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A randomized, multicenter, phase II study of vandetanib monotherapy versus vandetanib in combination with gemcitabine versus gemcitabine plus placebo in subjects with advanced biliary tract cancer: the VanGogh study

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Background: The management of biliary tract cancers (BTCs) is complex due to limited data on the optimal therapeutic approach. This phase II multicenter study evaluated the efficacy and tolerability of vandetanib monotherapy compared with vandetanib plus gemcitabine or gemcitabine plus placebo in patients with advanced BTC.

Patients and methods: Patients were randomized in a 1 : 1 : 1 ratio to three treatment groups: vandetanib 300 mg monotherapy (V), vandetanib 100 mg plus gemcitabine (V/G), gemcitabine plus placebo (G/P). Vandetanib (300 mg or 100 mg) or placebo was given in single oral daily doses. Gemcitabine 1000 mg/m^2 was i.v. infused on day 1 and day 8 of each 21-day cycle. The primary end point was progression-free survival (PFS). Secondary end points were: objective response rate (ORR), disease control rate, overall survival, duration of response, performance status and safety outcomes.

Results: A total of 173 patients (mean age 63.6 years) were recruited at 19 centers across Italy. Median (95% confidence intervals) PFS (days) were 105 (72–155), 114 (91–193) and 148 (71–225), respectively, for the V, V/G and G/P treatment groups, with no statistical difference among them ($P = 0.18$). No statistical difference between treatments was observed for secondary end points, except ORR, which slightly favored the V/G combination over other treatments. The proportion of patients reporting adverse events (AEs) was similar for the three groups (96.6% in V arm, 91.4% in the V/G arm and 89.3% in the G/P arm).

Conclusions: Vandetanib treatment did not improve PFS in patients with advanced BTC. The safety profile of vandetanib did not show any additional AEs or worsening of already known AEs.

Clinical trial number: NCT00753675.

Key words: vandetanib, gemcitabine, advanced biliary tract cancer

introduction

Biliary tract cancers (BTCs), including cholangiocarcinoma, gallbladder cancer and cancer of the Vater's ampulla, are relatively rare, accounting for ~0.6% of both new cancer cases and deaths among all cancer types in the United States [1]. Management of the disease is complex due to a suffering patient population (e.g. pain symptoms) and limited data on the optimal therapeutic approach. Although treatment options are available (fluoropyrimidines, gemcitabine and cisplatin plus gemcitabine), both to palliate symptoms and to prolong survival [2–4], there is significant scope for improved outcomes. Recently, in a randomized study, Valle et al. reported a statistically superior median overall survival (OS) among patients receiving a combination of

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cisplatin with gemcitabine, compared with those treated with gemcitabine alone [11.7 versus 8.1 months, hazard ratio (HR) = 0.64; 95% confidence interval (CI) = 0.52–0.80; $P < 0.001$] [2]. However, BTCs still remain a major challenge due to limited treatment options and because trials are difficult due to tumor rarity and low patients' performance status (PS), resulting in failure in the majority of trials undertaken. The epidermal growth factor receptor/human epidermal growth factor receptor 1 (EGFR/HER1) and its ligands EGF and transforming growth factor alpha (TGF-α) are important in cell proliferation, as well as motility, adhesion, invasion, survival, and angiogenesis [5, 6]. In BTCs, EGFR and TGF-α levels are increased [7, 8], and inhibition of EGFR tyrosine kinase activity has been shown to be effective in attenuating the proliferation of cholangiocarcinoma cells *in vitro* [9]. Erlotinib, an orally active, selective inhibitor of the EGFR/HER1 tyrosine kinase, has been shown to provide therapeutic benefit in patients with biliary cancer in a preliminary phase II study [10]. Another important factor for angiogenesis in various tumors is vascular endothelial growth factor (VEGF) [11], which has also been shown to be an independent negative predictor of extrahepatic biliary tract carcinomas [12].

