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TITLE PAGE

Panitumumab in combination with gemcitabine and oxaliplatin does not prolong survival in *KRAS* wild-type Advanced Biliary Tract Cancer: a randomized, Phase II trial (Vecti-BIL Study)

Running title

GEMOX and Panitumumab in wt*KRAS* BTC

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Condensed abstract

The combination of gemcitabine-oxaliplatin (GEMOX) and Panitumumab compared to GEMOX alone was evaluated in this phase II randomized trial as first-line treatment in advanced biliary tract cancer (BTC). Despite the molecular selection for KRAS-wild-type status, progression-free-survival (PFS) and overall survival (OS) were not improved.

Abstract

Background: Biliary tract cancer (BTC) is a rare and lethal disease with few therapeutic options. Preclinical data suggest that the EGFR pathway could be involved in its progression.

Methods: In this open-label, randomized Phase II trial we recruited chemotherapy-naïve patients with advanced BTC displaying a wild-type *KRAS* status. Patients were randomized to gemcitabine (1000 mg/m²) and oxaliplatin (100 mg/m²) with (Arm A) or without (Arm B) panitumumab (6mg/kg), for up to 12 cycles. The primary endpoint was progression free survival (PFS) analyzed by intention-to-treat. This study is registered with ClinicalTrials.gov (NCT01389414).

Results: We enrolled 89 patients (45 in Arm A and 44 in Arm B) between 06/2010 and 09/2013. After a median follow-up of 10.1 months, median PFS was 5.3 months in Arm A (95%CI 3.3–7.2) and 4.4 months (95%CI 2.6–6.2) in Arm B (p=0.27). No survival differences were observed, being median OS 9.9 months in Arm A and 10.2 months in Arm B (p=0.42). In subgroup analysis, no differences in PFS according to

the site of primary tumor was observed; patients with intrahepatic cholangiocarcinoma (IHC) treated with panitumumab may have a survival benefit compared to the control group (15.1 vs 11.8 months, $p=0.13$). As for safety, skin toxicity was the main adverse event in arm A (80% of patients). A higher incidence of diarrhea (55.5 vs 31.8%), mucositis (22.2 vs 13.7%) and constipation (24.4 vs 15.9%) was seen in Arm A.

Conclusions: Our results confirm the marginal role of anti-EGFR therapy even in wild-type *KRAS*-selected BTC.

Keywords: biliary cancer, panitumumab, Cholangiocarcinoma, *KRAS*, chemotherapy, GEMOX

Introduction

Biliary Tract Cancers (BTC) are a heterogeneous group of tumors that includes intrahepatic cholangiocarcinoma (IHC), extrahepatic cholangiocarcinoma (EHC) and gallbladder adenocarcinoma (GBC). BTC are rare in Western countries but extremely lethal¹; only a small percentage of patients are diagnosed with early-stage, resectable disease and patients who are operated have a high risk of recurrence, with 5-year survival rates in the range of 20–40%².

Regarding the metastatic or unresectable stage, palliative chemotherapy is, to date, the mainstay of treatment. Cisplatin plus gemcitabine is considered the first-line standard of care according to Valle's ABC-02 trial³. Compared to gemcitabine alone, the combination therapy yielded an advantage both in progression-free survival (PFS) (8.0 vs. 5.0 months; $p < 0.001$) and overall survival (OS) (11.7 vs 8.1 months $p < 0.001$).

Oxaliplatin is widely used in clinical practice instead of cisplatin: the safety profile of the GEMOX regimen and the good response rates (RRs) strongly suggest that it is reasonable to replace with GEMOX the standard schedule with cisplatin^{4,5}.

Preclinical data have suggested the involvement of the Epidermal Growth Factor Receptor (EGFR) pathway in BTC pathogenesis. EGFR is often overexpressed in this disease, and in some cases activating mutations have been detected^{6,7}. Initial Phase II studies using anti-EGFR targeted agents have shown promising results⁸ and have paved the way to randomized trials.

Panitumumab (Vectibix, Amgen) is a fully human IgG₂ monoclonal antibody (MoAb) against EGFR, initially approved for metastatic colorectal cancer with wild-type (wt) *KRAS* on exon 2.

Based on this knowledge, we designed this randomized Phase II trial to investigate the efficacy of gemcitabine and oxaliplatin chemotherapy plus panitumumab as a first-line treatment for patients with *KRAS* wt advanced BTC.

Patients and Methods

We designed a multi-center Phase II, open-label, randomized (1:1) study with the aim of evaluating the clinical activity of the combination of panitumumab with GEMOX chemotherapy, as a first-line treatment for unresectable and metastatic BTC.

