A Randomized Phase II Trial of Vismodegib Versus Placebo with FOLFOX or FOLFIRI and Bevacizumab in Patients with Previously Untreated Metastatic Colorectal Cancer

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Running title: Vismodegib with Chemotherapy in Metastatic Colorectal Cancer

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Disclosure of Potential Conflicts of Interest
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JB provided paid and unpaid consultancy to Roche–Genentech prior to becoming the principal investigator of this study and has received research funding from Roche–Genentech.

JCB, IF, and MFM have no potential conflicts of interest to declare. LLH's institution has received research funding from Roche–Genentech. IG has received research funding from Genentech. RCH has provided paid consultancy to and received research funding from Genentech. MMZ has received research funding from Roche. HMM, RLY, RAG, GLB, and JAL are employed by Roche–Genentech and own Roche stock.

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Translational Relevance

Hedgehog pathway inhibitors show antitumor activity across various tumor types and have demonstrated preclinical activity in colorectal cancer (CRC) models. In this randomized controlled study, vismodegib, a first-in-class small-molecule Hedgehog pathway inhibitor, was combined with FOLFOX or FOLFIRI chemotherapy plus bevacizumab for the first-line treatment of metastatic CRC. This is the first phase II trial of a Hedgehog pathway inhibitor in a tumor type that is not known to harbor mutations in the Hedgehog signaling pathway and tested the hypothesis that inhibition of paracrine signaling between tumor cells expressing Hedgehog ligands and nearby stromal cells may inhibit tumor growth in the setting of cytoreductive chemotherapy. The results failed to demonstrate incremental benefit from the addition of vismodegib to standard-of-care first-line therapy for CRC. Combined toxicity is one potential factor contributing to lack of efficacy. Overall, the results suggest that further testing of vismodegib in metastatic CRC is not warranted.
Abstract

Purpose: Vismodegib, a Hedgehog pathway inhibitor, has preclinical activity in colorectal cancer (CRC) models. This trial assessed the efficacy, safety, and pharmacokinetics of adding vismodegib to first-line treatment for metastatic CRC (mCRC).

Experimental design: Patients were randomized to receive vismodegib (150 mg/day orally) or placebo, in combination with FOLFOX or FOLFIRI chemotherapy plus bevacizumab (5 mg/kg) every 2 weeks until disease progression or intolerable toxicity. The primary endpoint was progression-free survival (PFS). Key secondary objectives included evaluation of predictive biomarkers and pharmacokinetic drug interactions.

Results: A total of 199 patients with mCRC were treated on protocol (124 FOLFOX, 75 FOLFIRI). The median PFS hazard ratio for vismodegib treatment compared with placebo was 1.25 (90% CI: 0.89–1.76; \( P = 0.28 \)). The overall response rates for placebo-treated and vismodegib-treated patients were 51% (90% CI: 43–60) and 46% (90% CI: 37–55), respectively. No vismodegib-associated benefit was observed in combination with either FOLFOX or FOLFIRI. Increased tumor tissue Hedgehog expression did not predict clinical benefit. Grade 3–5 adverse events reported for >5% of patients that occurred more frequently in the vismodegib-treated group were fatigue, nausea, asthenia, mucositis, peripheral sensory neuropathy, weight loss, decreased appetite, and dehydration. Vismodegib did not alter the pharmacokinetics of FOLFOX, FOLFIRI, or bevacizumab.
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**Conclusions:** Vismodegib does not add to the efficacy of standard therapy for mCRC. Compared with placebo, treatment intensity was lower for all regimen components in vismodegib-treated patients, suggesting that combined toxicity may have contributed to lack of efficacy.
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Introduction

For patients receiving first-line therapy for metastatic colorectal cancer (mCRC), fluoropyrimidine chemotherapy (parenteral 5-fluorouracil [5-FU]/leucovorin (LV) or oral capecitabine) in combination with oxaliplatin (FOLFOX or XELOX) or irinotecan (FOLFIRI) and bevacizumab (Avastin®, Genentech, South San Francisco, CA, USA) are considered to be standard-of-care regimens (1-4).

The Hedgehog (Hh) signaling pathway represents a novel target for cancer therapy. Excessive or inappropriate secretion of the Hh ligand by tumor epithelium, which initiates pathway activation in the tumor stroma via a paracrine mechanism, has been implicated in the pathogenesis of sporadic cancers of the gastrointestinal tract, lung, and prostate, suggesting that disruption of Hh signaling may be beneficial (5-9). Recent experience has shown that Hh pathway inhibitors can indeed inhibit the growth of a number of tumor types (10).

