TNE du grêle traitement médical (hors lutathérapie)

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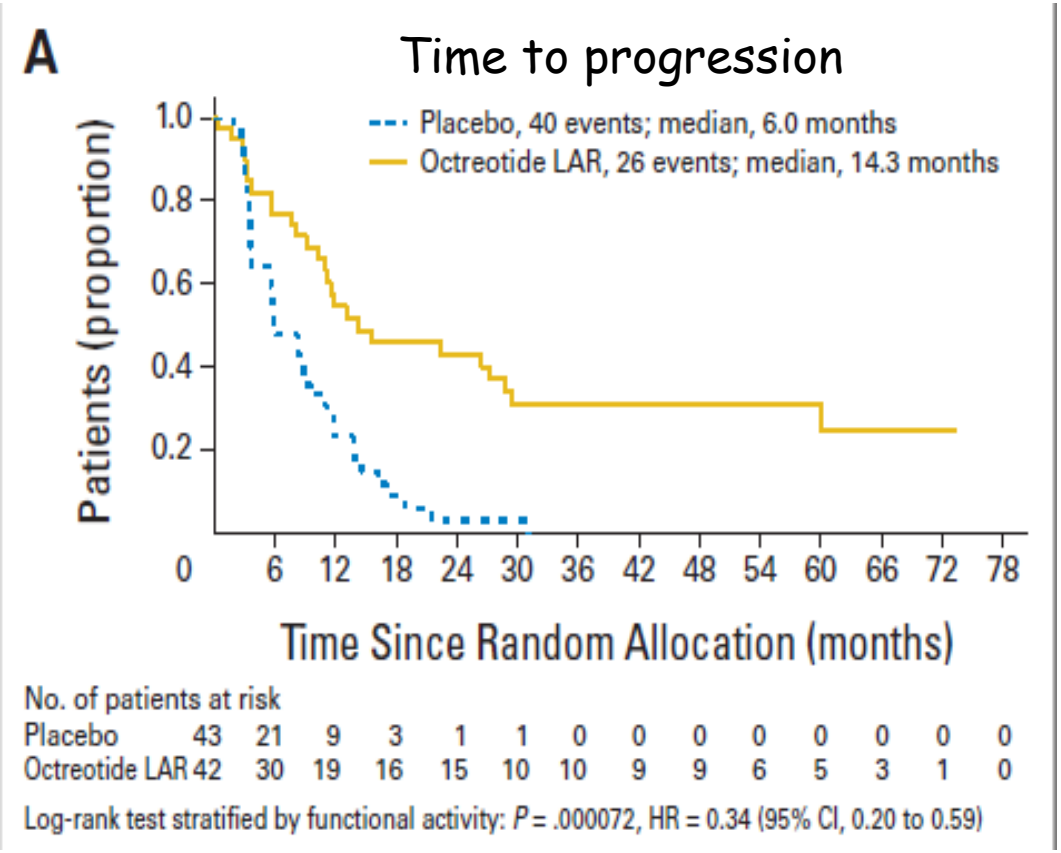
Analogues de la somatostatine

Octreotide **vs** Placebo dans les TNE (midgut): **Résultats de l'étude** PROMID



Rinke et al JCO 2009

Lanreotide Autogel ***vs*** Placebo dans les TNE : **Résultats de l'étude** CLARINET