Sorafenib, a novel inhibitor of the human VEGF receptors-2 and -3 (VEGFR-2/-3) and the platelet-derived growth factor receptor-β (PDGFR-β), has been shown to inhibit the proliferation of various human bile duct adenocarcinoma cell lines [13]. However, these promising preclinical findings have not been confirmed in a recent phase II trial where the addition of sorafenib to gemcitabine and cisplatin in patients with advanced BTC failed to show any improvement in outcome [14]. In contrast, in patients with advanced BTC, bevacizumab combined with gemcitabine and oxaliplatin showed antitumor activity with tolerable safety [15]. Therefore, there is a strong rationale for the use of another VEGFR, EGFR or combined VEGFR and EGFR tyrosine kinase inhibitor (TKI) in BTC. Vandetanib, is an orally active antagonist of VEGFR-2, EGFR/HER1 and rearranged during transfection (RET) kinase [16–18]. Previous *in vitro* studies of vandetanib in BTC, using cancer cell lines, showed promising results [19, 20]. An *in vivo* model of metastatic pancreatic cancer has also shown that vandetanib decreased primary pancreatic tumor growth and reduced lymph node and liver metastases compared with controls or gemcitabine alone and tumor growth was inhibited further in animals receiving vandetanib and gemcitabine in combination [21].

The aim of the present study (the VanGogh study) was to investigate the efficacy of vandetanib (V) monotherapy compared with its combination with gemcitabine (V/G) or gemcitabine and placebo (G/P) in advanced BTC patients.

patients and methods

patients

The VanGogh study, a randomized, multicenter, phase II, parallel-group trial; (ClinicalTrials.gov identifier: NCT00753675; http://clinicaltrials.gov/show/NCT00753675) included patients aged ≥18 years with histologically or cytologically confirmed advanced BTC (gallbladder cancer, cancer of the extrahepatic bile duct, intrahepatic cholangiocarcinoma or ampullary carcinoma) who were not receiving prior chemotherapy, who had an 'Eastern Cooperative Oncology Group' PS (ECOG-PS) of 0–2, measurable or assessable disease according to 'Response Evaluation Criteria in Solid Tumors' (RECIST), a life expectancy ≥12 weeks and no significant concomitant abnormalities. Patients were excluded if they had evidence of severe or uncontrolled systemic disease or any concurrent condition which in the Investigator's opinion made it undesirable for the patient to participate in the trial or which jeopardized compliance with the protocol. Compliance for each treated subject was calculated for all arms over the whole treatment period using the following approach: compliance (%) = (number of tablets taken/number of scheduled tablets) × 100. Patients were excluded if they had undergone prior radiation therapy or major surgery within 4 weeks before start of study therapy. Concomitant medication that could induce CYP3A4 function or could affect corrected QT interval (QTc) prolongation was disallowed. Patients who participated in the study gave written informed consent before entering in the study. The study protocol was approved by the Independent Ethics Committee of each participating site before any study-related procedure was started. This study was conducted in accordance with the principles of the Declaration of Helsinki.

randomization and masking

Eligible patients were randomized in a 1 : 1 : 1 ratio to receive V, V/G or G/P. Randomization was based on concealed treatment allocation using sequentially numbered opaque, sealed envelopes. The actual treatment given to individual patients was determined by a computer-generated randomization scheme. The randomization scheme was stratified by center.

treatment

Vandetanib was administered as single daily oral tablet of 300 mg as monotherapy or 100 mg when in combination with gemcitabine. The 100 mg dose of vandetanib in combination with gemcitabine was based on findings from a phase II study in nonsmall-cell lung cancer in combination with docetaxel [22] in addition to a dose finding study of vandetanib in combination with gemcitabine in locally advanced unresectable or metastatic pancreatic adenocarcinoma [23]. Gemcitabine was administered i.v. at 1000 mg/m^2 over 30 min on day 1 and 8 of each 21-day cycle, for up to a maximum of six cycles. Placebo tablets were not distinguishable from vandetanib tablets. Patients continued to receive randomized treatment until progression of their disease (according to RECIST criteria) [24]. Investigators remained at liberty to determine the most appropriate therapy after disease progression. In the combination arms, investigators were free to continue, at their discretion, gemcitabine after the six cycles established by the protocol.

