A phase II multicentre, open-label, proof-of-concept study of tasquinimod in hepatocellular, ovarian, renal cell and gastric cancers

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Abstract

Background: Tasquinimod is a small molecule with immunomodulatory, anti-angiogenic and anti-metastatic properties that targets the tumour microenvironment. It has previously been evaluated in patients with metastatic prostate cancer. This study aimed to obtain a clinical proof of concept that tasquinimod was active and tolerable in patients with other advanced solid tumours.

Patients and methods: This early stopping design, open-label, proof-of-concept clinical trial evaluated the clinical activity of tasquinimod in four independent cohorts of patients with advanced hepatocellular ($n = 53$), ovarian ($n = 55$), renal cell ($n = 38$) and gastric ($n = 21$) cancers that had progressed during or after standard therapies. Patients received tasquinimod 0.5 mg/day once daily for at least 2 weeks, with the dose then increased to 1 mg/day. Tasquinimod was given until radiological disease progression according to Response Evaluation Criteria in Solid Tumor (RECIST) 1.1 criteria, intolerable toxicity or patient withdrawal. The primary efficacy end point was the progression-free survival (PFS) rate according to RECIST 1.1 by central assessment.

Results: Interim futility analyses at 8 weeks (6 weeks for the gastric cancer cohort) found adequate clinical activity of tasquinimod only in the hepatocellular cohort and recruitment to the other three cohorts was stopped. At final analysis, PFS rates were 26.9 at 16 weeks, 7.3 at 24 weeks, 13.2 at 16 weeks and 9.5% at 12 weeks, respectively, in hepatocellular, ovarian, renal cell and gastric cancer cohorts. In all patients, the most common treatment-emergent adverse events related to treatment were fatigue (48.5%), nausea (34.1%), decreased appetite (31.7%), and vomiting (24.6%).

Conclusions: Clinical activity of tasquinimod in heavily pre-treated patients with advanced hepatocellular, ovarian, renal cell and gastric cancer was not sufficient to warrant further clinical investigation.

Trial registration: NCT01743469

Key words: gastric cancer, hepatocellular cancer, ovarian cancer, PFS, renal cell cancer, tasquinimod

Introduction

Tasquinimod is a second-generation oral quinoline-3-carboxamide with multiple effects in the tumour microenvironment that inhibit tumour growth and metastasis [1]. A key target of tasquinimod is S100A9, a multifunctional immunomodulatory protein found in high levels in the microenvironment of several tumour types [2], which interacts with the proinflammatory receptors, such as Toll-like receptor 4, expressed on myeloid-derived suppressor cells (MDSCs), macrophages, endothelial and other cells. MDSCs in the tumour microenvironment stimulate angiogenesis using both vascular endothelial growth factor (VEGF)-dependent and VEGF-independent mechanisms [3].

Studies show improved progression-free survival (PFS) in patients with metastatic castration-resistant prostate cancer (mCRPC) treated with tasquinimod [4, 5]. Resistance to treatment and disease relapse or progression is common in hepatocellular, ovarian, renal cell and gastric cancers. Angiogenesis is significantly involved in the development of these four tumour types, and resistance to angiogenesis inhibitors thought to occur by tumour cell adaptation through upregulation of pre-existing redundant or evasive mechanisms [6].

This study was undertaken to obtain clinical proof-of-concept that tasquinimod was active and tolerable in patients with advanced hepatocellular (HCC), epithelial ovarian (OC), renal cell carcinoma (RCC) or gastric cancers (GC).

Patients and methods

This phase II, open-label, proof-of-concept clinical trial (ClinicalTrials.gov identifier NCT01743469) was performed at 24 sites in Belgium, Canada, France, Spain and the UK (see Supplementary Material Table S1 available online). The study was conducted under the provisions of the Declaration of Helsinki, and in accordance with the International Conference on Harmonisation Consolidated Guideline on Good Clinical Practice. The protocol and amendments and documents for patients were reviewed and approved by an independent ethics committee or institutional review board prior to study start.

Study participants and treatment

The study included adult patients with histologically confirmed advanced HCC, OC, RCC and GC who had progressed during or after standard therapies. Full inclusion and exclusion criteria are provided in supplementary Table S2. All patients were to receive tasquinimod at a starting dose of 0.5 mg/day maintained for at least 2 weeks and then increased to 1 mg/day. The dose could be maintained or reduced in case of Treatment Emergent Adverse Events (TEAEs).

Study plan and design

Tasquinimod treatment was given until radiological disease progression according to Response Evaluation Criteria in Solid Tumor (RECIST) v1.1 criteria [7], toxicity or patient withdrawal. Full details of study visit schedule and clinical assessments are provided in Tables S3 and S4 in the Supplementary Material available online.