The Hh pathway inhibitor vismodegib (Erivedge™, GDC-0449; Genentech, South San Francisco, CA, USA) showed oral bioavailability and potent antitumor activity as a single agent and in combination with cytotoxic agents (e.g., irinotecan) in a variety of primary human tumor xenografts (9, 11).

Vismodegib was evaluated in a phase I study of patients with refractory solid tumors and advanced basal cell carcinoma (12-14). The most common toxicities were mild-to-moderate fatigue, anorexia, muscle spasms, alopecia, and dysgeusia. Preliminary efficacy was demonstrated in patients with advanced basal cell carcinoma and medulloblastomas and the dose...
Vismodegib with chemotherapy in metastatic colorectal cancer recommended for phase II clinical studies was 150 mg orally, once daily (13, 15). As no overlapping toxicities between vismodegib and the components of FOLFOX and FOLFIRI with bevacizumab were expected based on single-agent vismodegib studies, a safety "run-in" evaluation of combination therapy was performed as part of a single, phase II, proof-of-concept study rather than conduct a separate phase Ib safety study. Bevacizumab was included in these regimens as it is a standard part of first-line therapy for colorectal cancer (CRC).

This phase II study was designed to assess whether vismodegib would prolong progression-free survival (PFS) when combined with standard-of care therapy (either FOLFOX or FOLFIRI in combination with bevacizumab) in patients requiring first-line treatment for mCRC. Safety and pharmacokinetic outcomes were also assessed. Hh ligand expression in CRC was evaluated by examining archival tumor tissues, to determine its utility as a predictive biomarker for vismodegib clinical benefit.

Materials and Methods

Patient eligibility

Eligible patients were ≥18 years of age, with histologically confirmed mCRC and Response Evaluation Criteria in Solid Tumours (RECIST) (v.1.0) measurable or evaluable disease, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and adequate bone marrow, hepatic, and renal function.

All eligible patients were required to provide archival tumor samples for analysis of the putative predictive biomarker (Hh ligand expression) and other
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exploratory biomarkers either in the form of unstained thick sections or formalin-fixed, paraffin-embedded (FFPE) tissue blocks. Patients who received prior systemic therapy for metastatic disease at any time or adjuvant chemotherapy within 6 months of study entry were ineligible.

All patients provided written informed consent according to federal and institutional guidelines prior to any study-related procedures and after institutional review board approval of the study.

Study design and treatments

This was a randomized, placebo-controlled, double-blind study of vismodegib in combination with standard-of-care regimens (FOLFOX–bevacizumab or FOLFIRI–bevacizumab) for mCRC. Patients were randomized 1:1 and stratified on the basis of the chemotherapy regimen chosen by the physician and whether or not at least one measurable lesion was present at baseline as defined by RECIST.

On day 1 of each 2-week cycle all patients received bevacizumab, 5 mg/kg intravenously (IV) over 90 minutes for the first infusion (shortened to 30–60 minutes as tolerated for subsequent infusions). For the modified FOLFOX6 (16) cohort, bevacizumab was followed by oxaliplatin, 85 mg/m² IV over 90 minutes, with LV 400 mg/m² IV over 120 minutes; this was followed by 5-FU 400 mg/m² as an IV bolus and 5-FU 2400 mg/m² as a continuous infusion over 44–48 hours. In the FOLFIRI (17) cohort (after bevacizumab administration), irinotecan 180 mg/m² was given IV over 90 minutes with LV (as described above) followed by 5-FU, as described above for FOLFOX6. Vismodegib, 150 mg orally, or placebo, was self-administered once daily.
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beginning on cycle 1, day 3. Study treatment continued until documented disease progression or the occurrence of intolerable toxicity.

Doses of 5-FU/LV, oxaliplatin, or irinotecan could be reduced due to toxicity according to study or institutional guidelines. No bevacizumab or vismodegib/placebo dose reductions were permitted.

Daily vismodegib or placebo administration could be interrupted due to toxicity for up to 8 weeks, after which administration was permanently discontinued if not re-started. Patients could discontinue one or more study regimen components (including vismodegib or placebo) due to toxicity while continuing other regimen components at full or reduced doses.

Study assessments were performed after approval by local human investigations committees at each center and the study was conducted in accordance with an assurance filed with and approved by the Department of Health and Human Services.

