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Phase 3 Dose Selection for Ganitumab (AMG 479) in Pancreatic Cancer Based on Clinical Pharmacokinetics and Pharmacokinetic/Pharmacodynamic Assessments

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Background: Ganitumab (gmab) is an investigational, fully human monoclonal antibody against IGF1R. Population pharmacokinetic (PK) and PK/pharmacodynamic (PK/PD) assessments were performed to support gmab phase 3 (P3) study design in pancreatic cancer (PC) pts.
Methods: PK of gmab was characterized using concentration data from 4 Amgen-sponsored studies: two P1 studies (n = 64 pts) in advanced solid tumours (gmab monotherapy and gmab + gemcitabine [G]; ClinicalTrials.gov ID: NCT00562380 and NCT00974896) and 2 randomized, placebo-controlled P2 studies, one in breast cancer (BC, n = 104, gmab + exemestane [E] or fulvestrant [F] or placebo + E or F; NCT00626106) and one in PC (n = 35, gmab + G or placebo + G; NCT00630552). PK/PD analysis of the P2 PC study was performed with data from the gmab 12 mg/kg + G and placebo + G arms (~40 pts/arm). Effect of steady-state area under the concentration-time curve (AUC_{ss}) on overall survival (OS) and progression-free survival (PFS) was evaluated using a proportional Cox regression model. Kaplan–Meier estimates of PFS and OS were compared between pts with AUC_{ss} $\geqslant$median vs ss groups). Relationships between the gmab AUC_{ss} groups and adverse event (AE) rate and laboratory changes were investigated. Effects of confounding factors on the association between OS or PFS and AUC_{ss} were assessed by multivariate analyses. Potential P3 doses for gmab were explored with Monte Carlo simulations.
Results: The estimated gmab clearance (CL) was 0.0481, 0.0296, and 0.0283 L/h and the central volume distribution (Vc) was 5.13, 3.77, and 3.85 L for pts with PC, BC, and other solid tumours, respectively. The higher CL and larger Vc in PC pts resulted in ~40% lower gmab AUC_{ss} than in non-PC pts. In the high and low AUC_{ss} groups (median AUC_{ss}: 19.2 mg.h/mL), OS was longer in the high AUC_{ss} group (16 vs 4.7 months). There was a positive association between AUC_{ss} and both OS ($P < 0.001$) and PFS ($P < 0.001$). The effect of AUC_{ss} on PFS and OS remained significant after adjusting for potential prognostic factors including those associated with CL of gmab. The overall incidence of AEs was similar between the high and low AUC_{ss} groups. The incidences of grade 3/4 hyperglycemia and thrombocytopenia were slightly higher in the high AUC_{ss} group. There was no strong evidence of an association between AUC_{ss} and selected laboratory values (neutrophils, platelets, AST, ALT, fasting glucose). Simulations projected improved OS and PFS with 20 mg/kg vs 12 mg/kg gmab.
Conclusions: The reduced exposure of gmab in PC and the association between increased AUC_{ss} and improved clinical outcomes in PC support evaluation of the gmab 20 mg/kg dose. 12 and 20 mg/kg gmab are being evaluated in a P3 trial in PC (GAMMA: Gemcitabine and AMG 479 for Metastatic Adenocarcinoma of the Pancreas; NCT01231347).

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How Much Chemotherapy Are Patients With Advanced Pancreatic Cancer Receiving at the End of Life?

