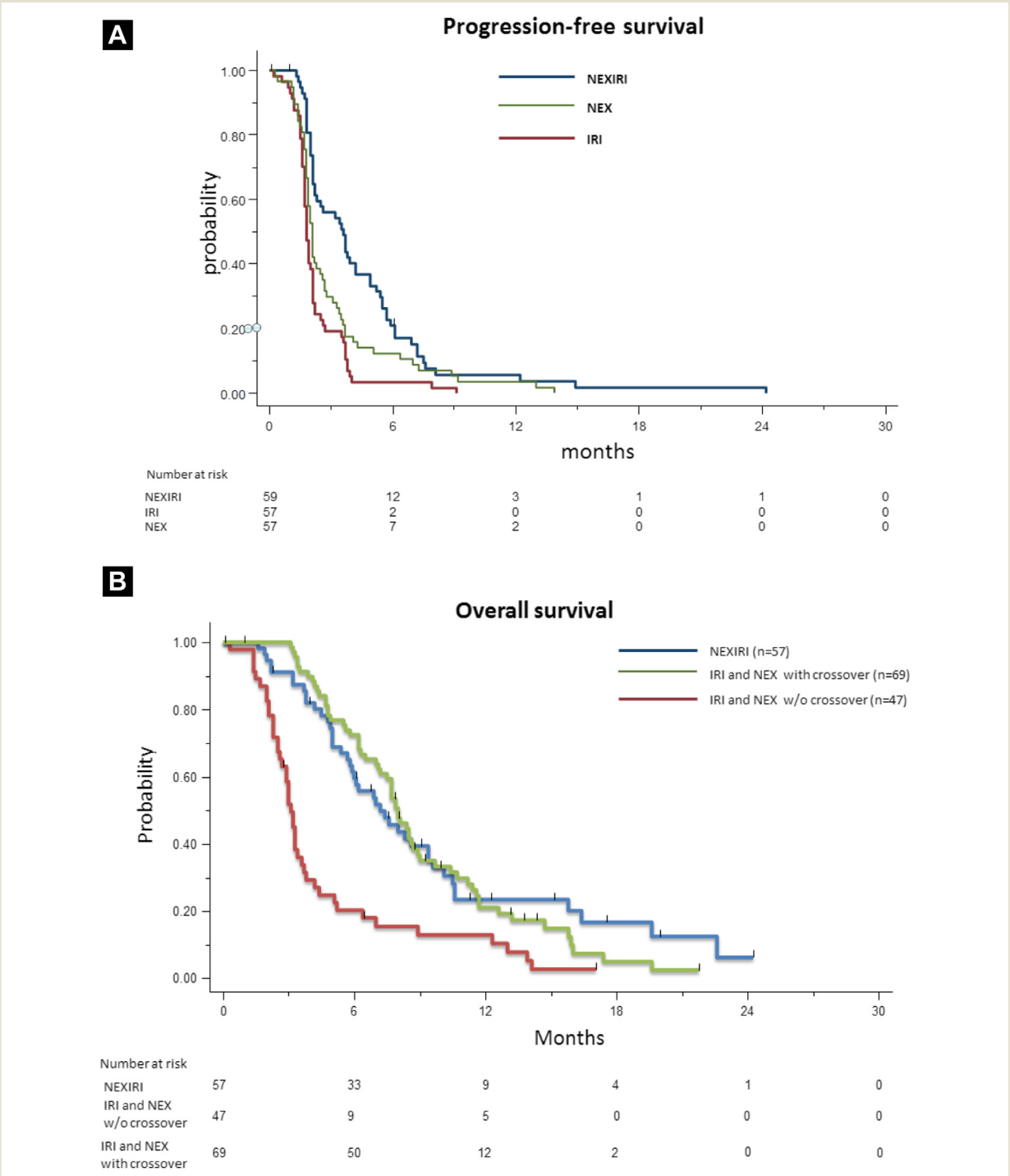
Quality of Life

Baseline quality of life (global health score) was similar in the 3 treatment arms, and did not change at 2 months.