We recruited patients across 12 Italian University Hospitals and Cancer Institutes. The protocol was approved by the institutional review board at each participating institution and the study was carried out in accordance with the Declaration of Helsinki.

Main inclusion criteria of the protocol were;

- Histologically- or cytological-documented unresectable or metastatic biliary tract adenocarcinoma, either at diagnosis or relapse after surgery.

- wt *KRAS* status, defined as no mutations in exon 2, codons 12-13, determined on the primary or metastatic tumor. Analyses were carried out at each participating institution on paraffin-embedded tumor tissue by validated assays such as PCR and Sanger sequencing. Tumor samples were then collected and centralized at our center in order to widen the assessment of other key gene expression or mutations, which could act as possible predictive markers of response or resistance. *RAS*, *BRAF* and *PI3KCA*-testing was carried out by using mass spectrometry technique (MALDI-TOF method-Sequenom).

- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0, 1 or 2.

- Adequate bone marrow, renal and hepatic function.

Patients with previous exposure to systemic treatment, either chemotherapy or targeted agents, were excluded, as well as patients with serious comorbidities or who were unable to fulfill the protocol requirements. All patients provided written, informed consent.

Once enrolled, eligible subjects were randomized through a Computed System, using a permuted-block randomization stratified according to ECOG PS (0 to 1 vs 2) and site of primary tumor (IHC vs EHC and GBC). As this was an open-label study, participants, investigators and trial staff were made aware of treatment allocations.

Patients in both arms received gemcitabine 1000mg/m² on day 1 and oxaliplatin 100mg/m² on day 2 of each 2-week cycle.

Patients who were assigned to Arm A also received panitumumab 6 mg/kg on day 1 of each 2-week cycle.

Each patient was treated for a maximum of 12 cycles or until disease progression, unacceptable toxicity or patient's refusal. Patients in the experimental arm without tumor progression at the end of chemotherapy (12 completed GEMOX cycles or interruption for unacceptable toxicity from chemotherapy) had the option to continue panitumumab 6 mg/kg once every 2 weeks until tumor progression or toxicity.

Subjects were evaluated for tumor progression every 8 (+/-□1) weeks. Tumor response assessment was performed by the Investigator using the Response Evaluation Criteria in Solid Tumors- RECIST criteria version 1.1.

The study was designed to have PFS as the primary endpoint, defined as the time from randomization to evidence of progression (RECIST, version 1.1), death, or last radiographic assessment in the absence of a PFS event. Secondary endpoints were the

objective response rate (ORR) (RECIST 1.1), OS and safety (NCI CTCAE version 3.0, with the exception of skin toxicity).

We assumed a median PFS time for the control arm (GEMOX) of 6 months⁹, and a median PFS of the experimental arm (P-GEMOX) of 10 months. This would correspond to a hazard ratio (HR) of 0.60. For specified $\alpha=0.10$ and the power $1-\beta=80\%$, 74 accumulated events were required for the log-rank test.

Accounting for a 10% loss to follow-up in both arms and a follow-up time of 12 months, a total sample of 88 patients was required to yield the necessary number of events in case of a constant accrual rate. The log-rank analysis was stratified by ECOG PS (0 to 1 vs 2) and site of primary tumor (IHC vs EHC and GBC).

Time to endpoint events was estimated using the Kaplan-Meier analysis and the log-rank test (pooled over strata) was used to compare data between treatment groups in an intention-to-treat (ITT) approach. Safety results were compared using Yates chi-squared test. Data were analyzed using IBM-SPSS Statistic version 20. This study is registered with ClinicalTrials.gov, number NCT01389414.

Results

A total of 89 patients were enrolled in the study between 06/2010 and 09/2013, with 45 patients randomly assigned to arm A and 44 patients to arm B. All subjects received at least one cycle of treatment with a median number of 7 cycles administered in each arm. Overall, 27 patients completed the treatment plan of 12 cycles, 12 in the P-GEMOX group and 15 in the GEMOX group. Nine patients in arm A then received maintenance with panitumumab until toxicity or disease progression (range 1-28 cycles). Reasons for discontinuing treatment in the remaining subjects included;

radiological progressive disease (PD) (30 patients), clinical PD (8 patients), adverse events (8 patients), death (5 patients), medical decision (5 patients), consent withdrawal (5 patients) and lack of compliance (1 patient). A total of 84 patients were evaluable for response according to the RECIST criteria 1.1. Radiological restaging was missing in five patients (1 in Arm A and 4 in Arm B) due to clinical PD (3 patients), adverse event (1 patient) or death (1 patient) before the first assessment. (Figure 1)

In the overall population, median age at the time of randomization was 64.1 years (range 36.8-78.5 years), with a higher percentage of females (64%). Almost half of the patients (47.1%) were diagnosed with IHC, while 31.4% were diagnosed with GBC and 21.3% with EHC. Patients were mostly metastatic (84.2%) and with ECOG PS 0 or 1 (98.8%). Baseline levels of tumor marker Ca 19.9 and Alkaline Phosphatase (ALP) were 79 UI/l (range 0-60000) and 187 UI/l (range 52-1254), respectively. Baseline characteristics were globally well-balanced between the study groups and are shown in Table 1.