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Background: Advanced pancreatic adenocarcinoma (APC) is a chemo-resistant cancer with poor prognosis. We evaluated the use of chemotherapy in the last months of life.
Methods: Retrospective analysis of patients with APC treated from 1993 to 2010 at the Oncology Institute of Southern Switzerland. Clinical and laboratory parameters starting from 28 days prior to the last administration of chemotherapy were recorded, including ECOG performance status, presence of ascites, haemoglobin (Hb), white blood cell (WBC) count, platelets, total bilirubin, albumin, LDH, C-reactive protein (C-rp) and Ca 19.9.
Results: The characteristics of the 231 patients were: males/females 53%/47%; metastatic/locally advanced disease 80%/20%; median age 66 years (range 32−85). Median overall survival calculated from diagnosis was 6.1 months (95% CI: 5.1−7.2); death was due to disease progression in all cases. At last chemotherapy administration, ECOG performance status was 0−1 in 38% and 2−3 in 62%. Fifty-nine percent of pts received first-line chemotherapy only (gemcitabine in 70%; gemcitabine-based doublets or 5FU in 30%), whilst 32%, 8% and 1% had second- (5FU 37%; oxaliplatin-based doublets 57%; phase I trial 6%), third- and fourth-line therapy (single agent or phase I trial), respectively. The interval between last chemotherapy administration and death was <4 weeks in 24%, $\geqslant$4−12 weeks in 47% and >12 weeks in 29%. Table 1 summarizes the proportion of patients treated according to the interval between last chemotherapy and death refered to chemotherapy line. Median survival from last chemotherapy delivery to death was 7.5 weeks (95% CI 6.7−8.4). In univariate analysis, presence of ascites, elevated WBC, total bilirubin, LDH, C-rp and Ca 19.9, and reduced albumin were found to predict shorter survival ($p < 0.05$ for each). However, none of them was an independent predictor in the multivariate analysis.
Conclusions: A significant proportion of patients with APC received chemotherapy in the last months of life. In our study, none of the clinical and laboratory parameters recorded 28 days priorto the last chemotherapy delivery were found to predict survival.

Table 1.

Last line	<4 weeks	$\geqslant$4−12 weeks	>12 weeks
1st line (n = 137)	27%	48%	25%
2nd line (n = 74)	20%	47%	33%
3th line (n = 18)	22%	39%	39%
4th line (n = 2)	0	50%	50%

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Phase IIa Study of TP300 as 1st-line Monotherapy in Patients With Advanced Gastric (GC) or Gastro-oesophageal Junction (GOJ) Carcinoma

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Background: TP300, a novel topoisomerase I inhibitor, had manageable toxicity in a Phase I study, in which 3 of 12 patients at the Maximum Tolerated Dose (10 mg/m^2) had dose-limiting toxicity. Consequently, 8 mg/m^2 was chosen as the starting dose in subsequent studies. The primary objective of this Proof of Concept study was to determine the objective response rate of TP300 in patients with advanced gastric (GC) or gastro-oesophageal junction (GOJ) carcinoma. Progression-free survival (PFS), time to progression (TTP), and safety were also determined.
Material and Methods: Eligible patients were those with advanced GC or Siewert Types II or III GOJ carcinoma, previously untreated with chemotherapy for advanced disease, with adequate performance status, hematologic, renal, and hepatic function, and with measurable disease. TP300 was administered as a 1-hour intravenous infusion every 3 weeks for up to 6 cycles at a starting dose of 8 mg/m^2 with intra-patient escalation to 10 mg/m^2 from cycle 2 based on cycle 1 toxicities. Tumour response (RECIST 1.1) was assessed every 6 weeks. Toxicity was recorded using the NCI-CTCAE version 3.0. Using a 2-stage design, a total of 43 patients would be included if there were $\geqslant$3 of 18 patients with objective response in the 1st stage. The study was sponsored by Chugai Pharma Europe Ltd (EudraCT No. 2009-012097-12).
Results: 20 patients (14 males, 6 females), median age 67 years (range 40−82), performance status ECOG 0/1, with GC (14) or GOJ carcinoma (6) received a median of 3 cycles (range 0−6) of TP300. 18 patients were evaluable for response (investigator assessment), 16 on external independent review. 11 patients had a dose increase to 10 mg/m^2 at cycle 2, 2 were decreased to 6 mg/m^2 (investigator decision), and 3/16 continued on 8 mg/m^2. There were no objective responses after 2 cycles of treatment. 12 patients had stable disease for 1−5 months and 4 had progressive disease. Median PFS was 4.1 months (CI [1.6−4.9]), median TTP was 2.9 months (CI [1.4−4.2]). Grade 3/4 toxicities (worst grade all cycles) included 7 patients (35%) with neutropoenia, 4 patients (20%) with anaemia, 2 patients (10%) with thrombocytopenia, 3 patients (15%) with fatigue.

Conclusion: TP300 was well tolerated but no objective responses were observed in 16 evaluable patients with GC or GOJ carcinoma, and recruitment of further patients was discontinued.