Patient Genotyping

A total of 130 blood samples were collected. For the rs9344 *CCND1* polymorphism, the frequency of the different genotypes (A/A, A/G, and G/G) alleles was not significantly different among the 3 arms. Notably, 33 patients (25.4%) were homozygous for the A allele (A/A), 27 patients (20.8%) for the G allele (G/G), and 70 (53.8%) were heterozygous (A/G). Genotype frequencies did not deviate from the Hardy-Weinberg equilibrium in the NEXIRI, IRI, and NEX arms. For NEXIRI, a significant correlation was found

Figure 2 (A) Progression-free (PFS) and (B) Overall Survival (OS) Data For Patients Who Received NEXIRI Versus Those Who Received IRI or NEX



Abbreviations: IRI = irinotecan; NEXIRI = NEX + IRI; NEX = sorafenib.

between the rs9344 *CCND1* polymorphism and tumor responses, and improved median survival was reported in these patients compared with patients with other genotypes. In patients with this rs9344*CCND1* A/A genotype treated with NEXIRI, the median OS was 19.6 months compared with 7 months in patients exhibiting other genotypes (Table 4).

Table 3 Grade 3–4 Adverse Events (AEs) by Treatment Arm

Toxicities, n (%)	NEXIRI n = 57	IRI n = 56	NEX n = 57	*P*-Value
Gr. 3–4 AEs of any kind	48/57 (84.2)	33/56 (58.9)	48/57 (84.2)	.001
Gr. 3–4 gastrointestinal AEs	20 (35.1)	7 (12.5)	13 (22.8)	.004
Diarrhea (gr. 3)	15 (26.3)	4 (7.1)	4 (7.0)	<.001
Nausea (gr.3)	2 (3.5)	0	1 (1.8)	.036
Vomiting (gr. 3 and gr.4)	4 (7.0)	1 (1.8)	1 (1.8)	ns
Mucositis/Stomatitis (gr. 3)	0	1 (1.8)	3 (5.3)	ns
Anorexia (gr. 3)	3 (5.3)	3 (5.4)	5 (8.8)	ns
Gr. 3 cutaneous AEs	10 (17.5)	0	14 (24.6)	<.001
Hand-foot skin reaction	10 (17.5)	0	9 (15.8)	<.001
Rash	1 (1.8)	0	2 (3.5)	.002
Gr. 3-4 hematological AEs	11 (19.3)	4 (7.3)	0	.006
Neutropenia				
Gr. 3	9 (15.8)	3 (5.4)	0	.044
Gr. 4	1 (1.8)	0	0	
Febrile neutropenia (gr. 3)	3 (5.3)	0	0	.004
Anemia (gr. 3)	1 (1.8)	2 (3.6)	0	
Thrombopenia (gr. 3)	1 (1.8)	1 (1.8)	0	

Abbreviations: Gr. = grade; IRI = irinotecan; NEXIRI = NEX + IRI; NEX = sorafenib; ns = not significant.

Protein Expression in Tumor Tissues

Formalin-fixed paraffin-embedded tissues were available for 111 patients. Cyclin D1 expression was not associated with treatment efficacy, toxicity, or patient outcome (data not shown). The rs9344 *CCND1* polymorphism was not associated with any specific pattern of cyclin D1 expression, either in terms of location (nuclear and/or cytoplasmic) or level of expression.

