

# Interferon- $\alpha$ and somatostatin analog in patients with gastroenteropancreatic neuroendocrine carcinoma: single agent or combination?

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In most cases gastro-enteropancreatic neuroendocrine tumors grow slowly. Interferon- $\alpha$  and somatostatin analogs have shown symptomatic, biochemical, and, in a minority of cases, antiproliferative activity. Generally, they are proposed as single-agent therapy. However, based on *in vitro* and *in vivo* evidence, the combined use of these drugs was proposed in several non-randomized trials, indicating that there is an additive effect of the combination. Nevertheless, the three randomized trials published so far did not show a statistically significant survival benefit for the combination compared to the same agents alone, even though an advantage for the combination came out in all three studies. On the other hand, data from non-randomized trials would justify the sequential use of the two drugs or the combination after progression on single agent therapy. Therefore, at present the up-front combined use of interferon- $\alpha$  and somatostatin analog is not justified, whereas it could be indicated after progression to single-agent therapy. Further larger, international, prospective, randomized, multicentric clinical trials studying homogeneous populations would be necessary to give a final answer, but the rarity and heterogeneity of this malignancy does not assure that it will be possible.

**Key words:** interferon, neuroendocrine tumors, somatostatin analogs, GEP, carcinoids

## introduction

Neuroendocrine tumors (NETs) represent a very heterogeneous and rare category of neoplasms, accounting for only 0.5% of all malignancies. Gastroenteropancreatic (GEP) NETs are the most common group [1], with gastrointestinal (GI) primary tumors being much more frequent than pancreatic ones. Ileum has the highest incidence.

These neoplasms are named *functioning* when they show a clinical syndrome related to hormones hypersecreted by the tumor, and *non-functioning* when no specific syndrome is present whereas symptoms are only related to the 'mass effect' caused by the tumor growth. Among the functioning tumors the main clinical entities are: the carcinoid syndrome [2], the hypoglycemia syndrome [3], the Zollinger-Ellison syndrome [4], the WDHA (watery diarrhea, hypokaliemia, achlorhydria) syndrome [5], and the glucagonoma syndrome [6].

The typical carcinoid syndrome can be found in less than 20% of carcinoids, particularly mid-gut primary and liver metastases [7]. In rare cases an atypical carcinoid syndrome can be present [8], particularly in patients with foregut carcinoid

tumors. About 30–40% of pancreatic-NET patients present without hormone-related symptoms; in the other cases syndromes related to a specific secreted hormone are present [9].

Global prognosis of NET patients is relatively favorable, with a five-year survival rate of around 70%, including all sites, stages and kinds of tumor. Local and distant metastases may allow a considerable 5-year survival rate of 72 and 39%, respectively. Among GEP NETs, rectal and appendiceal tumors are associated with the best survival [1].

According to the WHO classification, by Solcia and co-workers, published in 2000 [10], GEP NETs are distinguished in three types: well-differentiated tumors or *carcinoids*, well-differentiated carcinomas or *malignant carcinoids*, and poorly-differentiated carcinomas or *small-cell carcinomas*. The old classification, including foregut, midgut and hindgut carcinoids [11], should be considered obsolete by now.

## somatostatin analogs

### background

Somatostatin (sst) was discovered by Brazeau et al. [12] in 1973 at the Salk Institute in La Jolla, California. It is expressed in many tissues and organs of our body, including the central

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nervous system and gastrointestinal tract, and acts as a neurotransmitter, or exocrine and endocrine glands, GI motility, and vasotone regulator, depending upon its target tissue. Several forms exist, but a 14 and 28 amino acids cyclopeptide represent the most important forms. Somatostatin exerts its action via five specific receptors, named sstr 1–5 [13]. Because of its short half-life (< 3 min), sst was inconvenient for clinical use, and therefore analogs were developed at the beginning of the 1980s [14]. Two of them, octreotide and lanreotide, are regularly used in clinics [15]. They have a 1–2-h half-life and they can be administered subcutaneously, intravenously and intramuscularly. Native sst binds to all five subtypes of receptors (r), whereas the two analogs bind in particular to subtype 2, and with a somewhat lower affinity to the sstr-3 and sstr-5 subtypes. Somatostatin analogs can control hypersecretion in NETs that express sst-receptors. In addition, these agents may also exert some anti-proliferative activity [16].