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Improved 6-month Survival Rate in Subjects With Prostate Stem Cell Antigen (PSCA) Positive Tumours in a Global, Randomized Phase 2 Trial Comparing Gemcitabine Vs. Gemcitabine + Ags-1c4d4 (asp6182) in Metastatic Pancreatic Cancer (mPC)

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Background: AGS-1C4D4 (ASP6182) (A) is a CHO-derived fully human monoclonal antibody (MAb) generated from AGS-PSCA (P) a hybridoma MAb. PSCA is a cell surface protein expressed by about 50% of pancreatic cancers, and A significantly inhibited the growth and metastasis of established orthotopic HPAC tumours in combination with gemcitabine (G). These results are of the primary analysis preplanned for when the last randomized patient was followed for 6 months. Final overall survival data is expected by August 2011.
Methods: Previously untreated patients with pathologically-confirmed mPC and ECOG performance status (PS) of 0 or 1 were randomized 1:2 to G (1000 mg/m^2 IV over 30 minutes weekly $\times$7, 1 week rest, then weekly $\times$3 q4weeks) or G plus A (48 mg/kg loading dose, then 24 mg/kg q3weeks over 60 minutes IV), stratified by region (North America vs. Europe/Russia). Primary endpoint was 6-month (mo) survival rate (SR) in the intention-to-treat (ITT) population. With a planned sample size of 185 pts, the study was designed to detect an improvement in 6-mo SR from 45% to 65% with 90% power and one-sided $\alpha = 0.10$. Tumour samples were collected for pre-planned secondary analyses by PSCA expression.
Results: 196 pts (63 in G arm, 133 in G+A arm) enrolled 04/09–05/10 at 55 centers in USA, Canada, Spain, France, and Russia. For G/G+A arms: median age 63/62 years, male 40/56%, PS 1 83/73%, deaths to date 73/71%. Grade 3/4 adverse events (G/G+A; %): any 63/78%, neutropenia 14/26%, thrombocytopenia 2/9%, and pulmonary embolism 2/6%. Tumour tissue was available from 118 pts (60%) for immunohistochemistry (IHC): 64 pts strong/moderate (+) and 54 weak/no staining (−) for PSCA. Efficacy data for 6-mo SR are shown in the table. Disease control rate (95% CI) was 49% (36, 62) for G arm and 50% (41, 58) for G+A arm in the ITT population, and 57% (34, 78) for G arm and 70% (54, 83) for G+A arm in the PSCA+ population.

Population	6-mo. SR (%) (95% CI)			
	ITT	PSCA unavailable	PSCA −	PSCA +
G + A	56 (47, 64)	55 (41, 68)	34 (19, 52)	74 (59, 87)
G	44 (32, 58)	44 (23, 66)	32 (13, 57)	57 (34, 78)
Difference (G+A)–A (95% CI)	11 (−4, 26)	11 (−13, 35)	3 (−25, 30)	17 (−10, 42)
P-Value*	0.07	0.19	0.42	0.08

*One-sided Cochran-Mantel-Haenszel test.

Conclusions: A trend toward improved 6-mo SR was seen in mPC patients with tumours that stained strong or moderate for PSCA expression who were treated with G or G+A. Follow-up is ongoing for secondary endpoints.

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5-Fluorouracil/Leucovorin, Oxaliplatin and Irinotecan (FOLFOXIRI) as First-Line Treatment of Advanced Gastric Cancer

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Background: The aim of the present study was to evaluate the efficacy and safety of FOLFOXIRI as first-line treatment in patients with advanced gastric cancer (AGC) based on results of J. Lee y col. (Annals of Oncology 18: 88−92, 2007).

