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Updated Overall Survival Data From a Phase III Study of Sunitinib Vs. Placebo in Patients With Advanced, Unresectable Pancreatic Neuroendocrine Tumour (NET)

J. Valle[1], P. Niccoli[2], J.L. Raoul[3], Y.J. Bang[4], I. Borbath[5], E. Van Cutsem[6], R. Sandin[7], D. Lu[8], S. Patyna[9], E. Raymond[10]. [1]*Christie Hospital NHS Foundation Trust, Medical Oncology, Manchester, United Kingdom;* [2]*CHU Timone and Institut Paoli-Calmettes and RENATEN Network, Oncology Unit, Marseille, France;* [3]*Paoli-Calmettes Institute, Medical Oncology, Marseille, France;* [4]*Seoul National University College of Medicine, Department of Internal Medicine, Seoul, South Korea;* [5]*Cliniques Universitaires Saint-Luc, Gastroenterology, Brussels, Belgium;* [6]*University Hospital Gasthuisberg, Digestive Oncology Unit, Leuven, Belgium;* [7]*Pfizer Oncology, Global Health Economics and Outcomes Research, Solluentuna, Sweden;* [8]*Pfizer Oncology, Clinical Statistics, La Jolla, USA;* [9]*Pfizer Oncology, Clinical Development, La Jolla, USA;* [10]*Beaujon University Hospital, Medical Oncology, Clichy, France*

Background: A phase III trial revealed that sunitinib improved progression-free survival (PFS) and overall survival (OS) vs. placebo in patients with pancreatic NET [Raymond NEJM 2011]. Sixty-nine percent of patients randomized to placebo crossed over to sunitinib upon disease progression or upon closure of the trial. Crossover can confound the analysis of OS. Here, we provide updated OS data and estimate the effect of sunitinib on OS after adjusting for treatment crossover.
Materials and Methods: Patients were randomized 1:1 to sunitinib 37.5 mg as a continuous daily dose or to placebo, each with best supportive care. The primary endpoint was PFS; OS was a secondary endpoint assessed in the ITT population. Three methods were used to adjust for the effect of treatment crossover: (1) data for patients in the placebo arm were censored at time of crossover; (2) data were analyzed using the Cox model where treatment was a time-dependent covariate, or (3) data were analyzed using the Rank-Preserving Structural Failure Time (RPSFT) model which corrects for time-dependent changes in survival data while respecting the randomization.
Results: 171 patients were randomized, 86 to sunitinib and 85 to placebo; median follow-up time was 26.0 months (95% CI 23.2, 27.1). Patients randomized to placebo crossed over to sunitinib at disease progression (38/85, 45%), or when the trial was closed (21/85, 25%). OS analyses were conducted based on a June 2010 cut-off (73 [43%] deaths) and data are shown in the table.

OS Analyses	Hazard Ratio (95% CI) (Sunitinib vs. Placebo)
No Adjustment for Crossover	
ITT	0.737 (0.465, 1.168)
Adjusting for Crossover	
Analysis with Censoring at Crossover	0.416 (0.230, 0.752)
Time-Dependent Treatment Analysis	0.468 (0.268, 0.818)
RPSFT Model	0.499 (0.351, 0.947)

Conclusions: Despite a high degree of crossover from treatment with placebo to sunitinib, the ITT analysis demonstrates compelling evidence of an OS benefit for sunitinib in pancreatic NET. Additionally, three different methods of adjusting for crossover demonstrate similar adjusted estimates of the treatment effect on OS. Together, these data provide evidence that sunitinib may improve survival in patients with pancreatic NET.