outcome measures

Radiological evaluation using RECIST was carried out at screening (within 4 weeks before the first dose) and every 6 weeks during the study until objective disease progression up to week 19 and every 8 weeks thereafter. The primary end point of the study was progression-free survival (PFS), defined as the time from the date of randomization to the date of objective progression or death from any cause. Patients who had not progressed or died at the time of data analysis were censored at the time of their latest objective tumor assessment. Secondary efficacy end points were: OS, defined as the time from randomization to death due to any cause (for participants who were still alive, OS was censored at the last contact); objective response rate (ORR), defined as the rate of patients with complete response (CR) or partial response (PR); duration of response (DOR), defined as the time from first documentation of response to the date of documented disease progression or death from any cause in the absence of documented progression; disease control rate (DCR), defined as the percentage of patients with CR or PR or stable disease ≥6 weeks. Safety analyses included adverse events (AEs) recording, laboratory parameters, vital signs, electrocardiogram (ECG) and physical examination. Toxicities were graded according to the NCI CTCAE, Version 3.0.

statistical analysis

Assuming a median PFS of ~5 months for gemcitabine alone [25–27], a minimum of 174 patients (58 per arm) were planned in order to detect a 40% prolongation with V or V/G (the increase in PFS by 40% represents an increase of ~2 months), assuming an accrual period of 18 months and a minimum follow-up time of 6 months. All patients that were enrolled and received the study treatment were considered the intention-to-treat (ITT) population on which the analysis was carried out for all efficacy outcome variables. In the analysis of the primary efficacy variable (PFS), survival curves, medians and their 95% CI were estimated applying the Kaplan–Meier method. The log-rank test was used to compare PFS in the three treatment arms. Time-dependent secondary outcomes (OS and DOR) were analyzed as for the primary end point. Comparison between groups in ORR and DCR was carried out by the χ^2 test and univariate and multivariate (logistic regression) analyses.

From the safety population, AEs (both in terms of Medical dictionary for regulatory activities—MedDRA—preferred terms and CTCAE grade) were listed individually by patient and summarized by treatment group.

results

patient disposition and baseline characteristics

This study was conducted from October 2008 to September 2012 in 19 sites across Italy. Figure 1 shows the disposition of patients and reasons for withdrawal. Table 1 shows baseline demographic data of the safety population. All baseline characteristics were comparable in the three arms.

exposure to treatment

Mean [± standard deviation (SD)] and median (range) total exposure to vandetanib or placebo was 98.3 ± 128.2 and 45 (8–482) days, respectively, in the V arm, 132.4 ± 129.8 and 78 (8–379) days, respectively, in the V/G arm and 168.6 ± 193 and 75.5 (9–556) days, respectively, in the G/P arm; mean total exposure (±SD) and median (range) to gemcitabine was 99.1 ± 116 and 68 (1–358) days, respectively, in the V/G arm and 152.9 ± 178.1 and

