

The 2010 Gastrointestinal Cancers Symposium

General Session VI: Cancers of the Pancreas – Multidisciplinary Treatment

Abstract #127: Updated results of the phase III trial of sunitinib versus placebo for treatment of advanced pancreatic neuroendocrine tumors

Speaker: Eric Raymond, MD, PhD– University Hospital in Bichat-Beaujon, Clichy, France

Background

- Pancreatic neuroendocrine tumors are a very rare disease with a limited number of medical treatments that increase progression free survival and overall survival.
- The randomized double-blind phase III trial was based on preclinical and clinical data showing sunitinib may benefit advanced progressive pancreatic endocrine tumors.

History of Sunitinib in Neuroendocrine Tumors (NETs)

- In a mouse model of pancreatic islet cell carcinoma, sunitinib reduced tumor burden, increased survival and showed VEGFR and PDGFR inhibition.
- In phase I study of sunitinib in solid tumors, including four patients with non-pancreatic NETs, there was one confirmed partial response and one minor response of stable disease.
- In a phase II trial, sunitinib was given to 66 patients with advanced pancreatic NETs. Treatment with sunitinib led to:
 - Partial Response (PR) in 16.7% of patients
 - Stable Disease (SD) of ≥ 6 months in 56.1% of patients
 - Median Time To Progression (TTP) of 7.7 months
- This favorable work laid the foundation for the phase III trial of sunitinib versus placebo.

Eligibility criteria

- Well differentiated, malignant pancreatic endocrine tumor.
- Not amenable to treatment with curative intent.
- Disease progression in past 12 months.

Study Design

- N=340, randomized 1:1
 - Arm A – sunitinib 37.5 mg/day continuous daily dosing (CDD)+ best supportive care
 - Arm B – placebo + best supportive care

Endpoints

- Primary endpoint: Progression free survival (PFS)
- Secondary endpoints: Overall survival (OS), overall response rate (ORR), duration of response, safety and patient reported outcomes.

Demographic and Baseline Characteristics

	Sunitinib (n=86)	Placebo n=85
Median age (range) years	56 (25-84)	57 (26-78)
Male, n (%)	42 (48.8)	40 (47.1)
Female	44 (51.2)	45 (52.9)
ECOG Performance Status, n (%)		
0	53 (61.6)	41 (48.2)
1	33 (38.4)	43 (50.6)

Tumor Characteristics at Baseline and Prior Treatments

	Sunitinib (n=86)	Placebo n=85
Median time from diagnosis, years (range)	2.4 (0.1-25.6)	3.2 (0.1-21.3)
Presence of distant metastases, n (%) of patients		
Any	82 (95.3)	80 (94.1)
Extrahepatic	21 (24.4)	34 (40.0)
Disease sites, n (%) of patients		
Pancreas	35 (40.7)	31 (36.5)
Lymph nodes	29 (33.7)	41 (48.2)
Liver	79 (91.9)	78 (91.8)
Lung	9 (10.5)	15 (17.6)
Other	21 (24.4)	29 (34.1)
Prior Treatments (%)		
Had surgery	88.4	90.6%
Had radiation therapy	10.5	14.1
Had somatostatin analog	24.4	22.4

DSMB Halted the Trial Early

- The DSMB saw the number of events in the placebo arm was much higher than the sunitinib arm and recommended halting the trial early because sunitinib showed a significant benefit in progression free survival for patients with NETs who progressed on prior therapy.

Progression Free Survival (PFS) - Primary Endpoint

- The median PFS was 11.4 months in the sunitinib group and 5.5 months in the placebo group.
- Patients in the sunitinib arm had a 71.3% probability of being alive and disease free at six months compared with 43.2% in the placebo group.

	Sunitinib (n=86)	Placebo n=85
Number (%) with PFS events	30 (34.9)	51 (60.0)
Type of event		
Progression	27 (31.4)	48 (56.5)
Death without progression	3 (3.5)	3 (3.5)
Probability of being event free at 6 months	71.3%	43.2%
Kaplan-Meier estimate of median PFS, months	11.4	5.5
Hazard ratio	0.418	
Two-sided p-value	0.0001	

Overall Survival (OS) – Secondary Endpoint

- Overall survival had not been reached after a median follow-up of 10-11 months.
- Patients in the sunitinib arm had a 92.6% probability of being alive at six months and 82.5% probability in the placebo arm.

	Sunitinib (n=86)	Placebo n=85
Deaths, n (%)	9 (10.5)	21 (24.7)
Survival probability at month 6	92.6%	85.2%
Hazard ratio	0.409	
Two-sided p-value	0.0204	

RECIST-Defined Objective Tumor Responses

	Sunitinib (n=86)	Placebo n=85
Best Confirmed Tumor Response, n (%)		
Complete Response	2 (2.3%)	0
Partial Response	6 (7.0)	0
Stable Disease/no response	54 (62.8)	51 (60.0)
Objective Progression	12 (14.0)	23 (27.1)
Not Evaluable	12 (14.0)	11 (12.9)
Objective Response Rate	9.3%	0
Two sided p-value for treatment difference	0.0066	
Stable Disease >6 months, n (%)	30 (34.9)	21 (24.7)

Most Frequent All-Causality Adverse Events with Sunitinib 37.5 mg/day CDD

- Adverse events occurred more often in the sunitinib arm.

	Sunitinib (n=86)	Placebo n=85
Diarrhea	49 (59.0)	32 (39.0)
Nausea	37 (44.6)	24 (29.3)
Asthenia	28 (33.7)	22 (26.8)
Vomiting	28 (33.7)	25 (30.5)
Fatigue	27 (32.5)	22 (26.8)
Hair color changes	24 (28.9)	1 (1.2)
Neutropenia	24 (28.9)	3 (3.7)
Abdominal pain	23 (27.7)	26 (31.7)
Hypertension	22 (26.5)	4 (4.9)
Hand-foot syndrome	19 (22.9)	2 (2.4)
Anorexia	18 (21.7)	17 (20.7)
Stomatitis	18 (21.7)	2 (2.4)
Dysgeusia	17 (20.5)	4 (4.9)
Epistaxis	17 (20.5)	4 (4.9)

- The most common grade 3+ adverse events in patients who received sunitinib included neutropenia, hypertension, leucopenia and hand-foot syndrome.

Summary

- In patients with progressive, well-differentiated pancreatic endocrine tumors, sunitinib 37.5 mg/day CDD resulted in patients living twice as long without disease progression when treated with sunitinib compared with placebo.
 - Clinically significant improvement in median PFS versus placebo
 - 11.4 months vs 5.5 months, HR 0.418, p=0.0001
- More than 90% of patients in the sunitinib group remained alive at six months. Most of the survival benefit was attributable to disease stabilization.
- Adverse events observed with sunitinib CCD were generally tolerable and manageable by dose interruption, dose reduction and/or standard medical therapy.
 - Most frequent events were consistent with previous trials of sunitinib.
- This data supports the clinical safety and efficacy of sunitinib in patients with advanced pancreatic NETs.