Symptomatic and biochemical activities of sst-analogs are, by now, well recognized in small-bowel NETs, with a response rate of roughly 90% and 70% respectively [17, 18]. Similar results were reported in pancreatic endocrine tumors, with a lower activity in insulinoma, because in 50% of cases sst2 receptors are missing [19].

Tumour shrinkage was demonstrated in a very small percentage of cases with standard dose [20–23]. However, in some cases increasing doses translated into major activity [24–27]. Furthermore, dose titration revealed active also on symptoms and hormone levels [28] (Table 1).

Standard dose of octreotide varies from 0.1 to 0.3 mg/day, to be administered s.c. 2–3 times daily. High dose is more than 3 mg/day. In order to avoid multiple daily s.c. injections, a long-acting-release (LAR) formulation was introduced, with 10, 20, and 30 mg i.m. vials to be administered every four weeks [29]. These new forms were as active as the subcutaneous one [30]. Lanreotide is usually administered i.m. once every 4 to 6 weeks, through a recent prolonged release formulation of 60, 90 or 120 mg (Autogel®) [31].

### mechanism of action

In carcinoid tumors subtype 2 and 5 sst-receptors are expressed in the majority of cases. Octreotide showed the highest binding affinity to the subtype 2 [32], which makes this receptor highly probable to mediate the clinical effects of octreotide therapy in GEP NETs. The sstr binding activates multiple intracellular mechanisms, such as the adenylate cyclase activity inhibition, with an inhibitory effect on secretion processes [33].

The antiproliferative effect of sst-analogs can be due to several mechanisms, including inhibition of growth factor effects on tumor cells, induction of apoptosis at high dose [34], and inhibition of angiogenesis [35].

**Table 1.** NETs sst-analog treatment

Response	Standard dose (%) 100–1500 mg/d	High dose (%) >3 mg/d	SR (%) 20–30 mg/ 2–4w
Subjective	64	42	63
Biochemical	63	75	67
Tumor	5	13	3

## interferon

### background

$\alpha$ -Interferon was introduced by Oberg et al. for the treatment of carcinoid tumors in 1982 [36]. Six out of nine patients with small intestine carcinoid and carcinoid syndrome responded to leukocyte interferon 3 M IU per day during the first month and 6 M IU per day for another two months. Reduction of symptoms and amine levels, without effect on the tumor growth, was observed. Since then, several studies were published reporting 40–70% of symptomatic, 40–50% biochemical, and 10–15% antiproliferative activities [37–40]. The methods of response evaluation probably underestimate the activity, because some reports show a reduction in tumor cells and increase in connective tissue component without any change of the tumor on CT-scan in liver metastases from NET patients treated with IFN [41].

Dose and schedule varied from 3 M IU s.c. three times a week to 9 M IU s.c. daily (Table 2). The dose has to be individually titrated. IFN- $\alpha$  is the most evaluated of all the IFNs in the treatment of NETs. Nevertheless, a very recent study reported that the antitumor activity of IFN- $\beta$  in human pancreatic carcinoid BON cell lines is considerably more potent than IFN- $\alpha$  [42]. Polyethylene glycol-modified (pegylated) interferons are long-acting formulations of IFN- $\alpha$ . They are administered at doses of 50–150  $\mu$ g per week, s.c.

### mechanism of action

Interferons represent a large class of agents with anti-viral and anti-tumor activity [43]. They are divided into two groups: type I and type II. Type-I IFNs include IFN- $\alpha$  (leukocyte IFN), IFN-b (fibroblast IFN), as well as IFN-w and IFN-t. The only type-II IFN (immune IFN) is named IFN. IFN- $\alpha$  is the most evaluated type of IFN in the treatment of NETs, and acts through specific receptors on the cell surface activating cytoplasmic messengers, such as Janus kinase 1 (JAK-1) and Tyrosine kinase 2 (TYK-2). The action of IFN derives from a direct effect on the cell cycle, inducing the arrest in G1 and G0 [44], an inhibition of growth factors production, a class 1 antigens induction on the cell surface therefore activating the immune response, and an anti-angiogenic effect [45].