Discussion

In this population of patients with mCRC with *(K)RAS*mt tumors refractory to standard combined chemotherapies at the time of the study design (2011), the clinical results (toxicity, disease control rate, PFS and OS) of the NEXIRI combination are in line with those previously published[12] in our phase I/II study (overview of the main clinical results in Supplemental Table 1 in the online version). Disease control exceeded 50%, median PFS was 3.7 months, and median OS ranged from 7 to 8 months with an acceptable toxicity (17.5% severe hand-foot syndrome, 17.6% severe neutropenia, 26% severe diarrhea). The latter rate is lower than the one (35%) we reported in the NEXIRI-1 phase I/II trial,[12] probably related to the modification of the IRI dose administered in the NEXIRI2 regimen: IRI was started at 120 mg/m^2, and then increased in cases of good tolerance (no diarrhea > grade 1 and no other toxicity > grade 2) or decreased in cases of toxicity (diarrhea > grade 1 or other toxicity > grade 2). We acknowledge that NEXIRI-2 was not designed as a comparative study; however, it appears that NEXIRI provides numerically better 2-month non-progression rate, disease control rate, and median PFS than IRI or NEX without hampering quality of life. There is no apparent difference in OS across the different treatment arms of this NEXIRI-2 trial, but 40% of patients from the NEX and IRI arms crossed-over to NEXIRI. It should be noted that the OS curve of patients who crossed-over to NEXIRI appeared to be similar to that of patients who were primarily randomized in the NEXIRI arm. These features reinforce our understanding that NEXIRI has an impact on OS over NEX or IRI in patients with *(K)RAS*-mutated tumors that are refractory to standard combined chemotherapies at that time.

Interestingly, our ancillary study on rs9344 CCND1 polymorphisms confirms our previous findings, that is, patients treated with NEXIRI who harbored the A/A variant were more likely to be disease-controlled than patients with other genotypes. Moreover, these A/A individuals had numerically better median PFS (5.3 vs. 3.1 months) and median OS (19.6 vs. 7 months) than patients with other genotypes when treated with NEXIRI. To a far lesser extent, this better outcome with the A/A variant also applies to patients treated with IRI or NEX. In our study, rs9344 genotype was unrelated to the level of expression and localization of cyclin D1 protein. This common polymorphism (24%-30% in the European and North American population) is known to modulate the splicing of cyclin CCND1 to produce 2 transcripts (messenger RNA [mRNA]a and mRNAb). The A allele preferentially encodes a truncated mRNA (mRNAb) with an altered C-terminal domain, lacking the exon 5 coding for a protein-destabilizing (PEST) destruction box.[14] This transcript encodes a more stable CCND1 protein that may result in a higher concentration of CCND1 within the cell. Nevertheless, both transcripts are present with all genotypes.[15] This disconnection between genotype and protein expression may be also associated with the nature of immunohistochemistry that is a semiquantitative technology and cannot reveal subtle expression level changes. In this way, quantification of each mRNA transcript by reverse-transcriptase quantitative polymerase chain reaction may be a better alternative. Moreover, the antibody selected for the present study is described as recognizing preferentially proteins derived from the G allele,

Table 4 Two-month Nonprogressive Disease Rate, Median Progression-Free Survival (PFS), and Median Overall Survival (OS) by Treatment Arms and CCND1 rs9344 Genotypes

	NEXIRI n = 45		IRI n = 45		NEX n = 40		All Patients n = 130	
CCND1 rs9344 Genotypes	A/A Genotype n = 12	Other Genotypes n = 33	A/A Genotype n = 10	Other Genotypes n = 35	A/A Genotype n = 11	Other Genotypes n = 29	A/A Genotype n = 33	Other Genotypes n = 97
2-mo non-progressive disease rate (%)	11/12 (91.5)	15/33 (45.5)	0/10	10/35 (28.6)	0/11	8/29 (27.6)	11/33 (33.3)	31/97 (32)
Median PFS (months)	5.3	3.1	1.7	1.7	1.9	1.9	2.3[a]	1.9[a]
95% CI	1.6–5.7	1.9–4.9	0.8–2.0	1.6–1.8	1.6–3.9	1.7–2.1	1.8–3.9[b]	1.8–2.1[b]
Median OS (months)	19.6	7	9	6.2	8.1	4.4	10.5[c]	5.8[c]
95% CI	4.8–NR	5.0–9.4	1.4–11.7	3.8–7.7	3.0–13.9	3.6–7.5	5.4–12.6[d]	4.8–7.4[d]

Abbreviations: CI = confidence interval; IRI = irinotecan; NEXIRI = NEX + IRI; NEX = sorafenib; NR = non-reported.
[a]These are the 2-mo-non-progressive values in months of median PFS for the global population of the study (not per type of treatment arm but all patients) for A/A genotype patients and other genotype patients respectively.
[b]Idem for PFS CI values, all patients.
[c]Idem for OS values.
[d]Idem for OS CI vlaues.