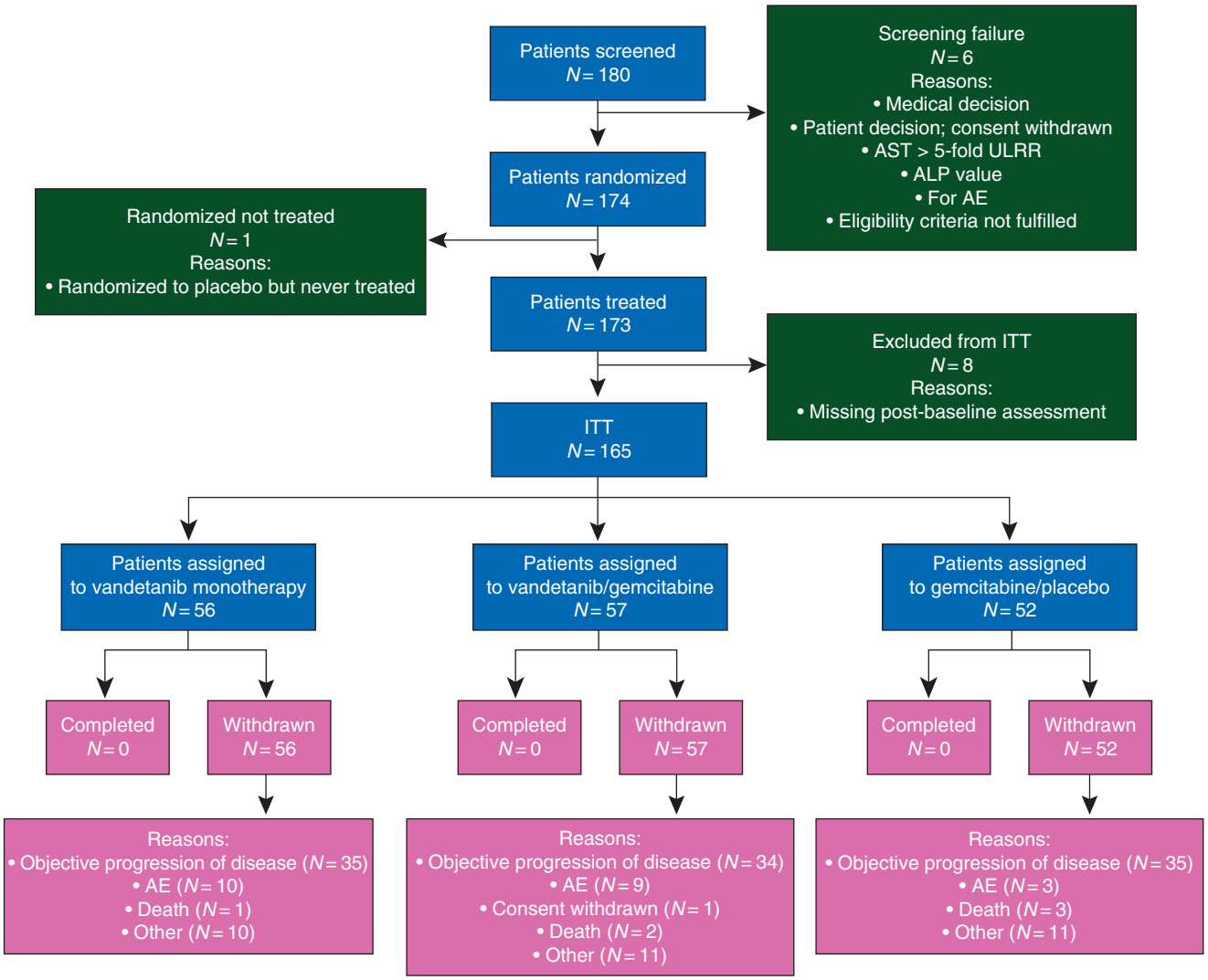

Figure 1. Disposition of patients and reasons for withdrawal. AE, adverse event; ALP, alkaline phosphatase; AST, aspartate aminotransferase; G, gemcitabine; *N*, number of patients; P, placebo; ULRR, upper limit of reference range; V, vandetanib.

68.5 (1–478) days, respectively, in the G/P arm. Patients in the G/P arm received a higher number of gemcitabine administrations compared with patients in the V/G arm (mean 10 versus 8). Similarly, the mean number of vandetanib/placebo tablets was higher in the G/P arm (142.9 ± 143.1 tablets) compared with the V/G (92.7 ± 74.4 tablets, corresponding to an average total of 9.3 g of vandetanib) and V monotherapy (88.5 ± 89 tablets, corresponding to an average total of 26.6 g of vandetanib) arms.

Compliance to V oral treatment was over 93% in the monotherapy group and 97% in the combination group, for the first 19 weeks of treatment, with a slight decrease in compliance in both groups treated with V thereafter.

efficacy

Table 2 summarizes efficacy results. Median PFS (Figure 2) did not differ among study groups: the log-rank test (unadjusted model with treatment factor only) in the ITT population showed a nonsignificant *P* value of 0.182. The Cox's proportional hazards regression model did not show statistically significant

Table 1. Demographic and anthropometric data in the safety population

Clinical characteristic	V (*N* = 59)	V/G (*N* = 58)	G/P (*N* = 56)*	Total (*N* = 173)
Gender, *n* (%)				
Females	34 (57.6)	27 (46.6)	31 (55.4)	92 (53.2)
Males	25 (42.4)	31 (53.4)	25 (44.6)	81 (46.8)
Age (years), mean (SD)	62.4 (10.1)	64.4 (9.5)	64.0 (8.8)	63.6 (9.5)
Race, *n* (%)				
White	58 (98.3)	56 (96.6)	56 (100)	170 (98.3)
Black	0 (0)	2 (3.4)	0 (0)	2 (1.6)
Other	1 (1.7)	0 (0)	0 (0)	1 (0.6)
WHO PS, *n* (%)				
Grade 0	38 (64.4)	36 (61.0)	34 (61.8)	108 (62.4)
Grade 1	20 (33.9)	20 (33.9)	20 (36.4)	60 (34.7)
Grade 2	1 (1.7)	3 (5.1)	1 (1.8)	5 (2.9)
Tumor type, *n* (%)				
Intrahepatic	27 (45.8)	31 (53.4)	29 (52.7)	87 (50.6)
Extrahepatic	16 (27.1)	10 (17.24)	13 (22.4)	39 (22.7)
Gallbladder	11 (18.6)	13 (22.4)	7 (12.7)	31 (18)
Periamp	5 (8.5)	4 (6.9)	6 (10.9)	15 (8.7)