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Update of AMC 0201 Study − a Randomized Phase III Trial Comparing Mitomycin-C Plus Short-term Doxifluridine (Mf) Versus Mitomycin-C Plus Long-term Doxifluridine Plus Cisplatin (MFP) After Curative Resection of Advanced Gastric Cancer (NCT00296335)

Y.J. Min[1], Y.K. Kang[2], B.Y. Ryoo[2], D.Y. Zang[3], G.Y. Kim[4], D.H. Yang[5], S.J. Jang[6], J.H. Yook[7], S.T. Oh[7], B.S. Kim[7]. [1]*Ulsan University Hospital, Division of Hematology-Oncology, Ulsan, Korea;* [2]*Asan Medical Center, Department of Oncology, Seoul, Korea;* [3]*Hallym University Medical Center, Division of Hematology-Oncology, Anyang, Korea;* [4]*Ulsan University Hospital, Department of Surgery, Ulsan, Korea;* [5]*Hallym University Medical Center, Department of Surgery, Anyang, Korea;* [6]*Asan Medical Center, Department of Pathology, Seoul, Korea;* [7]*Asan Medical Center, Department of Surgery, Seoul, Korea*

Background: Despite a continuing debate on the role of adjuvant chemotherapy, several studies have suggested that mitomycin-C (M) plus fluoropyrimidine (f) could improve the outcome of curatively resected advanced gastric cancer (AGC) patients (pts). To improve further the adjuvant Mf chemotherapy, we have prolonged the administration of oral fluoropyrimidine (F) and added cisplatin (P) to Mf (MFP) and performed a phase III randomized trial to determine whether this strategy could improve the 3-year relapse free survival (3yRFS) in curatively resected AGC pts (HR = 0.63, $\alpha = 0.05$, $\beta = 0.1$). Three year follow-up results were reported in 2008 ASCO meeting. Here we report long-term follow-up results for confirmation.
Methods: Three to 6 wks after R0 resection, the pts who had postoperative stage II-IV were randomized to receive either Mf or MFP adjuvant chemotherapy. For Mf group, 20 mg/m^2 of M was iv injected and 4 wks later, 460–600 mg/m^2/day of doxifluridine was administered orally for 3 months. For MFP group, the administration of doxifluridine was extended for a total of 12 months and 6 shots of monthly 60 mg/m^2 of cisplatin were added to Mf.
Results: Between Feb 2002 and Aug 2006, a total of 871 pts were randomized (435 in Mf, 436 in MFP). Sixteen pts were excluded because of ineligibility (11 in Mf, 5 in MFP). Postoperative stages were II in 51.0%, IIIA in 31.1%, IIIB in 9.4%, and IV in 8.5% of pts. With a median follow up of 6.6 yrs in April 2011, a total of 353 events (relapse or death) have been observed. There was no difference in RFS between the two groups (HR, 1.10; 95% C.I. 0.89–1.35; p = 0.3918; 5yRFS 61.1% in Mf and 57.9% in MFP). Difference in overall survival (OS) was also insignificant (HR, 1.11; 95% C.I. 0.89–1.39; p = 0.3349; 5yOS 66.5% in Mf and 65.0% in MFP).
Conclusions: Long-term follow-up results of AMC 0201 trial confirmed prolongation of doxifluridine administration and addition of cisplatin to adjuvant chemotherapy with mitomycin-C plus 3 months of doxifluridine did not improve the treatment outcome in curatively resected AGC pts.

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Impact of Prior Somatostatin Analog (SSA) Use on PFS in the Multicenter, Phase III Trial of Everolimus + Octreotide LAR Vs Placebo + Octreotide LAR in Patients With Advanced Neuroendocrine Tumours (RADIANT-2)

M. Pavel[1], N. Singh[2], V. Passos[3], K. Oberg[4]. [1]*Universitätsklinikum Charité, Campus Virchow-KlinikumMedizinische Klinik m.S. Hepatologie & Gastroenterologie, Berlin, Germany;* [2]*Novartis Healthcare Pvt. Ltd., Hyderabad, India;* [3]*Novartis Pharmaceuticals Corporation, Florham Park, USA;* [4]*University Hospital, Endocrine Oncology, Uppsala, Sweden*