Response assessments

Patients were evaluated for response and disease progression by computed tomography or magnetic resonance imaging every 8–9 weeks while on study. Confirmation of objective response (OR) was required at least 4 weeks after the initial scans showed a response.

For patients without measurable disease at baseline, disease progression was defined by an increase in the size of an unmeasurable lesion to a size that became measurable or would be considered progression of a non-target lesion by RECIST v.1.0, the occurrence of a new lesion not detected on previous scans, and/or new onset of cytologically confirmed malignant ascites or malignant pleural effusion. Post-progression, patients were followed for
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survival every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by the study sponsor.

Safety plan

After initiation of study treatment, all adverse events and serious adverse events, regardless of attribution, were reported until 45 days after the last administration of vismodegib or placebo. Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) v.3.0. Thereafter, only serious adverse events thought to be related to study treatment, and pregnancy that occurred up to 12 months after the last dose of vismodegib or placebo, were reported.

Pharmacokinetic assessments

Pharmacokinetic parameters (including an investigation into possible drug–drug interactions) were assessed from blood samples taken at defined intervals before and after treatment. For all patients, blood samples were drawn for the determination of vismodegib steady-state concentrations approximately every 8 weeks. A subset of patients (n = 19) at five clinical sites underwent extensive pharmacokinetic sampling every 2 weeks; 10 patients received FOLFOX–bevacizumab (four vismodegib and six placebo) and nine patients received FOLFIRI–bevacizumab (six vismodegib and three placebo). Levels of irinotecan and metabolites (SN-38 and SN-38 glucuronide), total and ultrafilterable platinum (as an estimate of oxaliplatin), 5-FU, and vismodegib were determined in plasma samples, whereas bevacizumab was measured in serum samples. All analytes were analyzed using validated assays (18).
Evaluation of putative predictive biomarkers

The diagnosis of CRC from archival tumor tissue samples obtained at baseline was verified by a pathologist. If overall tumor content was <75%, serially cut slides were macrodissected prior to nucleic acid isolation to enrich for tumor.

Quantitative reverse transcription polymerase chain reaction (qRT-PCR) profiling of Hh pathway genes

Tissue scraped from serially cut slides was deparaffinized using Envirene reagent (Hardy Diagnostics, Santa Maria, CA, USA) prior to isolation of RNA using the Roche High Pure FFPE RNA Micro Kit (Roche Diagnostics, Indianapolis, IN, USA). RNA was reversed transcribed using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA, USA) with random primers. PCR was carried out using the Taqman Universal PCR Master Mix (Applied Biosystems), according to the following cycling conditions: 50°C for 2 minutes; 95°C for 10 minutes; 40 cycles of 95°C for 15 seconds and 60°C for 1 minute. In order to detect both the Sonic Hh (SHH) and Indian Hh (IHH) ligand transcripts within the same reaction, an assay (SHH+IHH) was designed to cross-react with both ligand transcripts. In addition, assays were designed to specifically detect either the SHH or IHH ligand transcripts. The Desert Hh (DHH) ligand transcript was undetectable in banked colorectal tumor specimens (data not shown), and hence was not evaluated in this study. All assays were tested for amplification efficiency on RNA isolated from FFPE specimens and for lack of genomic DNA amplification. For analyses, Hh pathway gene expression was normalized to
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the average cycling threshold (Ct) of three housekeeping genes (GUSB, SDHA, and UBC). Primer/probes used are shown in Supplementary Table B1.

**KRAS genotyping**

Tissue scraped from serially cut slides was deparaffinized using Envirene reagent (Hardy Diagnostics) prior to isolation of DNA using the QIAamp DNA FFPE Tissue Kit (Qiagen, Manchester, UK). KRAS was genotyped using the DxS K-Ras Mutation Kit (DxS Limited, Manchester, UK), according to the manufacturer’s instructions.

**Statistics**

All efficacy analyses were conducted using the intent-to-treat (ITT) population defined as all randomized patients.

The primary analysis for this study was estimation of the PFS hazard ratio (HR) and its 90% confidence interval (CI) using a Cox proportional hazards model stratified by chemotherapy regimen and measurable versus evaluable disease, based on assessments of response and progression at each investigative site. Stratified and unstratified log-rank tests were also specified. PFS was defined as the time from randomization until the earlier of disease progression or death due to any cause within 30 days of study discontinuation. Patients who discontinued the study without a PFS event were censored at the time of their last tumor assessment.