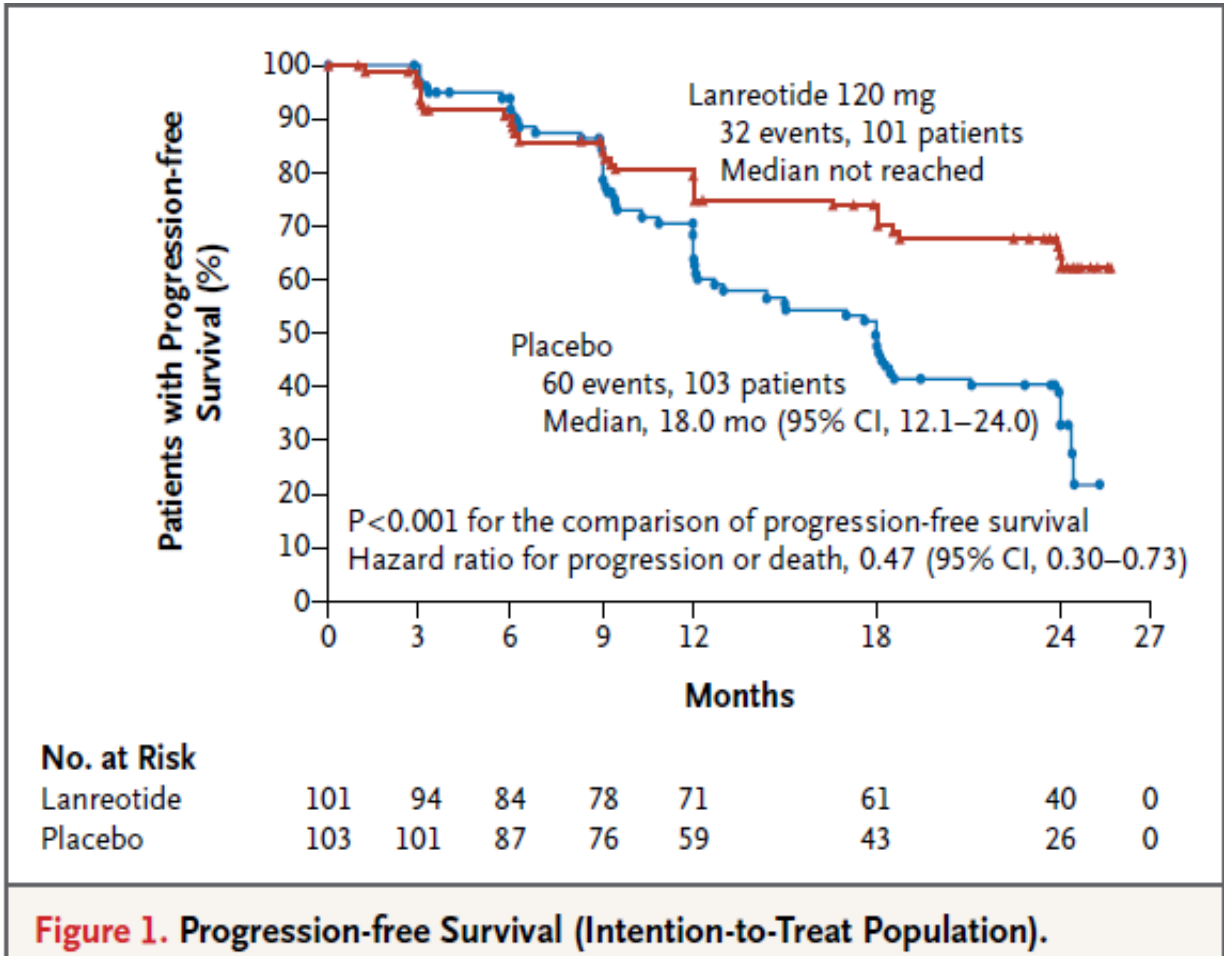


Figure 1. Progression-free Survival (Intention-to-Treat Population).

Caplin E et al NEJM 2014

Parameter	PROMID	CLARINET
N	85	204
Age	62 years (median)	62 years (mean)
Primary surgery	66%	40%
Prior treatment	Treatment-naive: 100%	Treatment-naive: 84%
Tumour locations	Midgut primary tumour (or NET of unknown origin believed to be of midgut origin)	Enteropancreatic NET (includes pNET and midgut, hindgut, gastrinoma [adequately controlled], and NET of unknown origin) Pancreas: 44% Ileum: 36% Other: 7% Unknown:13%
TNM status/tumour burden	Liver involvement: 85% Liver load <10%: 75%	Metastatic: 100% Liver load < 25%: 67%
Tumour functionality	Functioning: 39%	Functioning: 0%
WHO grading	G1 (Ki-67< 2%): 95%	G1: 70% G2 (< 10%): 30%
SRS status positive	74%	100% (Grade 2 or more)
Progression status	Unknown	Stable disease in majority of patients
Tumour slope	Unknown	Stable for 3–6 months: 96%
Median time since diagnosis	4.3 months	2.8 years