### medical treatment

The medical treatment of GEP NETs is based on the biological and clinical characteristics of the tumor. Chemotherapy, interferon- $\alpha$ , and sst-analogs represent the three possible systemic therapeutical options. Chemotherapy is indicated in two subgroups: poorly-differentiated NETs or NETs with rapid clinical progression, that respond to a combination of

**Table 2.** NETs IFN- $\alpha$  treatment

Response	Regular dose 3–6 MU $\times$ 3–7/w	High dose 24 MU/m <sup>2</sup> $\times$ 3/w
Subjective	53	32
Biochemical	49	39
Tumor	12	20

cisplatin and etoposide [46], and pancreatic endocrine carcinomas, in which streptozotocin-based chemotherapy has been proven active [47].

In well-differentiated and slow-growing tumors, biotherapy is preferred to chemotherapy. If sst-receptors are expressed, a sst-analog should be proposed in functioning and in progressive, metastatic disease, even without the syndrome [48]. If sst-receptors are negative IFN- $\alpha$  is indicated in functioning or progressive disease. In metastatic, sstr-negative, IFN- $\alpha$ -resistant GEP NETs a shift to chemotherapy can be evaluated. In sstr-positive diseases resistant to sst-analog, a dose-escalation of the analog or the addition of IFN- $\alpha$  is usually applied, in particular in functioning diseases. However, the withdrawal of the analog and its substitution with IFN- $\alpha$  can be considered in non-functioning, sstr-positive diseases.

Therefore, some settings exist in which the two forms of biotherapy, sst-analog and IFN- $\alpha$ , are used together. This prompted some authors to study whether the combination is better than the single-agent use. In this review we analyze the non-randomized and randomized trials that addressed this topic.

### non-randomized trials

The combination of IFN- $\alpha$  and sst-analogs has been studied in some non-randomized trials (Table 3).

However, the first evidence of some activity due to the combination of interferon and octreotide, rather than the same drugs used as single agent, appeared as a case report by Joensuu in 1992 [49]. A 43-year-old man with several symptoms due to a retroperitoneal unknown-primary NET, who had been receiving IFN- $\alpha$ -2b, 10 M IU s.c. three times a week, with incomplete symptom control, benefited from the addition of octreotide 0.1 mg twice daily (b.i.d.) subcutaneously. Symptoms totally disappeared and both tended to reappear when octreotide was reduced to 0.05 mg b.i.d. and IFN was gradually withdrawn. In both cases symptoms disappeared when octreotide dose was increased again and interferon resumed.

In the same year Janson et al. [50] reported the efficacy of interferon/octreotide combination in 24 NET patients clinically progressive to octreotide alone. Patient population was quite homogeneous, with 23 of 24 having a mid-gut carcinoid and 18 of 24 showing a carcinoid syndrome. All patients had a

biochemical progression after having received octreotide for a median time of eight months. Ten of them initially responded to the regular dose (0.05–0.1 mg twice a day), but then did not respond to the dose escalation (up to a median of 0.3 mg/day). The other 14 showed symptomatic or biochemical progression just after three months of octreotide. IFN- $\alpha$  addition, with a median s.c. dose of 9 M IU/week, produced a 77% of biochemical response rate, lasting for a median of 12 months (range 5–46). Nine of the 17 responding patients had previously been treated with IFN- $\alpha$  9 M IU/week but were progressive or intolerant, leading one to suppose that the combination is better not only for efficacy but also for tolerability. The authors stated that the benefit is due to the combination and not to IFN alone, because the known biochemical response rate of IFN- $\alpha$  alone is 44% and an increase of biochemical markers occurred when IFN was withdrawn. However, no WHO partial responses, but only four stable diseases, were obtained. Considering that, four out of five patients showing an increase in tumor size and had a concurrent biochemical response (> 50% decrease of HIAA urinary level), it is difficult to understand the clinical meaning of the biochemical markers behavior. However, of the 18 patients presenting with the carcinoid syndrome three had a complete relief of all their symptoms and/or signs, while five obtained a complete relief of one of the symptoms, demonstrating that the addition of IFN- $\alpha$  is effective on symptom control. The reappearance of symptoms and re-increasing of HIAA in each of the eight patients where IFN- $\alpha$  was withdrawn, and the effective re-introduction of IFN- $\alpha$  in three of these patients, showed the benefit of the combination rather than the single agents. Toxicity increased with IFN- $\alpha$ , including temporary flu-like symptoms, tiredness, anorexia, dryness of skin, leukopenia, and thrombocytopenia, but no side effects caused clinical complications or induced definitive drug withdrawal. Finally, it is not possible to draw any conclusion about the anti-tumor activity of the IFN addition, because the radiological status of the disease at the beginning of the therapy in the 15 patients who showed stable disease with IFN- $\alpha$  addition has not been specified.