This trial was designed to be hypothesis generating, and the sample size was determined based on a 90% confidence interval for the PFS HR, with 90 events and an assumed HR of 0.75. The study planned for accrual of 150
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patients. Due to a higher than expected early drop-out rate prior to progression, the protocol was amended to enroll an additional 40 patients.

Kaplan–Meier estimates were used to describe time to event endpoints.

A key secondary analysis was the inclusion of Hh-ligand expression in the Cox proportional hazards model specified in the primary analysis as either a continuous or semi-quantitative variable using apparent or meaningful ordinal groupings. Exploratory efficacy analyses included the effects of Hh ligand expression on OR rate (ORR) and overall survival (OS) and of other downstream pathway intermediaries on PFS, ORR, and OS.

Safety analyses included all patients who received at least one dose of vismodegib or placebo, and included summaries of adverse events, serious adverse events, and adverse events leading to discontinuation of chemotherapy, bevacizumab, or vismodegib/placebo.
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Results

Patient population

Between March 2008 and July 2009, 199 patients from 35 study sites in the United States were randomized to receive either vismodegib or placebo plus standard-of-care treatment (Fig. 1). A total of 101 and 98 patients were assigned to receive placebo and vismodegib, respectively. Three patients (one vismodegib, two placebo) did not receive any investigational drug treatment after randomization.

One hundred ninety-six patients who received at least one dose of investigational drug were evaluable for safety. One patient randomized to placebo erroneously received vismodegib for part of his treatment. This patient is allocated to the placebo arm for demographics and efficacy summaries and the vismodegib arm for safety and exposure summaries. A total of 124 evaluable patients were treated with FOLFOX–bevacizumab, and 75 were treated with FOLFIRI–bevacizumab (Table 1). All study patients except one had at least one measurable lesion at baseline. The data cutoff for the efficacy analyses was March 15, 2010 and the median duration of follow-up was 12.6 months. Safety analyses included all data through the conclusion of the study, December 10, 2010. A total of 140 (70%) patients provided archival tumor tissue that was adequate for assessment of Hh ligand expression by qRT-PCR. In contrast, 90 (45%) patients provided tumor tissue suitable (i.e., freshly cut tissue sections derived from FFPE blocks) for optimal immunohistochemistry (IHC) results. Hence, we focused our Hh ligand, predictive biomarker analysis using qRT-PCR assay methodology. A total of
165 (83%) patients provided tumor tissue adequate for determining KRAS mutation status (19).

Baseline demographic and disease characteristics for the all-randomized study population were mostly balanced between placebo and vismodegib treatment groups (Table 1). There were no meaningful differences in baseline characteristics between subgroups defined for the purpose of assessing the predictive value of putative biomarkers (e.g., Hh ligand expression, KRAS mutation status) on PFS (data not shown).

**Efficacy**

Vismodegib in combination with standard-of-care treatment for first-line mCRC did not confer incremental clinical benefit as measured by PFS (Table 2, Fig. 2A) or ORR (Table 2). The HR of PFS for the all-randomized patient population was 1.25 (90% CI: 0.89–1.76; \( P = 0.28 \)). The ORRs for placebo and vismodegib-treated patients were 51% (90% CI: 43–60) and 46% (90% CI: 37–55), respectively (Table 2).

There was no vismodegib-associated clinical benefit as measured by either PFS or ORR in patient subgroups defined by chemotherapy regimen (data not shown).

Forty-five patients had died at data cutoff, yielding 12-month Kaplan–Meier OS rates of 80.1% and 81.4% for placebo-treated and vismodegib-treated patient groups, respectively (Table 2).

Increased levels of Hh ligand expression in tumor tissue, as assessed by qRT-PCR (Fig. 2B) or IHC (data not shown), did not correlate with an improvement in median PFS. Additionally, there were no differences in median PFS estimates based on KRAS mutational status (Fig. 2B) or
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expression levels of exploratory mRNA biomarkers including SMO and two pathway transcriptional target genes, GLI1 and PTCH1 (data not shown).

Safety

A pre-planned, interim, blinded review of adverse events, treatment exposure, and study discontinuations did not identify differences in the frequency or severity of adverse events as a function of treatment arm and the study was continued.

In the final analysis, grade 3–5 fatigue, nausea, asthenia, mucositis, peripheral sensory neuropathy, weight loss, decreased appetite, and dehydration were ≥5% more frequent in vismodegib-treated patients, regardless of chemotherapy regimen (Table 3). Compared with placebo, grades 1–4 vomiting, asthenia, weight loss, decreased appetite, dehydration, muscle spasms, and dysgeusia were noted ≥10% more frequently in vismodegib-treated patients, regardless of the chemotherapy regimen administered (data not shown).