Lanreotide Autogel ***vs*** Placebo dans les TNE : **Résultats de l'étude** CLARINET

- **Etude de phase III randomisée, contrôlée, en double aveugle**

- **Critères d'inclusion:**
  - **TNE bien ou moyennement différenciées**
  - **Ki-67 < 10%**
  - **Non fonctionnelle**
  - **Localement avancée ou métastatique**
  - **Progressive ou non**
    (deux scans distants de 12 à 24 semaines avant randomisation)
  - N'ayant **jamais reçu d'analogues retard**
  - **Octréoscan <6 mois: fixation > ou = 2**
  - N'ayant reçu **aucun autre traitement dans les 6 mois**

Caplin M. et al., ENETS 2014, Abs K2

Lanreotide Autogel **vs** Placebo dans les TNE : **Résultats de l'étude** CLARINET

- **Caractéristiques des patients à la Baseline**

	Lanreotide Autogel (n = 101)	**Placebo (n = 103)**
Tumeurs progressives, n (%)	4 (4)	**5 (5)**
Traitements antérieurs, n (%)	16 (16)	16 (16)
Grade tumoral n (%)		
- G1 (Ki-67: 0-2%)	69 (68)	72 (70)
- G2 (Ki-67: 3-10%)	32 (32)	29 (28)
- Non précisé	0	2 (2)
Envahissement hépatique, n (%)		
0%	16 (16)	18 (17)
0 – 10%	33 (33)	40 (39)
10 – 25%	13 (13)	17 (17)
25 – 50%	23 (23)	12 (12)
> 50%	16 (16)	16 (16)

84%

Stratégie antitumorale en pratique

- Analogues de la somatostatine à visée anti-proliférative, en première intention
  possible si:

- envahissement hépatique <25-50%
- non progressives et non symptomatiques
- KI67 <10%

tncd.org

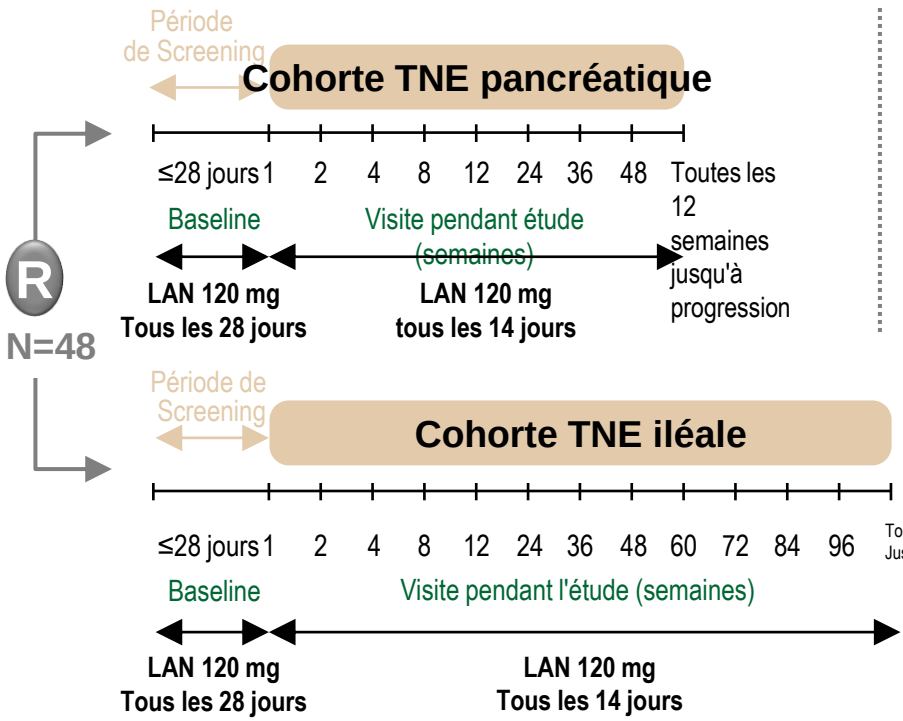
Efficacité et sécurité du lanréotide autogel (LAN) 120 mg tous les 14 jours en cas de TNE progressive du pancréas ou l'intestin moyen : CLARINET FORTE