Another trial was conducted by Frank and co-workers [51] on 21 patients with metastatic GEP NET. In this study the population was less homogeneous than Janson's, including nine patients with carcinoid syndrome, eight with non-functioning pancreatic NET, and four with gastrinoma. Nevertheless, unlike Janson's study, all patients had CT-documented tumor progression before entering the study. All patients received the combination of octreotide 0.2 mg three times daily (t.i.d.) and IFN- $\alpha$  5 M IU three times a week. Sixteen patients had already been treated with octreotide 0.2 mg t.i.d. An inhibition of tumour growth was obtained in 67% (14/21) of patients, lasting for more than three months. Thirteen patients had WHO stable disease, for a median of 12 months (range 3–52), and one had a hepatic WHO complete response (lasting for four years). Also this study showed that biochemical response does not correlate to the inhibition of tumour growth. Although this was not a phase-III trial, the authors underlined in the discussion that responders had a significantly longer survival (median, 68 months) than non responders (median, 23 months). Interferon-related side effects were more severe than those attributable to octreotide; however, general toxicity was mild and did not

**Table 3.** IFN- $\alpha$ /sst-analog combination therapy: published non randomized trials

Author	No. pts	Subjective (%) resp. pts	Biochemical (%) resp. pts	Radiological resp. pts
Janson, 1992	24	10/18 (55)	17/22 (77)	15 SD
Frank, 1999	21	NR	9/13 (69)	14 SD 1 CR
Fjallskog, 2002	16	NR	10/16 (63)	11 SD 3 PR
Artale, 2005	11	3/4 (75)	6/9 (66)	7 SD 4 PR
Pavel, 2006*	17	NR	6/15 (40)	11 SD 2 PR

\*With PEG-IFN.

require dose reduction. Only two patients refused further treatment after four months of therapy despite stabilization of tumor growth, because of interferon-induced flu-like side effects.

Three out of 20 patients who underwent octreoscan did not express sstr-2 and -5 receptors. However, all but one responding patients had a positive octreoscan. Also five out of seven non-responders had a positive octreoscan. Unfortunately, it is not possible to draw any clinical conclusion from these data, regarding the possible predictive role of sst-receptors. It remains unexplained why patients with a negative octreoscan received an sst-analog. While the Janson's study showed the better symptomatic effect of the combination on the single agent therapy, the Frank's one showed the better antiproliferative activity.

The third non-randomized trial was published in 2002, by Fjällskog et al. from the Uppsala group [52]. It reported the results of IFN + octreotide or lanreotide in 16 patients with metastatic pancreatic endocrine tumors, eight of which were non-functioning. Doses of IFN- $\alpha$  and sst-analog were individually titrated, IFN varying between 9 and 25 MU/week and octreotide and lanreotide at a dose of 0.1–1.5 mg and 6 mg daily, respectively. Eight of 16 patients had previously received IFN alone, six analog alone, and seven IFN or analog plus chemotherapy. All patients were defined as progressing when starting the new treatment, but the kind of progression, radiological or biochemical, is not specified. A partial response (PR), according to the WHO criteria, was seen in three patients (19%), with a median duration of 23 months (range 19–25), and a stable disease (SD) in 11 patients (69%), with a median duration of 13 months (range 4–32). Among the eight patients previously progressing on IFN alone, one PR and five SD were obtained; whereas all patients previously progressing on sst-analog showed a SD. The biochemical response rate was 38% among IFN-progressing patients and 33% among sst-analog patients. All three patients previously progressing on both IFN and sst-analog as single drug achieved a biochemical and radiological stabilization of the disease with the combination. All side effects were mild except for two patients experiencing grade 3 cortical neurological toxicity. The authors conclude that the combination of IFN and sst-analog can be proposed to patients progressing on single treatment with IFN or sst-analog or to patients who fail during chemotherapy. However, the radiological response evaluation is suboptimal in this study, considering that two patients were only examined with ultrasonography and in two other patients CT examinations were misplaced. Furthermore, toxicity should be considered as a possible factor limiting the feasibility, at least at some doses of IFN, given that three of 16 patients ended the treatment because of grade 2–3 side effects. Nevertheless, this is the only one out of the three non-randomized trials that showed some activity data of the combination in patients progressing to IFN- $\alpha$ .