Data are presented as number (%) of patients. Intrahepatic tumors include peripheral cholangiocarcinoma, right and left hepatic duct; extrahepatic tumors include Klatskin, common hepatic duct and cystic duct; Periamp includes common bile duct and ampulla. Percentages of patients by tumor type in the G/P arm were based from a total of 55 patients as a cancer diagnosis was missing for one patient.
V, vandetanib; G, gemcitabine; P, placebo; *n*, number of subjects; SD, standard deviation; WHO PS, performance status according to the 'World Health Organization' criteria.

Table 2. Summary of efficacy results in the ITT population

Parameter	V (*N* = 56)	V/G (*N* = 57)	G/P (*N* = 520)	*P* value[a]
Follow-up (months), median (range)	7 (1–38)	8.5 (1–31)	8 (1–35)	
Censored, *n* (%)	8 (14.3)	8 (14)	6 (11.5)	
PFS (days), median (95% CI)	105 (72–155)	114 (91–193)	148 (71–225)	0.18
ORR, *n* (%)	2 (3.6)	11 (19.3)	7 (13.5)	0.03
DOR[b] (days), median (95% CI)	277 (267–286)	179 (85–369)	127 (85–152)	
DCR, *n* (%)	14 (25.0)	17 (29.8)	20 (38.5)	0.31
OS (days), median (95% CI)	228 (190–364)	284 (213–359)	307 (254–523)	0.07

[a]Log-tank test (unadjusted model with treatment factor only) in survival function data and χ^2 test in proportions.
[b]Assessable only for 20 patients (see ORR).
V, vandetanib; G, gemcitabine; P, placebo; PFS, progression-free survival; CI, confidence interval; *n*, number of subjects; ORR, objective tumor response rate (CR + PR); CR, complete response; PR, partial response; DCR, disease control rate (CR + PR + SD ≥8 weeks); SD, stable disease; DOR, duration of response; OS, overall survival. Data are presented as number (%) of patients.

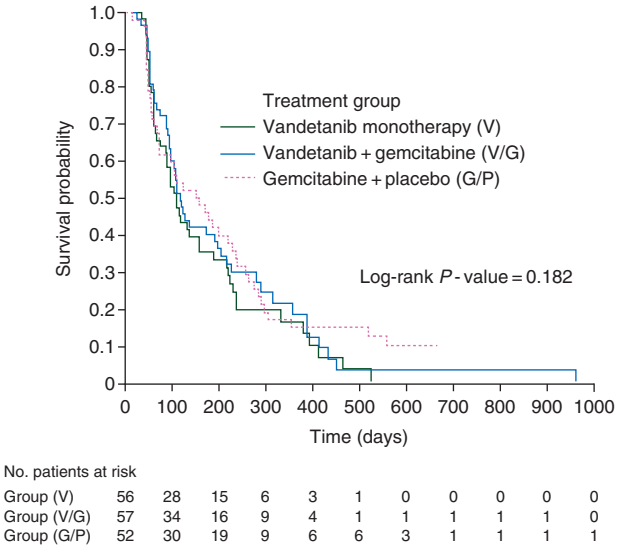

Figure 2. Progression-free survival (PFS): Kaplan–Meier estimate of survival distribution function—unadjusted.

differences: in the ITT population the, HR was 1.3 (0.86–1.96) for V versus G/P and 1.3 (0.75–1.7) for V/G versus G/P. For the secondary outcomes, a significant difference between treatments was found only for ORR (χ^2 test, $P = 0.035$, favoring the V/G combination). OS analysis showed a borderline value for differences among study groups ($P = 0.066$) due to a slight OS improvement in the G/P arm. Post first-line treatment rate was similar across the three arms, even if the treatment type was found to be different among the regimens previously received (supplementary Table S1, available at *Annals of Oncology* online). The ECOG-PS did not significantly change from the baseline values during the study, with the exception of the 30-day visit, where the rate of patients who showed a worsened ECOG-PS class ranged between 22.6% and 45.5%. This trend did not differ between treatments.