Background: SSA have been the foundation of therapy used to treat symptoms associated with carcinoid syndrome in pts with advanced NET. Octreotide LAR has been shown to significantly increase TTP in SSA-naive patients with metastatic midgut NET (Rinke et al, JCO 2009). In the RADIANT-2 trial (NCT00412061; ESMO 2010 Abstract LBA8), the largest randomized placebo controlled trial in patients with advanced NET and a history of flushing and/or diarrhea, everolimus plus octreotide LAR (E+O) demonstrated a clinically meaningful 5.1-mo improvement in PFS compared with placebo plus octreotide LAR (P+O). This post hoc analysis was conducted to characterize the effect of octreotide LAR therapy on PFS in the large RADIANT-2 trial pt population.
Materials and Methods: 429 pts (ITT population) with low- or intermediate-grade advanced NET received either everolimus 10 mg/d plus octreotide LAR 30 mg im q28d (n = 216) or placebo plus octreotide LAR 30 mg im q28d (n = 213). Primary endpoint was PFS per central adjudicated review (RECIST v1.0). Pts with and without prior receipt of SSA therapy at baseline were identified.

Primary tumour site	Median PFS, mo E+O (N = 216)		Median PFS, mo P+O (N = 213)	
	No Prior SSA (N = 43)	Prior SSA (N = 173)	No Prior SSA (N = 47)	Prior SSA (N = 166)
All	25.2 (12.0, NR) (N = 43)	14.3 (12.0, 20.1) (N = 173)	13.6 (8.2, 22.7) (N = 47)	11.1 (8.4, 14.6) (N = 166)
All except small intestine	13.8 (8.6, 27.8) (n = 26)	14.0 (11.0, 20.1) (n = 79)	8.3 (5.6, 22.2) (n = 30)	11.0 (6.6, 14.3) (n = 70)
Small intestine	NR (13.7, NR) (n = 17)	17.1 (11.2, 24.8) (n = 94)	22.7 (11.1, 30.4) (n = 17)	11.1 (8.3, 19.3) (n = 96)

NR, not reached.

Results: At baseline, 47/213 (22%) of P+O and 43/216 (20%) of E+O pts were SSA-naive. Among patients with prior SSA therapy, >90% had a history of octreotide LAR use; median duration of prior SSA exposure was 1.7 years for E+O and 1.8 years for P+O. Median PFS was longer among pts without prior SSA therapy in both treatment arms compared to those with prior SSA therapy across different tumour sites, particularly in those with small intestinal NET (Table).
Conclusions: In this large randomized study, the combination of everolimus plus octreotide LAR provided additional benefit prolonging PFS regardless of prior SSA use for each tumour site. Furthermore, patients with

progressing advanced NET who were SSA-naive had longer median PFS when treated with octreotide LAR alone compared to patients who had prior SSA, supporting the antitumour effects of octreotide LAR demonstrated in the PROMID trial.
Study supported by Novartis.

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Effect of Everolimus + Octreotide LAR in Patients With Advanced Lung Neuroendocrine Tumours − Analysis From RADIANT-2

N. Fazio[1], D. Granberg[2], A. Grossman[3], S. Saletan[4], R.E. Winkler[5], A. Panneerselvam[6], E.M. Wolin[7]. *[1]European Institute of Oncology, Medicine, Milan, Italy; [2]University Hospital, Medical Sciences and Endocrine Oncology, Uppsala, Sweden; [3]Oxford Centre for Diabetes University of Oxford, Centre for Diabetes Endocrinology and Metabolism, Oxford, United Kingdom; [4]Novartis Pharmaceuticals Corporation, Oncology, Florham Park, USA; [5]Novartis Pharmaceuticals Corporation, Clinical Development, Florham Park, USA; [6]Novartis Pharmaceuticals Corporation, Oncology Biometrics and Data Management, Florham Park, USA; [7]Cedars-Sinai Medical Center, Medicine, Los Angeles, USA*