Sample size

This study used a two-stage early stopping design (with a futility analysis at stage 1) to assess the activity of tasquinimod based on the proportion of patients who had neither progressed nor died at predefined time points (the PFS rate [8]) in each of four cohorts. For each cohort, the sample size was calculated based on a one-sided α of ≤0.1 and a power of ≥90% together with the constraints that the chance of early stopping given the null hypothesis (i.e. tasquinimod showed inadequate clinical activity) was ≥50% and the chance of early stopping given the alternative hypothesis was ≤10%.

The interim futility analysis was performed for each cohort after a predefined number of patients reached Week 8 (Week 6 for the GC cohort; T1). If the number of patients who had neither progressed nor died at this time was lower than expected so the null hypothesis was not rejected, recruitment would be stopped; otherwise, recruitment continued. The expected PFS rate for an active treatment at T1 (and to pursue the recruitment until T2) was 60% for the HCC, 65% for the OC and RCC and 40% for the GC cohort. At T2 the expected PFS rates for an active treatment were 40% for both the HCC and RCC cohorts at 16 weeks, 55% for the ovarian cancer (OC) cohort at 24 weeks and 35% for the gastric cancer (GC) cohort at 12 weeks. The cohort patient numbers, analysis timings and expected PFS rates are shown in Supplementary Material Table S5.

Efficacy and safety end points and assessments

The primary efficacy end point was the proportion of patients who neither progressed nor died (PFS rate) according to RECIST v1.1 by central assessment at the final analysis (T2; see Supplementary Material Table S5 for time points). Secondary efficacy end points were PFS duration, response rate, clinical benefit, time to

progression (TTP), and overall survival (OS). A patient was considered to have had clinical benefit if a complete response, a partial response or stable disease was observed for ≥12 weeks after the first study medication according to RECIST criteria. All tumour assessments were appraised by investigators and then secondly by a central independent reviewer. Overall response was evaluated using the RECIST v1.1 guideline for all cohorts and also by Choi criteria in HCC cohort.

Safety assessments were performed regularly throughout the study: adverse events (AEs), laboratory test values, ECOG performance status, vital signs and 12-lead electrocardiographic findings were monitored and recorded. AEs and laboratory tests were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) classification version 4.03 (or severity) and coded using MedDRA dictionary.

A range of blood biomarkers of angiogenesis, immunomodulation and inflammation at screening and regularly during the study treatment, tumour tissues (archive or biopsy) at screening and 4 weeks after tasquinimod start (cohort HCC only) were also assessed (see Supplementary Material Tables S3 and S4). Biomarker data were analysed for investigational objectives exploring the potential association of biomarkers with drug effects, such as PFS duration, clinical benefit and TEAEs, to better characterise the tumour types in each patient cohort and the mechanism of action of tasquinimod.

Statistical analysis

Efficacy and safety analyses were performed on all patients receiving at least 1 dose of tasquinimod. The primary efficacy analysis was the PFS rate (presented with its 95% confidence interval (CI) calculated using the Clopper-Pearson exact method)

according to RECIST v1.1 by central assessment at the final analysis (T2). For each cohort, the primary analysis was performed at T2 by comparing the PFS rate with the prespecified threshold using a one-sided α of 0.1. For analysis of the time dependent parameters as PFS, TTP and OS, the Kaplan-Meier method was used.

Safety data were analysed for the Safety Population, separately for each cohort and in an overall pooled analysis at T2. The safety analysis was based on treatment emergent AEs (TEAEs). For each TEAEs, worst NCI CTCAE (Version 4.03); grade per patient was tabulated by System Organ Class (SOC) and Preferred Term (PT). Laboratory values were presented by worst NCI CTCAE grade per patient or descriptive statistics.

Results

Patients and treatment

From December 2012 to July 2014, 201 patients were screened and 167 patients subsequently enrolled in the four separate cohorts. There were 53 patients with HCC, 55 patients with OC, 38 patients with RCC and 21 patients with GC. The original planned total for the HCC cohort was 52 but due to an additional ongoing enrolment, this number increased to 53. Patient disposition through the study is shown in Figure 1 and demographic and selected clinical characteristics in the four separate cohorts at baseline are shown in Table S6 in the Supplementary Material.

Dose escalation to 1 mg/day was achieved in the majority of patients (62–77%), while few required a reduction of treatment dose. The median duration of treatment ranged from 5.9 weeks in the GC cohort to 9.4 weeks in the HCC cohort (Table S7 in the Supplementary Material).

Efficacy

For the HCC cohort, the observed PFS rate at T1 was superior to the predefined rate required to proceed and more patients were enrolled up to the planned total (plus one additional patient - see above). For the OC cohort, recruitment as planned was completed before the T1 futility analysis results were available. For the RCC and GC cohorts, the pre-specified PFS rate was not achieved and further recruitment was stopped.