After a median follow-up of 10.1 months, at the time of the final analysis, 86 PFS events were observed. Median PFS was 5.3 months in arm A (95% CI 3.3–7.2) and 4.4 months (95% CI 2.6–6.2) in arm B (HR 0.78, 95% CI 0.51-1.21; log-rank test $p=0.27$) (Figure 2A). No differences in OS were observed, with a median OS of 9.9 months (95% CI 5.4-14.3) in arm A and 10.2 months in arm B (95% CI 6.4-13.9) (HR 0.83, 95% CI 0.53-1.3; $p=0.42$) (Figure 2B).

Among the evaluable patients, RR was 26.6% in arm A and 18.1% in arm B and disease control rate (DCR) 75.5% and 68.1% respectively (chi-square $p=0.99$). One patient from each group achieved a complete response (CR). Responses in each arm are shown in Table 2.

We carried out subgroup analyses as specified in the protocol; this entailed analyzing the survival variables according to the site of the primary tumor (IHC vs EHC and GBC), which was also a stratification factor. Median number of cycles was 8 in the IHC group and 6 in EHC-GBC.

In the ITT population, median PFS for the 42 IHC patients was 5.7 in Arm A (95% CI 2.7–8.7) and 6.2 months in Arm B (95% CI 3.1–9.2) (Figure 2C). Median PFS for EHC and GBC was 4.9 months in arm A (95% CI 2.4–7.4) and 3.8 months in arm B (95% CI 2.3–5.3) (Figure 2D).

However, IHC patients exposed to panitumumab had an improvement in OS of 3.3 months compared to the control group, which was not statistically significant (15.1 vs. 11.8 months; $p=0.13$) Figure 2E. We explored any potential explanation for this survival advantage in IHC patients despite similar PFS. In this subgroup, median number of cycles was 6 (range 3-12) in the P-GEMOX group and 11 (range 2-12) in GEMOX group, with more patients in the standard arm completing the preplanned 12-cycles treatment (10 patients in GEMOX group vs 6 patients in P-GEMOX group). Moreover, we could not demonstrate any significant difference among causes of end-of-treatment, occurrence of AEs, second line treatments or surgery between the arms (data not shown).

We also conducted a post-hoc analysis on patients who were wild-type on *KRAS*, *NRAS*, *BRAF* and *PI3KCA*. Only 56 samples of 89 could be analyzed and, among these, we found 3 patients with *BRAF* V600E mutations, 2 with *NRAS* mutations (A146S and Q61R) and 2 with *PI3KCA* E545K mutations. Mutated patients were equally distributed over study arms. No difference in PFS or OS was seen in quadruple wild-type patients treated with panitumumab. Survival results are summarized in Table 3.

We collected all adverse events (AEs) and serious adverse events (SAE) from randomization to the end of treatment (EOT) visit. Treatment was generally well tolerated in both arms and the safety profile of panitumumab was consistent with that observed in other panitumumab-based combinations. As anticipated, skin toxicity was the main AE in the P-GEMOX arm affecting up to 80% of patients: conjunctivitis (11.1%) and ungueal toxicity (20%) were also increased. Neurotoxicity, constitutional and gastrointestinal symptoms were equally common in both groups, although a higher incidence of diarrhea (55.5 vs 31.8%, chi-square $p= 0.04$), mucositis (22.2 vs 13.7%, $p= 0.61$) and constipation (24.4 vs 15.9%, $p= 0.46$), hypomagnesemia (15.5 vs 2.2%, $p= 0.06$), and hypokalemia (22.2 vs 4.5%, $p= 0.03$) was seen in patients treated with panitumumab. Previous experience with panitumumab in combination with chemotherapy in a neoadjuvant setting, in which also pathological data were available, did not anticipate considerable hepatic toxicity¹⁰; nevertheless, we noticed a higher incidence of transaminase increase ($p= 0.16$) and cholestasis ($p= 0.67$) in arm A (non-significant) which might be a specific feature of tumors prone to cholestasis, such as BTC. Patients with EHC-GBC had a similar incidence of transaminitis, cholestasis and cholangitis compared to IHC (data not shown). The main AEs are summarized in Table 4.