All three studies above led to suggest a better activity for the combination than for single-agent therapy.

A recently published Italian experience [53] strengthens this concept. Interferon- $\alpha$  5 MU  $\times$  3/w plus LAR octreotide 30 mg q4w, were administered in 11 patients, four of whom pre-treated, with well-differentiated NETs. The obtained rate of PR (36%) is higher than known from literature for IFN or octreotide as single agent, and suggests a synergic or additive effect of combination.

Unfortunately, higher toxicity of the combination remains a concern. However, we did not observe significant toxicity with lower doses of IFN [54]. At the European Institute of Oncology we treated 16 well-differentiated NETs patients (12 of whom were pre-treated) with IFN- $\alpha$  1 MU a day over 5 days/week plus LAR octreotide 20 mg q4w. No G2-4 toxicity was seen, in particular no flu-like syndrome. Notably, two PR and two SD (in previously progressive patients) were obtained (25%) (unpublished data). On the other hand, we did not find any correlation between blood levels of Vascular Endothelial Growth Factor (VEGF) and basic Fibroblast Growth Factor (bFGF) and clinical behavior, even though an antiangiogenic activity of low and protracted doses of IFN- $\alpha$  has been reported in preclinical studies [55].

Further interesting results in terms of activity and low toxicity of the combination come from a very recent published experience with PEG-IFN. In 17 patients with well-differentiated metastatic GEP NETs treated with LAR octreotide, PEG-Interferon- $\alpha$  in 11 and IFN- $\alpha$  in 6 were added 3–108 months after initiation of octreotide therapy. IFN- $\alpha$  was added at a dose of 5 MU thrice weekly, but treatment was stopped in all six patients because of severe side effects. At further progression PEG-IFN was added. PEG-IFN was given at a dose of 50–100  $\mu$ g/week s.c. Partial regression was observed in two patients and stable disease in 11. The median duration of response was 12 months [56].

### randomized trials

A randomized trial was conducted by Kolby et al., to study the effect of IFN- $\alpha$  addition to octreotide on survival [57]. Sixty-eight patients with metastatic mid-gut carcinoid were included in 10 centers between 1991 and 1998 (Table 4). All patients had been operated on their primary tumors and treated with hepatic trans-arterial embolization (TAE) before having been randomized to either octreotide or a combination of octreotide and IFN- $\alpha$ . At the time of randomization all patients

**Table 4.** IFN- $\alpha$ /sst-analog combination therapy: published randomized trials

Author	No. pts	Arms	Results
Kölby 2003	68 1991–98	IFN $\alpha$	5-year-survival (%) 36.6
		OCT+IFN $\alpha$	56.8 HR 0.62 (CI 95% = 0.3–1.1) P = 0.132
Faiss 2003	80 1995–98	IFN $\alpha$	1-year PFS (%) 44.4
		LAN	44
		IFN $\alpha$ +LAN	50 p = 0.69 Median survival (months)
Arnold 2005	109 1995–98	OCT	35
		OCT+IFN $\alpha$	51 HR 1.19 (CI 95% = 0.67–2.13) P = 0.55

LAN, lanreotide; OCT, octreotide; IFN, interferon; HR, hazard ratio  
PFS, progression free survival.