The results presented correspond to the final analysis of all patients enrolled and treated at 12 weeks for the gastric cohort, 16 weeks for renal and hepatic cohorts and 24 weeks for the ovarian cohort. Clinical efficacy parameters are shown in Table 1 for all four cohorts. None of the PFS rates at T2 reached the predefined threshold for efficacy.

Kaplan-Meier estimates of PFS and OS in the HCC cohort (n = 53) based on central review showed a median (95% CI) of 15.9 (8.0–23.1) and 29.3 (25.0–38.7) weeks, respectively (Figure 2).

Safety

All patients experienced at least one TEAE (Table 2); serious TEAEs occurred in 26–35% of patients (Table S8 in the Supplemental Material). The majority of TEAEs were considered related to study treatment, but most were low grade. Across all patients, the most common TEAEs related to treatment were fatigue (48.5%), nausea (34.1%), decreased appetite (31.7%), and vomiting (24.6%).

In all four cohorts, changes in laboratory parameters of grade 3 severity were experienced by less than 5% of patients. Increases in liver function tests were reported in 14 patients (26.9%) in the HCC cohort and occasionally in the other three cohorts. Of particular interest in this study were blood levels of amylase and lipase. Abnormal

increases of grade 3 or higher severity were noted in 22 patients for lipase and five patients for amylase (see Table S9 in the Supplementary Material).

Exploratory analyses

Multivariate analyses of PFS relative to baseline expression of tumour markers identified by immunohistochemistry and retrospectively assessed found two significant correlations for the HCC cohort. First, when taking into account histological grade and alcohol, low staining scores for the Ki67 proliferation marker were associated with higher PFS values (ie PFS > 16 weeks; p = 0.0207). Second, when taking into account time since diagnosis, increased expression of glycoprotein CD68 correlated with higher densities of macrophages in stroma and also with higher PFS values (p = 0.0324). No other investigated biomarkers were remarkable in this cohort or in the GC. No conclusion could be made regarding the RCC or OC due to the small number of patients between low and high PFS.

Discussion

The aim of this study was to evaluate tasquinimod activity in patients with solid tumours (liver, ovarian, gastric and renal cancers). At the time of protocol finalisation, tasquinimod had only been evaluated in prostate cancer. The study population selected included patients with advanced cancer types with a high unmet medical need reflecting high rates of treatment resistance. In addition, the four advanced cancer disease cohorts were selected because the immunomodulatory, antiangiogenic and antimetastatic properties of tasquinimod underpin a mechanism of action potentially beneficial in these advanced cancers, especially given the lack of standard second- or third-line systemic treatments for these patient populations.

The four cohorts can be viewed as separate proof-of-concept studies that were enrolled through a single protocol. While each cohort of patients was analysed separately for efficacy, the protocol allowed broader capture of information on exploratory end points. Notably, the study incorporated an early stopping design with futility analyses since, with limited data available regarding the efficacy of tasquinimod in other tumour types, exposure to a potentially ineffective drug should be kept minimised.

The efficacy analysis revealed that the clinical activity of tasquinimod monotherapy was modest even in the HCC cohort, which proceeded to the second stage of the statistical design based on the T1 analysis. Tasquinimod, with its mechanism of action related to the microenvironment, showed no activity in the selected study population with advanced and resistant disease. In developing drugs of this type, it might be beneficial to evaluate them in patients with minimal residual disease as maintenance therapy after chemotherapy [9].

In previous phase I and II clinical studies, tasquinimod was administered in escalating doses starting with 0.25 mg/day for 2 weeks, followed by 0.5 mg/day for 2 weeks then, with acceptable tolerability, rising to 1.0 mg/day. In the current study, use of 0.5 mg/day as the starting dose allowed dose escalation earlier in the course of treatment and proved feasible. The majority of patients then received the higher dose of tasquinimod within a flexible dose regimen in which titration based on individual tolerability mitigated treatment-related toxicities. In this respect, the overall safety profile of tasquinimod was similar across the four cohorts and consistent with previous studies [10].

Alternatives to chemotherapy for advanced and resistant disease in the four malignancies included in this study are actively being sought and equally, further

research is needed to identify and validate biomarkers to monitor such new cancer treatments. The biomarkers results in this study are exploratory as there were no control group and few patients.

In summary, adequate clinical activity of tasquinimod in patients with advanced HCC, OC, RCC and GC was not demonstrated in this study. The safety profile of tasquinimod across the four cancer patient cohorts was consistent with that previously reported in mCRPC and no new safety concerns were identified.

Figure legends

Figure 1. Patient disposition. ITT, intent to treat; TEAE, treatment-emergent adverse event.

Figure 2. Kaplan-Meier estimates of (A) progression-free survival (PFS) based on central review and (B) overall survival (OS) for the hepatocellular cancer cohort.

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Please observe that we are using endnote. Any changes to references required please add as a note in the body text and not to the ref list

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