Background: The lung is the second most common site of occurrence of neuroendocrine tumours (NET). No approved antitumour agents are available for the treatment of lung NET. An antitumour effect of everolimus, an oral mTOR inhibitor, in human bronchial carcinoid tumour cells in vitro has been reported. In the RADIANT-2 trial (NCT00412061; ESMO 2010 Abstract LBA8), everolimus plus octreotide LAR (E+O) provided a clinically meaningful 5.1-mo prolongation of median progression-free survival (16.4 mo E+O vs 11.3 P+O; HR, 0.77; 95% CI, 0.59–1.00; $P = 0.026$) vs placebo plus octreotide LAR (P+O) in pts with advanced NET and a history of flushing or diarrhea. Exploratory analysis of PFS by tumour site demonstrated that E+O was beneficial across all primary tumour site patient subgroups, including lung NET. An analysis of pts with lung NET and their response to E+O is presented.
Materials and Methods: 429 pts (ITT population) with low- or intermediate-grade advanced NET were randomly assigned to either everolimus 10 mg/d plus octreotide LAR 30 mg intramuscularly q28d (n = 216) or placebo plus octreotide LAR (n = 213). The primary endpoint was PFS per central review (RECIST v1.0). Baseline demographics, disease characteristics, biomarker levels, and tumour response to treatment were analyzed for the subset of pts with lung NET.
Results: 44 pts with lung NET were identified: 33 in the everolimus arm and 11 in the placebo arm. Baseline demographics and disease characteristics of lung NET pts were similar to those of the overall patient population. Among the lung NET pts, a higher proportion of pts receiving E+O vs P+O were >65 years (42% vs 18%), were diagnosed $\geqslant$2 years earlier (76% vs 55%), and had elevated baseline CgA (>2 $\times$ ULN) and 5-HIAA (>median) (52% vs 36%). Median PFS for pts with lung NET was 13.63 mo in the E+O group vs 5.59 mo in the P+O group (HR, 0.72; 95% CI, 0.31–1.68; $P = 0.228$). More E+O than P+O lung NET pts experienced some degree of tumour shrinkage consistent with the findings in the overall study population (67% vs 27% for lung NET, 75% vs 45% for overall population).
Conclusions: Everolimus plus octreotide LAR improved PFS in pts with advanced low-/intermediate-grade lung NET similar the overall population despite the poor prognosis of these pts. The imbalance in the frequency of this important baseline prognostic factor favoring the P+O arm should be considered when interpreting the overall results of the trial.
Study supported by Novartis.

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Effect of Everolimus Treatment on Markers of Angiogenesis in Patients With Advanced Pancreatic Neuroendocrine Tumours (pNET) − Results From the Phase III RADIANT-3 Study

J.C. Yao[1], Z. Tsuchihashi[2], A. Panneerselvam[3], R.E. Winkler[4], R. Bugarini[2], M. Pavel[5]. *[1]University of Texas MD Anderson Cancer Center, Gastrointestinal Medical Oncology, Houston, USA; [2]Novartis Pharmaceuticals Corporation, Oncology Biomarkers and Clinical Imaging, Florham Park, USA; [3]Novartis Pharmaceuticals Corporation, Oncology Biometrics and Data Management, Florham Park, USA; [4]Novartis Pharmaceuticals Corporation, Clinical Development, Florham Park, USA; [5]Charité Universitätsmedizin Berlin, Gastroenterology and Hepatology Endocrinology and Diabetes, Berlin, Germany*

Background: The mammalian target of rapamycin (mTOR) is a cytoplasmic protein kinase that regulates cellular metabolism, growth, proliferation, and angiogenesis. Inhibition of mTOR is thought to inhibit angiogenesis through a mechanism distinct from VEGF inhibitors and has been shown to reduce endothelial cell proliferation in vitro and tumour vascularization in vivo. In the RADIANT-3 trial (NCT00428597), everolimus, an oral inhibitor of mTOR, significantly prolonged progression-free survival (PFS) in patients with advanced pNET (Yao et al., NEJM, 2011). We determined the effects of everolimus treatment on levels of several angiogenic biomarkers in patients in the RADIANT-3 trial.
Materials and Methods: Patients with progressive, advanced low- or intermediate-grade pNET were randomly assigned to everolimus 10 mg/d orally (n = 207) or placebo (n = 203). Serum samples were collected and analyzed for VEGF, PLGF, bFGF, sVEGFR1, and sVEGFR2 at baseline and on day 1 of cycles 2 through 4. Treatment effect on change from baseline over time was analyzed using a repeated-measures model adjusting for other prognostic factors.
Results: Everolimus vs placebo resulted in a significant reduction of sVEGFR2 ($P < 0.001$) and PLGF ($P = 0.04$). No significant changes in sVEGFR1 ($P = 0.62$), bFGF ($P = 0.13$), or VEGF ($P = 0.35$) were observed. Everolimus compared with placebo was associated with a consistent reduction in the mean fold change from baseline in sVEGFR2 (everolimus vs placebo, respectively: cycle 2, 0.75 vs 0.95; cycle 3, 0.73 vs 0.92; cycle 4, 0.69 vs 0.90; $P < 0.001$ each cycle). This effect was independent of potential prognostic factors, including WHO by histologic grade. Everolimus compared with placebo was associated with a reduction in the mean fold change from baseline in PLGF; however, the overall magnitude of the reduction was small (everolimus vs placebo, respectively: cycle 2, 0.93 vs 1.00 [$P < 0.001$]; cycle 3, 0.98 vs 1.00 [$P = 0.32$]; cycle 4, 1.00 vs 1.01 [$P = 0.34$]).
Conclusions: Everolimus demonstrates a significant antiangiogenic effect in patients with advanced pNET. These data confirm previous findings from studies with everolimus in patients with RCC.
Study supported by Novartis.