Grade 5 adverse events occurred in 4.1% (4/98; 95% CI: 1.4–9.6%) of vismodegib-treated patients. Of these patients, three were treated with FOLFOX–bevacizumab and one was treated with FOLFIRI–bevacizumab. Three of the four Grade 5 adverse events happened within 30 days of last investigational drug treatment and none were attributed to vismodegib.

In the FOLFOX–bevacizumab cohort, 13% of patients receiving placebo or vismodegib discontinued investigational drug therapy due to adverse events (Table 3). Among FOLFIRI-treated patients, fewer receiving placebo (3%) discontinued investigational drug therapy due to adverse events compared with vismodegib-treated patients (22%).
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**Treatment administered**

Cumulative doses of all regimen components were consistently lower among patients randomized to vismodegib regardless of the chemotherapy regimen given (Table 4). Patients treated with FOLFIRI–bevacizumab received more therapy overall than patients treated with FOLFOX–bevacizumab.

**Pharmacokinetics**

In vismodegib-treated patients, levels of vismodegib (12), oxaliplatin (20, 21), irinotecan (22), 5-FU (19, 23), and bevacizumab (24) were within the expected ranges for the doses administered (Supplementary Figs A1–A5). There were no clinically meaningful changes in post-infusion levels of 5-FU, irinotecan or its metabolites (SN-38 and SN-38g), or levels of total and free oxaliplatin when comparing days 1 and 28 in vismodegib-treated patients (Supplementary Figs A2–A4). Similarly, there was no effect of vismodegib treatment on plasma concentrations of bevacizumab (Supplementary Fig. A5).
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Discussion

This is the first randomized, placebo-controlled clinical trial of an Hh pathway inhibitor to report efficacy results, and the first phase II trial of a Hh pathway inhibitor in a tumor type that is not known to harbor mutations in the Hh signaling pathway (unlike the mutation-driven tumors basal cell carcinoma and a subset of medulloblastomas). The results of this study failed to demonstrate incremental benefit from the addition of vismodegib to standard-of-care first-line treatment for mCRC. The lack of treatment effect was evident from the primary efficacy analysis of PFS involving all randomized patients as well as analyses of subgroups defined by chemotherapy backbone and levels of Hh ligand expression in archival tumor tissue. Additional analyses explored median PFS in the subgroup of patients treated to progression as well as patients who achieved an OR (data not shown); neither subgroup benefited from the addition of vismodegib to standard-of-care therapy. The median PFS estimates reported for the ITT patient population in this study were generally consistent with those reported in other studies of patients receiving fluoropyrimidine-based chemotherapy with bevacizumab (3, 25, 26).

There are several potential explanations for the lack of vismodegib-associated treatment effect in this study. The simplest explanation is that the inhibition of the Hh signaling pathway is insufficient to meaningfully affect the clinical course of mCRC. Although preclinical data suggested that inhibition of Hh signaling could lead to tumor growth delay in primary xenografts, tumor regression was not seen in animal models (9). Inhibition of Hh signaling appears to increase stromal vascularity thereby improving chemotherapy penetration in preclinical models of pancreatic cancer (27). These results did
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not translate to efficacy in the mCRC setting. Phase II clinical trials of vismodegib and other Hh pathway inhibitors are ongoing in several other tumor types in combination with other therapies, and may shed further light on the role of the Hh pathway in the progression of nonmutation-driven tumors.

Another possible explanation is that there was a negative interaction between vismodegib and other regimen component(s), thereby confounding the detection of a potential contribution to treatment benefit by vismodegib. Consistently lower cumulative dosing of all regimen components (except bevacizumab in FOLFIRI-treated patients) was seen for vismodegib-treated patients, suggesting a possible unsuspected negative safety interaction, or a lack of efficacy in combination with vismodegib. The number of patients who discontinued chemotherapy prior to progression was higher among vismodegib-treated compared with placebo-treated patients (73 vs 58 patients). However, a review of the type and relative incidence of adverse events as a function of treatment assignment did not reveal particular adverse events as associated with treatment discontinuation. The overall proportion of patients experiencing at least one grade 3–5 adverse event in the study (~75–82%) was balanced across treatment arms and comparable to that reported in a much larger study of FOLFOX or FOLFIRI plus bevacizumab (26).