whereas antibodies directed against a common region to both variant proteins will be more adequate. In addition, the absence of relation between the A/A genotype and CCND1 expression level in CRCs as previously been reported.[16] Finally, one may not exclude the hypothesis of a functional alteration in cyclin D1 linked to the studied SNP that is not detected in IHC expression. Similarly, Dahan et al.[17] previously reported a better response and longer median time to progression for patients harboring the rs9344*CCND1* A/A genotype in a series of patients with mCRC treated with a cetuximab-irinotecan combination. The rs9344 *CCND1* polymorphisms, especially the A/A variant, may be considered as a marker of favorable outcomes in patients with mCRC treated with anti-proliferative agents and warrants further validation.

Despite these promising results, NEXIRI-2 did not reach its primary objective. As per protocol, NEXIRI-2 could have been a positive trial if 31 patients (instead of 30) from the NEXIRI arm had been found non-progressive at 2 months. Unfortunately, our primary criterion, the 2-month non-progression rate, was too stringently defined with no room to accept more or less than 1 week around the 2-month non-progression rate point assessment. The NEXIRI-2 results should be interpreted carefully because it has other limitations such as its limited size and non-comparative design.

Because we ran this NEXIRI-2 trial, 2 new compounds, regorafenib and trifluridine/tipiracil, have become available as salvage therapies for patients with mCRC who failed standard treatments (Supplemental Table 1 in the online version). In brief, regorafenib, an oral multikinase agent that inhibits angiogenic, stromal, and oncogenic receptor tyrosine kinases (including VEGFR1/3, PDGFR-b, FGFR-1, TIE-2, c-KIT, RET, RAF1, and B-RAF),[18] has been shown to increase OS over placebo in patients with mCRC who progressed on standard therapies.[19] Furthermore, the clinical benefit of regorafenib in terms of OS and PFS was of the same magnitude in patients with *KRAS*mt or *KRAS*-wild-type tumors.[19] Although it is hazardous to compare results across different studies, it was observed that NEXIRI provides numerically better disease control, median PFS, and median OS than regorafenib or placebo in the CORRECT trial.[20] This is indeed remarkable, as patients from NEXIRI-2 were all *(K)RAS*mt (vs. 54%) and appeared to be more heavily pretreated than patients from the CORRECT study. Subsequently, a significant OS and PFS benefit over placebo was reported with the cytotoxic agent trifluridine/tipiracil, a combination of the fluoropyrimydin trifluridine to a thymidine phosphorylase inhibitor.[21] This survival improvement was observed in both *KRAS*mt and *KRAS*wt tumors.[21]

This NEXIRI-2 trial provides additional evidence that the NEXIRI combination can delay disease progression in patients with mCRC with *RAS*mt tumors who progress after all approved standard combined chemotherapies at the time the study was designed. The NEXIRI combination does not pretend to qualify as a new standard, accounting with the newly developed oral therapies such as regorafenib or trifluridine/tipiracil. However, our trial results open perspectives of new combined treatments, that is, chemotherapies and newly approved oral tyrosine kinase inhibitors such as regorafenib, in patients with mCRC, especially in the rs9344*CCND1* A/A subgroup of patients.