Etude prospective non randomisée Phase II (2 cohortes: Pancréatiques et iléales)

Objectif : Sécurité et efficacité (Médiane de survie sans progression) dans chaque cohorte

Patients avec une TNE non résécable iléale ou pancréatique métastatique ou localement avancé :

- SSTR2+
- Grade 1 ou 2
- Ki67 ≤20%
- Fonctionnelle ou non
- Relecture centralisée de la progression (Critère RECIST 1.0) et ayant reçu dans les 2 ans un traitement par Lanréotide (120mg tous les 28 jours) pour au moins 24 semaines.



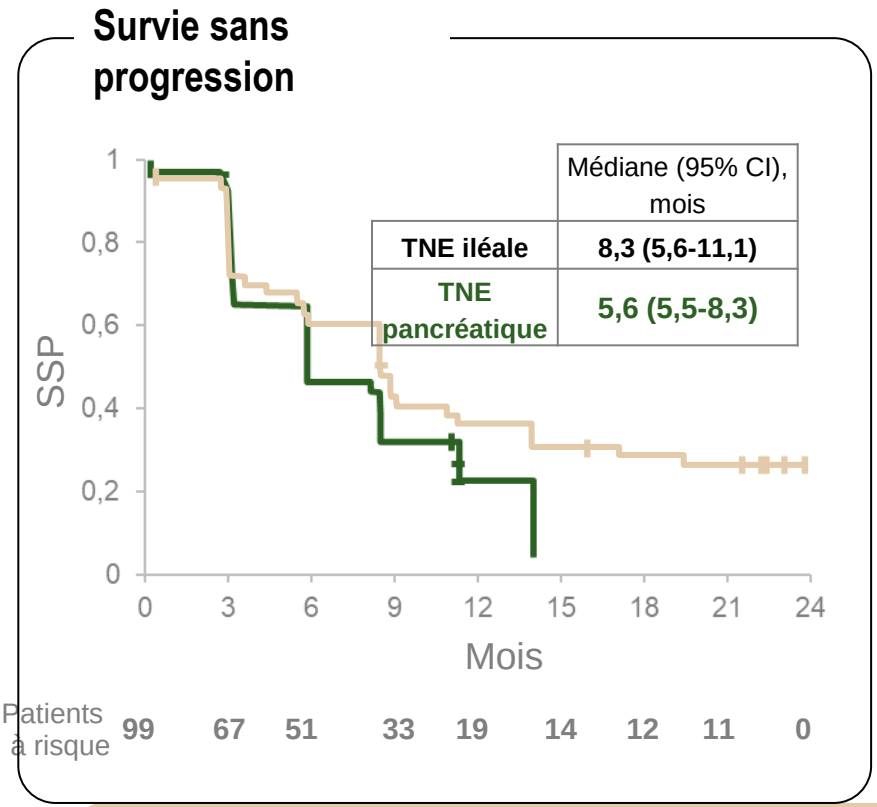
Objectif principal :

- Survie sans progression avec relecture centralisée

Objectif secondaire :

- Taux de contrôle de la maladie (DCR), Meilleure réponse globale, sécurité

Efficacité et sécurité du lanréotide autogel (LAN) 120 mg tous les 14 jours en cas de TNE progressive du pancréas ou l'intestin moyen : CLARINET FORTE



Analyse Post-hoc de l'efficacité

	TNE pancréatique	TNE iléale
Survie sans progression en fonction du Ki67, median (95% CI), mois		
Ki67 ≤10% (n=43 ; n=47)	**8,0 (5,6-8,3)**	**8,6 (5,6-13,8)**
Ki67 >10% (n=5 ; n=4)	**2,8 (2,8-2,9)**	**5,5 (2,6-NC)**

Dans les TNE en progression, l'augmentation de la fréquence d'administration du Lanreotide autogel peut être une option avant l'introduction d'un autre traitement plus toxique

M. E. Pavel, et al., ESMO® 2020, Abs # 1162MO

Analogues en association ?