Globally, 30 patients experienced SAEs (18 patients in arm A and 12 in arm B) either related or unrelated to the therapy, which lead to discontinuation of panitumumab, gemcitabine and/or oxaliplatin treatment in 11 cases. Among the seven deaths due to SAEs (5 in arm A and 2 in arm B), only one case of sepsis was related to P-GEMOX: in the remaining cases, death was deemed unrelated or related to disease progression.

Discussion

Our results show that the addition of panitumumab to GEMOX chemotherapy in *KRAS* wt biliary cancer, although generally well tolerated, resulted in a marginal, not significant, improvement in PFS.

These results are consistent with recent randomized studies and provide additional evidence of the marginal role of anti-EGFR therapy in BTC.

At the time of trial design, a strong preclinical rationale suggested the effectiveness of an EGFR-inhibitor in BTC, and a few case reports and initial data of a Phase II study of GEMOX and cetuximab were also promising. More recently, the results of several studies conducted worldwide with either MoAbs and kinase-inhibitors have been published. Phase II non-randomized studies have shown up to 63% of ORR or median OS of up to 20.3 months^{8, 11-15}. However, in two randomized phase II studies of GEMOX with or without cetuximab, anti-EGFR therapy only marginally improved PFS and ORR, with no impact on OS in both European¹⁶ and Asian populations¹⁷. Similar disappointing results have been obtained using a different approach of EGFR inhibition. In a Phase III trial, erlotinib added to GEMOX in an Asian population, was only able to demonstrate a statistically significant improvement in ORR and a trend towards better survival in the experimental arm¹⁸. In this study, cholangiocarcinoma patients obtained a statistically significant advantage in PFS from the treatment with erlotinib plus GEMOX (5.9 months) compared with those treated with GEMOX alone (3 months).

In our population, all patients were *KRAS* wt on exon 2 as a result of a key inclusion criterion. At the time of the trial design and considering the strong preclinical evidence of EGFR involvement in BTC, this was a reasonable hypothesis both for *KRAS* biological function within the EGFR-pathway, and for its predictive role in colorectal cancer patients treated with panitumumab or cetuximab. This rationale is partially

supported by published results. In particular, Hezel observed the best results in terms of OS and PFS (20.3 and 10.6 months respectively) in *KRAS* wt patients, along with a very high ORR (45%)¹⁵. As for randomized trials, some retrospective data are available from studies by Malka¹⁶ and Lee¹⁸ but, due to the low percentage of samples analyzed, the predictive value of *KRAS* and *BRAF* mutations and EGFR overexpression is inconclusive. In a trial by Cheng, patients were stratified for the presence of the *KRAS* mutation, and an advantage in wt patients was observed regardless of the treatment received, thus envisaging a prognostic, rather than predictive, role. These studies are summarized in Table 5.

In a subgroup analysis, we reported a possible improvement in OS, only in patients with IHC treated with panitumumab. The reason for this finding is difficult to interpret due to the lack of statistical significance. However, also other studies have shown a trend towards better outcomes in IHC patients treated with anti-EGFR targeted agents^{17,18}. Is there any underlying biology that could explain why patients with IHC may benefit from EGFR inhibition? Our findings themselves do not justify the design of a new randomized clinical trial in this setting of patients; however, we think that data of available studies should be put together to draw solid conclusions.

It is likely that the complexity of activated pathways in malignant cholangiocytes does not fit the paradigms of efficacy that have been built up for other diseases. Could there be a benefit of anti-EGFR treatment, which was not immediately evident, even by selecting the patients as we did? In our population a deeper analysis on downstream EGFR effectors has not produced meaningful results. If we think about the differences in etiology, the different behaviors according to tumor site, the molecular subtypes of BTC and the recent discovery of new driving pathways, we get a picture of a rare and very heterogeneous disease. Therefore, it is difficult to identify a subset of patients in

whom anti-EGFR- targeted agents could have an impact on the natural history of the disease.

As data have been obtained from many similar studies, a pooled analysis of the results could help in identifying the patients who may benefit from anti-EGFR therapy. Until then, the history of anti-EGFR therapy in BTC does not deserve further investigations and we have to explore alternative strategies for future trials in such a rare and varied disease.