Clinical Practice Points

- The therapeutic options for patients with *RAS*mt mCRC are limited compared with those for patients with *RAS*wt. At the time this current trial was designed, there were no effective therapies for patients with CRC with *RAS*mt tumors who had failed standard combined chemotherapies and regorafenib or trifluridine/tipiracil were not available.
- The randomized phase 2 NEXIRI-2 study assessed the combination of irinotecan and sorafenib (NEXIRI) versus irinotecan (IRI) versus sorafenib (NEX) in 173 patients with *RAS*mt mCRC refractory to standard combined chemotherapies. The 2-month non-progression disease rate (primary endpoint of the study) was numerically favorable to the NEXIRI arm, 52.6% (95% CI: 39%−66%) versus 21.4% (10%−33%), and 19.3% (9%−30%) in monotherapy arms of IRI and NEX, respectively. Median PFS was also greater 3.6 (95% CI: 2.0−4.2) versus 1.7 (1.7−1.8), and 2 (1.8−2.3) months, respectively. For NEXIRI rs9344*CCND1* A/A genotype patients, median OS was 19.6 months (95% CI: 4.8−not reached) versus 7 months for other genotypes.
- The NEXIRI combination does not pretend to qualify as a new standard, accounting with the newly developed oral therapies such as regorafenib or trifluridine/tipiracil. However, our trial results open perspectives of new combined treatments, that is, chemotherapies and newly approved oral tyrosine kinase inhibitors such as regorafenib, in patients with mCRC, especially in the rs9344*CCND1* A/A subgroup of patients with an ongoing French randomized phase 2 study NEXT-REGIRI (NCT03829462) assessing regorafenib + irinotecan versus regorafenib alone in patients with mCRC refractory to standard treatment combinations.

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Disclosures

The following authors have declared conflicts of interest for honoraria (participation to boards, experts, advisory role or speaker), research funding or travel and meeting expenses: E. Samalin: Lilly, Amgen, Bayer, Ipsen, Sanofi, Roche, and Merck; C. de la Fourchardière: Bayer; V. Boige: Bayer, Merck Sereno, MSD, Roche, Sanofi, Ipsen, Amgen. R. Guimbaud: Roche, Ipsen, Novartis, Merck, Bayer, Servier, Keocyt, MSD; J. Taieb: Roche, Amgen, MSD, Merck, Sanofi, Servier, Shire, Lilly, Sirtex; E. François: Roche, Merck, Amgen, Sanofi, Servier, Bayer; M.-P. Galais:

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Supplemental Data

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Supplemental Data

Supplemental Table 1 Sorafenib, Sorafenib Plus Irinotecan, Regorafenib, and TAS-102 in *(K)RAS*mt mCRC Tumors Refractory to Standard Therapies: Overview of the Main Clinical Results

	Nexiri-1	Nexiri-2		Correct		Recourse	
	NEXIRI	NEXIRI	NEX	REGO	Placebo	Placebo	TAS-102
No. of patients	54	59	57	505	255	266	534
1 metastatic site, % *(K)RAS*mt, %	51.8	52.5	57.9	NR	NR	NR	NR
Previous chemotherapy, %	100	100	100	54	62	51	51
Fluorouracil	100	100	100	83	87	100	100
Bevacizumab	90.7	93.2	96.5	80	84	100	100
Irinotecan	100	98.3	100	80	90	100	100
Oxaliplatin	96.3	100	100	55	63	100	100
DCR, % (95% CI)	64.9 (51–77)	50.9 (37.9–63.9)	19.3 (09–30)	41 (36.7–45.3)	14.9 (10.5–19.3)	16 (11.4–20.2)	44 (37.2–45.6)
Median PFS (m) (95% CI)	3.7 (3.2–4.7)	3.7 (2.2–4.9)	2.1 (1.9–2.5)	1.9 NR	1.7 NR	1.7 (1.7–1.8)	2 (1.9–2.1)
Median OS (m) (95% CI)	8.0 (4.8–9.7)	7.2 (5.8–9.4)	5.6 (4–8)	6.4 NR	5 NR	5.3 (4.6–6)	7.1 (6.5–7.8)
12-mo OS, %	26	21	15	24.3	24	18	27
Toxicity, %							
Gr 3–4 diarrhea	37	26.3	07	08	09	04	02
Gr 3 HFSR	13	17.5	24.6	17	09	0	0
Gr 3–4 neutropenia	35.2	17.6	0	NR	NR	0	38

Abbreviations: CI = confidence interval; DCR = disease control rate; GT = grade; HFSR = hand-foot skin reaction; NEX = Sorafenib; NEXIRI = NEX + IRI; NR = Nonreported; OS = overall survival; 12-m OS: 12-month overall survival rate; PFS = progression-free survival; *RAS*mt = *RAS* mutated.