had liver metastases. Patients received octreotide 0.1 mg b.i.d., increased to 0.2 mg t.i.d. in case of persistent carcinoid symptoms. The IFN started with 3 MU  $\times$  3/week and was increased to a maximal dose of 5 MU  $\times$  5/week. The study endpoints were death, progressive tumor growth (more than 25% of increase at CT or ultrasonography, or more than 25% of HIAA level increase, or new metastases), or life-threatening side-effects of the treatment. An overall five-year survival rate of 46.5% during a follow-up period of 33–120 months was obtained. No statistically significant difference in survival between the two groups resulted, even though in the combination group 5-year survival was longer than in the octreotide group (56.8% and 36.6% respectively;  $P = 0.132$ ). As for risk of tumor progression, patients treated with octreotide and IFN- $\alpha$  had a significantly lower risk of progressive disease (HR 0.28, 95% CI 0.16–0.45;  $P = 0.008$ ). Of the 25 patients reported to have tumor progression, 19 were treated with octreotide alone compared to six who received the combination. Toxicity was relatively equivalent between the two groups, even though the only severe side effect occurred in the combination arm. The authors reported two statistical considerations. One is that the statistical power of this study is too low to lead to any definitive conclusion, considering that 230 patients would be required in each group to give an 80% probability of achieving a statistically significant difference in survival. The other is that the lack of a blinded design could have overestimated the prolongation of the progression free interval by IFN- $\alpha$ .

The second randomized trial was published in July 2003, in the *Journal of Clinical Oncology*, by Faiss et al. [58], and was a three-arm trial. Between 1995 and 1998, 84 untreated patients with CT- or US-documented progressive well-differentiated metastatic NETs were randomized to lanreotide 1 mg s.c. t.i.d., IFN- $\alpha$  5 MU s.c.  $\times$  3/week, or a combination of the two drugs at the same doses. The main objective of this study was the 1-year (1-y) progression-free survival (PFS) rate. Sample-size calculations were based on the hypothesis that 1-y PFS rate of patients with metastatic NETs treated with IFN is lower (15%) than the corresponding rate of patients with lanreotide (25%) and that the combination of the two drugs (45%) is superior to the corresponding monotherapies. The population of patients was quite heterogeneous, and most diseases were non-functioning. Although there were more PRs in the combination arm compared to the single agent arms (two, one, and one, respectively), no significant difference in rates of PR, SD and progressive disease (PD) between the three arms was recorded. Partial response rate was 4%, 3.7%, and 7.1%, and SD rate 28%, 25.9%, and 17.9%, for lanreotide, IFN- $\alpha$ , and combination group, respectively. Within 1 year of therapy, tumor progression was observed in 56% of patients in the lanreotide arm, 55% in the IFN- $\alpha$  arm, and 50% in the combination arm, without a statistically significant difference. However, one of the 11 patients progressed on lanreotide and shifted to the combination showed a clear reduction in the rate of tumor growth. Furthermore, a statistically significant reduction of symptoms was only observed in the combination arm ( $P = 0.037$ , Wilcoxon test). Biochemical response did not differ among the treatment groups, and this study showed once again that it was not correlated with inhibition of tumor growth. Combination therapy seemed to be more toxic than monotherapy with seven

of 28 patients who had to stop treatment compared to 4 of 27 in the IFN arm and 3 of 25 in the lanreotide arm. However, difference in time in study between the three arms was not statistically significant ( $P = 0.337$ , Kruskal-Wallis test).

Some criticisms were moved to this study, not completely clarified by the authors' reply. We [59] remarked that in this study it is not clear if all patients were evaluated by CT-scan, as requested by the WHO. As a matter of fact, this is a drawback found also in Fjallskog's, Kölby's, and Janson's trials. Unfortunately, ultrasound is a very operator-dependent examination and therefore it should not be used alone for response evaluation. Considering the very low PR rate in NETs, even very small differences can be crucial to conclude for the activity of some drugs, and therefore the less subjective examination should be used to evaluate the response, all patients undergoing the same kind of examination. Other criticisms [60] regarded the statistical aspects of this study. In particular, it was closed after 80 patients instead of the 105 planned patients. Furthermore, it is not clear on what the authors based their assumption of a 15% of PFS at one year for IFN and 25% for lanreotide. Finally, heterogeneity of patients and lack of optimization of treatment were other points of criticisms.