Figure Legends

Figure 1: Trial profile

Figure 2: A: Progression Free Survival in Arm A and Arm. B: Overall Survival in Arm A and Arm B. C: Progression Free Survival in intrahepatic cholangiocarcinoma carcinoma according to the treatment arm. D: Progression Free Survival in extrahepatic cholangiocarcinoma - galbladder according to the treatment arm. E: Overall Survival in intrahepatic cholangiocarcinoma carcinoma according to the treatment arm. F: Overall Survival in extrahepatic cholangiocarcinoma - galbladder according to the treatment arm

REFERENCES

1. Khan SA, Toledano MB, Taylor-Robinson SD. Epidemiology, risk factors, and pathogenesis of cholangiocarcinoma. *HPB (Oxford)*. 2008;10: 77-82.
2. Lim H, Seo DW, Park do H, et al. Prognostic factors in patients with gallbladder cancer after surgical resection: analysis of 279 operated patients. *J Clin Gastroenterol*. 2013;47: 443-448.

3. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med.*362: 1273-1281.
4. Sharma A, Dwary AD, Mohanti BK, et al. Best supportive care compared with chemotherapy for unresectable gall bladder cancer: a randomized controlled study. *J Clin Oncol.*28: 4581-4586.
5. Marino D, Leone F, Cavalloni G, Cagnazzo C, Aglietta M. Biliary tract carcinomas: from chemotherapy to targeted therapy. *Crit Rev Oncol Hematol.* 2013;85: 136-148.
6. Leone F, Cavalloni G, Pignochino Y, et al. Somatic mutations of epidermal growth factor receptor in bile duct and gallbladder carcinoma. *Clin Cancer Res.* 2006;12: 1680-1685.
7. Nakazawa K, Dobashi Y, Suzuki S, Fujii H, Takeda Y, Ooi A. Amplification and overexpression of c-erbB-2, epidermal growth factor receptor, and c-met in biliary tract cancers. *J Pathol.* 2005;206: 356-365.
8. Gruenberger B, Schueller J, Heubrandtner U, et al. Cetuximab, gemcitabine, and oxaliplatin in patients with unresectable advanced or metastatic biliary tract cancer: a phase 2 study. *Lancet Oncol.*11: 1142-1148.
9. Andre T, Tournigand C, Rosmorduc O, et al. Gemcitabine combined with oxaliplatin (GEMOX) in advanced biliary tract adenocarcinoma: a GERCOR study. *Ann Oncol.* 2004;15: 1339-1343.
10. Leone F, Artale S, Marino D, et al. Panitumumab in combination with infusional oxaliplatin and oral capecitabine for conversion therapy in patients with colon cancer and advanced liver metastases: The MetaPan study. *Cancer.* 2013.
11. Jensen LH, Lindebjerg J, Ploen J, Hansen TF, Jakobsen A. Phase II marker-driven trial of panitumumab and chemotherapy in KRAS wild-type biliary tract cancer. *Ann Oncol.* 2012;23: 2341-2346.

12. Rubovszky G, Lang I, Ganofszy E, et al. Cetuximab, gemcitabine and capecitabine in patients with inoperable biliary tract cancer: a phase 2 study. *Eur J Cancer*. 2013;49: 3806-3812.
13. Borbath I, Ceratti A, Verslype C, et al. Combination of gemcitabine and cetuximab in patients with advanced cholangiocarcinoma: a phase II study of the Belgian Group of Digestive Oncology. *Ann Oncol*. 2013;24: 2824-2829.
14. Sohal DP, Mykulowycz K, Uehara T, et al. A phase II trial of gemcitabine, irinotecan and panitumumab in advanced cholangiocarcinoma. *Ann Oncol*. 2013;24: 3061-3065.
15. Hezel AF, Noel MS, Allen JN, et al. Phase II study of gemcitabine, oxaliplatin in combination with panitumumab in KRAS wild-type unresectable or metastatic biliary tract and gallbladder cancer. *Br J Cancer*. 2014;111: 430-436.
16. Malka D, Cervera P, Foulon S, et al. Gemcitabine and oxaliplatin with or without cetuximab in advanced biliary-tract cancer (BINGO): a randomised, open-label, non-comparative phase 2 trial. *Lancet Oncol*. 2014;15: 819-828.
17. Chen JS, Hsu C, Chiang NJ, et al. A KRAS mutation status-stratified randomized phase II trial of gemcitabine and oxaliplatin alone or in combination with cetuximab in advanced biliary tract cancer. *Ann Oncol*. 2015.
18. Lee J, Park SH, Chang HM, et al. Gemcitabine and oxaliplatin with or without erlotinib in advanced biliary-tract cancer: a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol*. 2012;13: 181-188.