The adverse events that tended to be more prevalent among vismodegib-treated versus placebo-treated patients (i.e., vomiting, weight loss, decreased appetite, dehydration, muscle cramps, dysgeusia, and asthenia/fatigue), regardless of chemotherapy backbone, were primarily those previously reported in association with vismodegib monotherapy (12). The frequent occurrence of low-grade toxicities associated with vismodegib, superimposed
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on toxicities associated with the FOLFOX–bevacizumab or FOLFIRI–
bevacizumab treatment regimens, may have increased treatment
discontinuation among vismodegib-treated patients. While these regimens did
not undergo phase I study prior to this clinical trial, it is unlikely that phase I
investigation would have predicted these treatment discontinuations since
dose escalation studies focus on serious adverse events in early cycles and,
as mentioned, the grade 3-5 toxicities were balanced between treatment
arms.

To assess whether a potential pharmacokinetic interaction might have
compromised treatment outcomes for vismodegib-treated patients,
pharmacokinetic analyses were performed on a subset of patients in the trial
and showed that vismodegib did not impact blood levels of other regimen
components or their active metabolites. Furthermore, steady-state plasma
concentrations of vismodegib in this study did not appear to be meaningfully
different from those observed in a cohort of patients who received vismodegib
monotherapy (13, 15).

In conclusion, the results from this randomized, placebo-controlled, phase
II clinical trial suggest that further testing of vismodegib in this clinical setting
is not warranted.
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References


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# Table 1. Demographic and baseline disease characteristics

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<th>FOLFIRI/bev</th>
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<td>Vismodegib (n = 60)</td>
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Abbreviation: bev, bevacizumab.
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Table 2. Efficacy analyses

<table>
<thead>
<tr>
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<th>FOLFOX/bev (n = 124)</th>
<th>FOLFIRI/bev (n = 75)</th>
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<td>Vismodegib (n = 60)</td>
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<td>Median PFS (months)</td>
<td>9.9 (7.4 to 11.6)</td>
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<td>HR (90% CI)</td>
<td>1.32 (0.86 to 2.04)</td>
<td>1.15 (0.66 to 1.99)</td>
<td>1.25* (0.89 to 1.76)</td>
</tr>
<tr>
<td>P value</td>
<td>0.29</td>
<td>0.69</td>
<td>0.28*</td>
</tr>
<tr>
<td>ORR (%) (90% CI)</td>
<td>47 (36 to 57)</td>
<td>47 (36 to 58)</td>
<td>59 (46 to 72)</td>
</tr>
<tr>
<td>One-year survival† rate, %</td>
<td>75.2</td>
<td>79.6</td>
<td>87.2</td>
</tr>
</tbody>
</table>

Abbreviation: bev, bevacizumab.
*Stratified by chemotherapy regimen.
†Kaplan–Meier estimate.
Vismodegib with chemotherapy in metastatic colorectal cancer

Table 3. Grade 3–5 adverse events occurring in ≥5% of patients and vismodegib/placebo treatment discontinuation (safety evaluable population, n = 196)

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>FOLFOX/bev</th>
<th>FOLFIRI/bev</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 62)*</td>
<td>Vismodegib (n = 61)*</td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (8.1)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>16 (25.8)</td>
<td>12 (19.7)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1 (1.6)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (14.5)</td>
<td>5 (8.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (3.2)</td>
<td>6 (9.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (1.6)</td>
<td>4 (6.6)</td>
</tr>
<tr>
<td>Abdominal pain, upper</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (9.7)</td>
<td>10 (16.4)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>0</td>
<td>3 (4.9)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>0</td>
<td>3 (4.9)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>1 (1.6)</td>
<td>4 (6.6)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>0</td>
<td>4 (6.6)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>2 (3.2)</td>
<td>10 (16.4)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>3 (4.8)</td>
<td>5 (8.2)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>6 (9.7)</td>
<td>3 (4.9)</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>0</td>
<td>8 (13.1)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>3 (4.8)</td>
<td>5 (8.2)</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Palmar–plantar erythrodysaesthesia</td>
<td>2 (3.2)</td>
<td>4 (6.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (4.8)</td>
<td>0</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>0</td>
<td>4 (6.6)</td>
</tr>
<tr>
<td>Infections†</td>
<td>7 (11.3)</td>
<td>6 (9.8)</td>
</tr>
</tbody>
</table>

Treatment discontinuation, n (%)

<table>
<thead>
<tr>
<th></th>
<th>Placebo/vismodegib/all patients†</th>
<th>Discontinuation due to adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/vismodegib/all patients†</td>
<td>62 (100)</td>
<td>8 (12.9)</td>
</tr>
<tr>
<td>Discontinuation due to adverse event</td>
<td>61 (100)</td>
<td>8 (13.1)</td>
</tr>
<tr>
<td></td>
<td>36 (100)</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td></td>
<td>37 (100)</td>
<td>8 (21.6)</td>
</tr>
</tbody>
</table>

Abbreviation: bev, bevacizumab.