Material and Methods: 35 patients (p) diagnosed with locoregional, recurrent or metastatic AGC, <75 years old, chemotherapy naïve, PS 0−3, with accurate renal, hepatic and bone marrow functions, were treated from April/27 to March/11 with 5-Fluorouracil 2000 mg/m^2 48 h continuous infusion/d1−3, Leucovorin 100 mg/m^2/d1 and Irinotecan 150 mg/m^2/d1; cycles were administered every 2 weeks, up to 12 cycles, tumour progression or unacceptable toxicity. A total of 35 p were evaluable for toxicity and 33 p for response (2 p early exits from the study).
Results: Median age: 64 years (51−75); male/female: 26/9; PS 0/1/2/3: 3/20/10/2. Advanced locoregional 5 p, metastatic 28 p and recurrent 2 p. Affected organs 1/2/>2: 2/10/23. Sites: Distal lymph nodes 30%, peritoneum 22%, liver 20% and others 26%. A total of 367 cycles were administered with a median of 10 per patient. Effectiveness analysis: 1 RC and 23 RP (RR global 72.7%) and 8 p EE (24.2%). Most relevant toxicities per patient were: anemia G1+2: 77%, neutropenia G3+4: 48%, thrombocytopenia G1+2: 37%, neurotoxicity G1+2:45%, mucositis G1+2: 22%, diarrhea G1+2: 48% and emesis G3+4:42%. 17 p (48%) underwent dose reduction. 6 p received second line QT. Rescue gastrectomy was performed in 2 p. Median time to progression was 8.9 months and median overall survival was 10.3 months.
Conclusions: FOLFOXIRI treatment as first-line treatment of AGC on daily based practice has demonstrated a high activity with a manageable acute toxicity profile, reproducing previously reported results in series of selected patients.

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Phase II Trial of MiniDOX in "Suboptimal" Patients With Advanced Gastric Cancer (AGC). TTD 08−02 (Nº EudraCT: 2008-001825-32)

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Background: Chemotherapy has improved the overall survival (OS) in patients (p) with AGC. We defined "Suboptimal" p as those with PS ECOG-2 and/or weight loss 10−25% and/or age $\geqslant$70 years. This population is usually underrepresented in AGC clinical trials.
Methods: We explored in 43 previously untreated "suboptimal" AGC p the "miniDOX" regimen (docetaxel(D) 40 mg/m^2 iv, d1; oxaliplatin (O) 80 mg/m^2 iv d1; capecitabine (C) 625 mg/m^2 po bid, d1 to 21, every 21d; after 6 courses only C was maintained). D and O dose were allowed to be increased to 45 $\rightarrow$ 50 and to 90 $\rightarrow$ 100 mg/m^2 respectively if less than grade 2 toxicity after the first 2 courses. One included p that did not received any dose of chemotherapy, was included in the ITT efficacy analysis but not in the safety analysis. After the inclusion of the first 10 p the protocol was amended: close vigilance of thromboembolic disease and prophylactic use of G-CSF was recommended. Primary endpoint was Response Rate (RR) and toxicity was the main secondary objective.
Results: *Patient characteristics*: PS ECOG-2:12 p, Weigh loss 10−25%:23 p; median age 73.3 years (40.2–87.7); 32 males; locally advanced: 8 p/metastatic:35 p; Primary site: Gastric 32 p/EGJ 11; Lauren histological type: diffuse 8 p/intestinal 19 p/mixed 1 p/unknown 15 p; Prior gastrectomy: 10 p. In 19 p the dose of D and O were increased to 45 and 90 mg/m^2 respectively and in 8 p to 50 and 100 mg/m^2. Six courses of O and D were administered in 46% and 53% respectively and 58% were treated with 6 or more courses of C. Worst toxicity per p (Grade 3−4): neutropenia: 5 p; febrile neutropenia: 3 p; thrombocytopenia: 1 p; Pulmonary embolism (PE): 4 p (3 of them suffered sudden death and the PE was suspected but not confirmed); diarrhoea: 9 p; paronychia: 2 p; ictus: 1 p; renal failure: 1 p (this p suffered infection/bacteraemia without neutropenia and died); Hand-foot syndrome: 4 p and asthenia: 5 p. Response: CR: 1 p, PR: 27 p (RR: 65%), SD: 8 p, Progression: 2 p, No determined: 5 p; With a median follow-up of 9.2 months, 21 p have died (toxicity: 4 p, progressive disease: 16 p, toxicity of second line treatment 1 p) and 22 p are alive with disease. Median and one year actuarial progression free survival and OS are 5.6 months/17% and 14.6 months/58% respectively.
Conclusions: Although the toxicity (mainly PE) of miniDOX has been important, its activity has been very interesting in "suboptimal" pts with AGC and this combination should be further investigated in this setting.