

6569

POSTER

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

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**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.

6570

POSTER

# 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)

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**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<sup>2</sup> of M was iv injected and 4 wks later, 460–600 mg/m<sup>2</sup>/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<sup>2</sup> 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.

6571

POSTER

# 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)

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**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-naïve 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-naïve. 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