*For each event, incidence is expressed as number (percentage) of patients affected in the respective treatment group.
†Includes patients with one or more of the following: abdominal abscess, sepsis, diverticulitis, peri-rectal abscess, urinary tract infection, skin infection, pneumonia, tooth abscess, catheter-site infection, gastroenteritis, clostridial or Escherichia coli infection.
‡Treatment discontinuation for any reason (including disease progression).
Vismodegib with chemotherapy in metastatic colorectal cancer

Table 4. Treatment administered

<table>
<thead>
<tr>
<th>Treatment administered</th>
<th>FOLFOX/bev (n = 123)</th>
<th>FOLFIRI/bev (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vismodegib (n = 61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (n = 36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vismodegib (n = 37)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5-FU, median (range)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Vismodegib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of doses*</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>(1–47)</td>
<td>16</td>
<td>(2–51)</td>
</tr>
<tr>
<td>Cumulative dose†</td>
<td>62.1</td>
<td>48.8</td>
</tr>
<tr>
<td>(g)</td>
<td>(1–165)</td>
<td>(5–239)</td>
</tr>
<tr>
<td>Oxaliplatin/irinotecan, median (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of doses*</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>(1–27)</td>
<td>13</td>
<td>(2–47)</td>
</tr>
<tr>
<td>Cumulative dose†</td>
<td>1.7</td>
<td>1.5</td>
</tr>
<tr>
<td>(g)</td>
<td>(0–4)</td>
<td>(0–5)</td>
</tr>
<tr>
<td>Bevacizumab, median (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of doses*</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>(1–46)</td>
<td>15.5</td>
<td>(2–47)</td>
</tr>
<tr>
<td>Placebo/vismodegib, median (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of doses*</td>
<td>206.5</td>
<td>166</td>
</tr>
<tr>
<td>(6–703)</td>
<td>260</td>
<td>(25–647)</td>
</tr>
<tr>
<td>Cumulative dose†</td>
<td>31.0</td>
<td>24.9</td>
</tr>
<tr>
<td>(g)</td>
<td>(1–105)</td>
<td>(1–108)</td>
</tr>
<tr>
<td>Treatment duration (months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.4</td>
<td>5.7</td>
<td>9.1</td>
</tr>
<tr>
<td>(0.2–23.7)</td>
<td>(0.2–25.2)</td>
<td>(0.8–21.4)</td>
</tr>
<tr>
<td>(0.4–16.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: bev, bevacizumab.

*Dose number refers to the number of partial or completed infusions, irrespective of the administration of a concurrent bolus. Doses could be reduced by eliminating the bolus. The amount of drug administered is reflected in the cumulative dose.

†Cumulative doses are not corrected for body surface area.
Vismodegib with chemotherapy in metastatic colorectal cancer

Figure legends

Fig 1. CONSORT study diagram
*One patient randomized to placebo erroneously received vismodegib for 32 out of 201 days on study treatment and was allocated to the vismodegib arm for safety and exposure summaries.
†Safety data cutoff date—December 10, 2010.
Abbreviation: D/C, discontinued.

Fig 2. Kaplan–Meier curves for PFS (A) and Forest plot of PFS HRs for subgroups defined by levels of Sonic plus Indian Hh ligand mRNA expression as assessed by qRT-PCR and KRAS mutation status (B). The vertical dashed line indicates the HR for all patients. The diameter of a circle is proportional to the square root of the total n value.
*Median PFS was estimated using the Kaplan–Meier method.
†Hazard ratio relative to chemo–bev+pbo and 95% CI for the hazard ratio were estimated using Cox regression.
Abbreviations: bev, bevacizumab; chemo, chemotherapy; pbo, placebo; vismo, vismodegib.
Assessed for eligibility  \( n = 240 \)

Patients \( \geq 18 \) years with mCRC, ECOG PS 0 or 1, and RECIST (v.1.0) measurable or evaluable disease

Excluded  \( n = 41 \)

Not meeting inclusion criteria  \( n = 34 \)
Consent not given  \( n = 7 \)

Number of patients randomized  \( n = 199 \)