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Thirty-four Cases of Advanced Ampullary Carcinoma Receiving Non-surgical Treatment − Experience at a Single Center

H. Shoji[1], C. Morizane[1], T. Taniyama[1], T. Yamaguchi[1], S. Kondo[1], H. Ueno[1], T. Okusaka[1]. *[1]National Cancer Center Hospital, Hepatobiliary and Pancreatic Oncology Division, Tokyo, Japan*

Background: Ampullary carcinomas are a fairly disease entity, and little information regarding these tumours, particularly non-surgical treatment, is available. Only one previous report describing 29 patients with advanced ampullary adenocarcinoma treated using cisplatin-based combination chemotherapy has been made (Kim ST et al. Med Oncol.2010). The aim of the present study was to clarify the clinical behavior, treatment strategy, and outcome of ampullary carcinoma treated using a non-surgical approach.
Methods: This study retrospectively reviewed data from patients with advanced ampullary carcinoma who receive non-surgical treatment between 1997 and 2010.
Results: We identified 34 patients (male/female, 19/15; median age, 62.5 yrs, ranging from 45−79 yrs). Patients characteristics were as follows: adenocarcinoma/neuroendocrine cell carcinoma/undifferentiated carcinoma accounted for 28, 5, and 1, respectively; PS of 0, 1 and 2−4 for 23, 11 and 0, respectively; Stage IV and recurrence accounted for 17 each; and metastatic sites were the liver, lung, lymph nodes, peritoneum and pleura in 22, 7, 21 1 and 1, respectively. The treatment group consisted of chemotherapy (n = 30), TACE (n = 1) and best supportive care (n = 3). The chemotherapy group were treated with 5-FU+CDDP (n = 3), CDDP+Epirubicin+5-FU (n = 1), UFT+Doxorubicin (n = 5), S-1 (n = 3), GEM (n = 11), GEM+CDDP (n = 6) and CDDP+ETP (n = 1). When the data for the adenocarcinoma group who received chemotherapy were analyzed, the over-all response rate was 7.7%. The median progression-free survival was 3.2 months (3.2 months in the 5-FU containing regimen group: 5-FU group vs. 3.8 months in the GEM containing regimen group: GEM group) and the median over-all survival time was 8.2 months (8.0 months in the 5-FU group vs. 9.1 months in the GEM group). There was no statistically significant difference between the 5-FU group and the GEM group.
Conclusions: The treatment outcome in patients with advanced ampullary carcinoma was poor. As com-pared with 5-FU-based regimen, the GEM-based regimen showed a favorable outcome, but the difference was not statistically significant.

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Biliary Tract Carcinomas − a Retrospective Analysis of First Line Chemotherapy Based on Platinium Compounds and Second Line Based on 5 Fluororacil

F. Fiteni[1], T. Nguyen[1], C. Borg[1]. *[1]Hôpital Minjoz, Doubs, Besançon, France*

Purpose: The goal of this study was to examine the survival and safety in patients with metastatic unresecable biliary tract carcinomas (BTC) treated in first line chemotherapy by the association of gemcitabine with