The third randomized trial, by Arnold et al. [61], has been recently published in *Clinical Gastroenterology and Hepatology*. Between January 1995 and March 1998 109 patients with advanced GEP NETs were randomized to octreotide 0.2 mg t.i.d.  $\pm$  IFN- $\alpha$  4.5 MU  $\times$  3/week. The dose of IFN was adapted to strategies in hepatitis B before pegylate interferons had been introduced. Population was quite homogeneous, pancreatic and midgut NETs representing the main group. Carcinoid syndrome was present in 40% of patients. Surprisingly, 45% of patients, fairly distributed in the two groups, had negative or unperformed octreoscan. Unlike previous studies, only patients with CT-scan or MRI documented tumor progression were included. Pre-treatment with IFN was an exclusion criteria, whereas octreotide  $\leq 150$   $\mu$ g per day against carcinoid syndrome was allowed. Although median survival was longer in the combination arm (51 versus 35 months) the hazard ratio of 0.82 (95% CI 0.52–1.29) and  $P = 0.38$  concluded for a non-statistically significant advantage. The Kaplan-Meier plot for long-term survival described an advantage for patients in the combination arm of between 24 and 84 months. However, the study population was too small to prove statistically a survival advantage of the combination arm for long-term survival. Time to treatment failure, that was the primary endpoint of this study, was similar between the two arms within six months and slightly better but not statistically significant in the combination arm after six months. Also radiological, biochemical and subjective responses were not significantly different between the two groups. Notably, a partial regression was more frequent at month 12 in the combination arm, arguing a possible late effect on the tumor growth. Patients with slowly growing (TTP  $> 6$  months) tumors prior to treatment and those with low Ki67 had a survival advantage compared with patients with a more rapid progression and higher Ki67. Adverse events were more frequent in the combination arm, which resulted in discontinuation of treatment in 11 of 54 patients, unlike the monotherapy arm with two of 51. Likewise, quality of life after 3 months of treatment was lower in the combination than in the

monotherapy arm ( $56.3 \pm 23.4$  versus  $69.3 \pm 14.6$ ;  $P = 0.039$ ). This study showed for the first time that response with stabilization or partial regression to octreotide or octreotide plus interferon- $\alpha$  affects survival favorably.

From the above described randomized trials, a non-statistically significant advantage in terms of survival for the combination comes out. Furthermore, all three studies were too small to show a statistically significant advantage. Unfortunately, this is not enough to use the combination as an upfront treatment.

## conclusion

Clinical trials studying the efficacy of IFN- $\alpha$  combined with sst-analog in patients with NETs are supported by some *in vitro* and *in vivo* evidence.

Interferon produces an up-regulation of somatostatin receptors *in vitro* [62]. The two cyclin-dependent kinase inhibitors p21 and p27 involved in the cell-cycle block in the G2-S phase induced by IFN [63, 64], can be up-regulated by somatostatin analogs [65]. Reduction in growth factors and their receptors as well as antiangiogenic activity can be effected by both drugs. Finally, IFN and sst-analog in combination showed a stronger antiproliferative effect than either drug alone, in an *in vivo* model with xenografted BON cells [66].

Nevertheless, it has not yet been clearly defined whether the combined use of IFN- $\alpha$  and sst-analog is clinically more effective than the use of the same drugs as a single agent. Some non-randomized studies indicate that there is an additive effect of the combination, but the only three randomized trials published so far did not show any statistically-significant differences in terms of survival because of their different design and low statistical power.

Furthermore, the combination seems to be more toxic than monotherapy, at least at  $3 \text{ MU} \times 3/\text{week}$  or more of IFN. Lower dose of IFN showed to be active in combination with analog and therefore should further be studied in randomized trials.

At present we do not have enough statistical evidence for an upfront use of the combination of IFN- $\alpha$  and sst-analog in patients with NETs, but we have some clinical evidence coming from non-randomized studies and the sub-analysis of randomized trials, that would justify the sequential use of the two drugs or the combination after progression to single agent therapy.

To have a conclusive response, larger clinical trials in international, prospective, randomized, multicentric settings studying a homogeneous population are necessary, possibly with a placebo arm, even though the rarity and heterogeneity of this malignancy makes this aim very difficult.

## conflict of interest

None declared.

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