Allocated to receive vismodegib  \( n = 98 \)
(+ bevacizumab + FOLFOX or FOLFIRI)

Received vismodegib*  \( n = 97 \)

Did not receive vismodegib  \( n = 1 \)

Allocated to receive placebo  \( n = 101 \)
(+ bevacizumab + FOLFOX or FOLFIRI)

Received placebo*  \( n = 99 \)

Did not receive placebo  \( n = 2 \)

Included in efficacy analysis  \( n = 98 \)

Included in efficacy analysis  \( n = 101 \)

Did not receive vismodegib  \( n = 2 \)

Did not receive vismodegib  \( n = 2 \)

Died while on study treatment  \( n = 3 \)

Died while on study treatment  \( n = 1 \)

D/C study treatment for progressive disease  \( n = 38 \)

D/C study treatment for progressive disease  \( n = 48 \)

D/C study treatment due to adverse event*  \( n = 16 \)

D/C study treatment due to adverse event*  \( n = 9 \)

Subject/physician decision to discontinue study treatment  \( n = 34 \)

Subject/physician decision to discontinue study treatment  \( n = 22 \)

Continuing study treatment at data cutoff date†  \( n = 2 \)

Continuing study treatment at data cutoff date†  \( n = 0 \)

Discontinued study treatment at data cutoff  \( n = 2 \)

Discontinued study treatment at data cutoff  \( n = 16 \)

Other  \( n = 3 \)

Other  \( n = 2 \)
Fig 2A

Number at risk:
- FOLFOX + pbo: 64, 53, 36, 24, 12, 6, 3, 0, 0
- FOLFOX + vismo: 60, 48, 25, 13, 2, 1, 0, 0, 0
- FOLFIRI + pbo: 37, 32, 25, 18, 6, 2, 0, 0, 0
- FOLFIRI + vismo: 38, 30, 21, 14, 4, 3, 0, 0, 0

FOLFOX + pbo: median PFS = 9.9 months
FOLFOX + vismo: median PFS = 8.2 months
FOLFIRI + pbo: median PFS = 10.1 months
FOLFIRI + vismo: median PFS = 10.5 months
<table>
<thead>
<tr>
<th>Baseline risk factor</th>
<th>Total</th>
<th>Median* (months)</th>
<th>Median* (months)</th>
<th>Hazard ratio† (95% CI)</th>
<th>Chemo-bev + pbo better</th>
<th>Chemo-bev + vismo better</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>199</td>
<td>101</td>
<td>10.1</td>
<td>98</td>
<td>9.3</td>
<td>1.25 (0.89 to 1.76)</td>
</tr>
<tr>
<td>RT-PCR SHH and IHH expression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤33th%</td>
<td>46</td>
<td>30</td>
<td>9.4</td>
<td>16</td>
<td>9.2</td>
<td>1.14 (0.58 to 2.22)</td>
</tr>
<tr>
<td>34th to 67th%</td>
<td>46</td>
<td>28</td>
<td>11.3</td>
<td>18</td>
<td>7.4</td>
<td>2.38 (1.01 to 5.61)</td>
</tr>
<tr>
<td>&gt;67th%</td>
<td>47</td>
<td>17</td>
<td>14.4</td>
<td>30</td>
<td>10.7</td>
<td>1.64 (0.70 to 3.82)</td>
</tr>
<tr>
<td>Not available</td>
<td>60</td>
<td>26</td>
<td>9.5</td>
<td>34</td>
<td>9.2</td>
<td>0.93 (0.49 to 1.77)</td>
</tr>
<tr>
<td>KRAS mutational status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wild-type</td>
<td>98</td>
<td>52</td>
<td>11.3</td>
<td>46</td>
<td>9.2</td>
<td>1.51 (0.94 to 2.41)</td>
</tr>
<tr>
<td>Mutant</td>
<td>67</td>
<td>33</td>
<td>9.9</td>
<td>34</td>
<td>11.0</td>
<td>0.97 (0.51 to 1.86)</td>
</tr>
<tr>
<td>Not available</td>
<td>34</td>
<td>16</td>
<td>10.1</td>
<td>18</td>
<td>13.7</td>
<td>0.73 (0.30 to 1.79)</td>
</tr>
</tbody>
</table>
Clinical Cancer Research

A Randomized Phase II Trial of Vismodegib Versus Placebo with FOLFOX or FOLFIRI and Bevacizumab in Patients with Previously Untreated Metastatic Colorectal Cancer


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