safety

No overt differences were found between the treatment arms in the proportion of patients who experienced serious AEs [respectively, 16 (27.1%), 15 (25.9%) and 12 (21.4%)]. The study drugs exhibited different safety profiles. Gemcitabine predominantly showed hematological toxicity (neutropenia, leukopenia, anemia), as expected. In contrast, patients in the vandetanib monotherapy group had a greater tendency to experience dermatological events (rash) and hypertension than with gemcitabine. Gastrointestinal events were common to both study drugs, as well as changes in liver enzymes and in renal function. Frequently occurring AEs are presented in supplementary Table S2, available at *Annals of Oncology* online. Slight mean increases in QTc interval occurred in subjects receiving vandetanib. One patient in the 300 mg arm developed Torsades de Pointes and recovered 11 days after discontinuation of the drug. He experienced an acute myocardial infarction 10 years ago and has since then been treated with cardioaspirin and β-blocker. Baseline QTc was 416 ms and no ECG abnormalities were recorded before the event or during treatment. No other patients developed a serious arrhythmia.

discussion

The rationale for this study was based on the limited availability of standard therapies in advanced BTC at the time this study was designed, although novel biological therapies targeting angiogenesis (bevacizumab and sorafenib) and inhibiting epidermal growth factors (cetuximab and erlotinib) were under investigation at the time, and have since provided preliminary findings [28–31]. Findings from BINGO, a recent randomized, open label, noncomparative, phase II trial, failed to show any survival advantage of cetuximab added to gemcitabine and oxaliplatin [median PFS: 6.1 months (95% CI 5.1–7.6)] versus gemcitabine and oxaliplatin [5.5 months (3.7–6.6)] in BTC, although it was well tolerated [31]. This and other studies indicate that no conclusive evidence of the higher efficacy of biologics has yet come from large randomized trials in this setting.

In a previous study, Valle et al. demonstrated a clear advantage in both PFS and OS of gemcitabine in combination with cisplatin over gemcitabine alone; in particular, PFS increased from 5 months with gemcitabine to 8 months with gemcitabine and cisplatin [2]. This study was not available at the time our study was designed, and we therefore chose the standard arm as gemcitabine as monotherapy, one of the most common schedules used in Italy and one that it is well tolerated. Results of the present study did not show an improvement in PFS, or other secondary end points, in subjects with advanced BTC treated with vandetanib, compared with gemcitabine. A statistically significant higher objective tumor response rate was found with the two gemcitabine arms compared with vandetanib 300 mg; moreover, OS was slightly longer in the G/P arm. The critical review of the study design, the baseline patients characteristics and their distribution in the study groups, the study conduct, the statistical analysis and the compliance to the treatment do not allow the identification of specific features which might have adversely affected on the study results. The study recorded a higher number of AEs leading to a discontinuation in the two vandetanib arms and an increased number of treatment cycles received by the G/P arm patients; taken together, these two evidences could partially explain the lack of improved efficacy in the V/G arm.

In general, the treatment with vandetanib was relatively well tolerated both as monotherapy and in combination with gemcitabine, without unexpected toxicities. Safety analysis indicated that the most frequent AEs during treatment with vandetanib are related to the occurrence of rash, gastrointestinal events, slight alteration of the liver function, hypertension and slight prolongation of the cardiac repolarization. The onset of serious arrhythmias was infrequent.

conclusion

Findings from the VanGogh study did not demonstrate any superiority of vandetanib alone or in association with gemcitabine in the PFS of patients affected by advanced BTC compared with gemcitabine alone. The safety profile of vandetanib given alone or in combination with gemcitabine does not show any additional AEs or worsening of already known AEs.

Promising results have recently been published on the identification of new major genomic alterations, which offer the possibility that less toxic targeted therapies may be available for patients currently being treated with conventional 'one-size-fits-all' approaches [32]. In the absence of a more in-depth knowledge of the biomolecular status of patients from this setting, with a better understanding of the role of the targeted therapies, chemotherapy with cisplatin plus gemcitabine remains the standard of care for patients with advanced BTCs.

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disclosure

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