- Everolimus

  - essai RADIANT 4 (intestin+ autres « non pancréas »): Octreotide LAR + Everolimus ou placebo

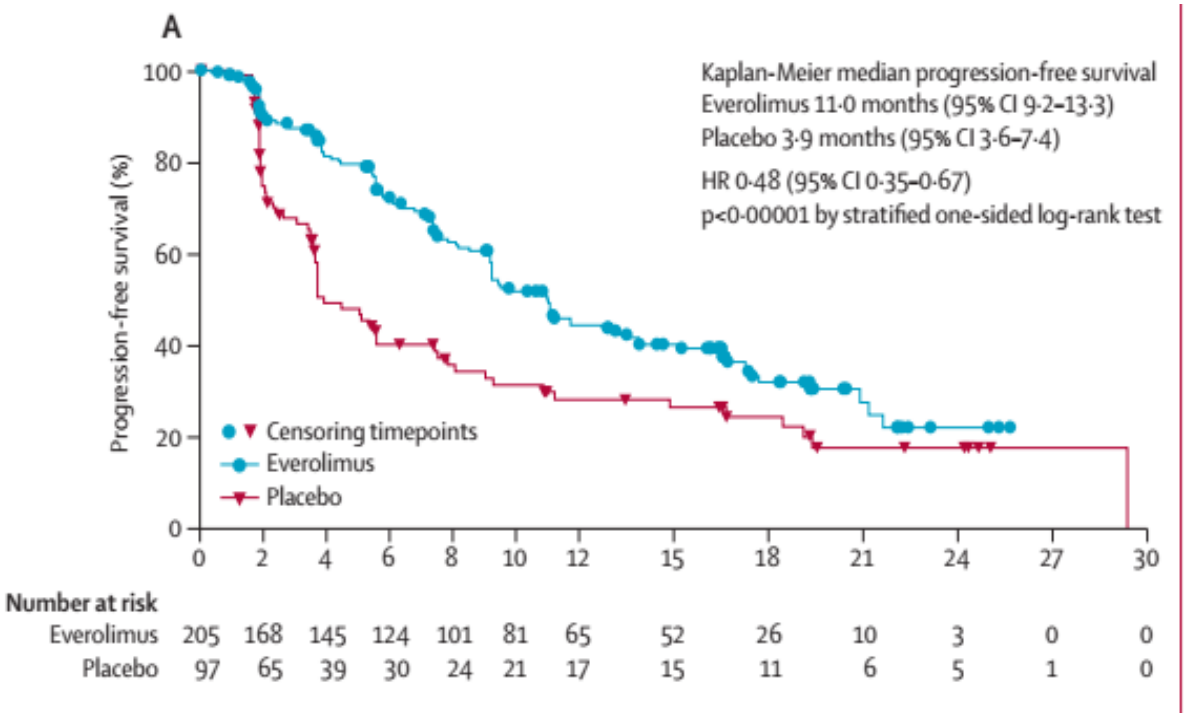
- Sunitinib

  - essai SUNLAND (intestin): Lanreotide AG + Sunitinib ou placebo

- Chimiothérapie
  - ???

Everolimus

Radiant-4


A
Progression-free survival (%)
100
80
60
40
20
0
Kaplan-Meier median progression-free survival
Everolimus 11·0 months (95% CI 9·2–13·3)
Placebo 3·9 months (95% CI 3·6–7·4)
HR 0·48 (95% CI 0·35–0·67)
p<0·00001 by stratified one-sided log-rank test
Censoring timepoints
Everolimus
Placebo
0 2 4 6 8 10 12 15 18 21 24 27 30
Number at risk
Everolimus 205 168 145 124 101 81 65 52 26 10 3 0 0
Placebo 97 65 39 30 24 21 17 15 11 6 5 1 0

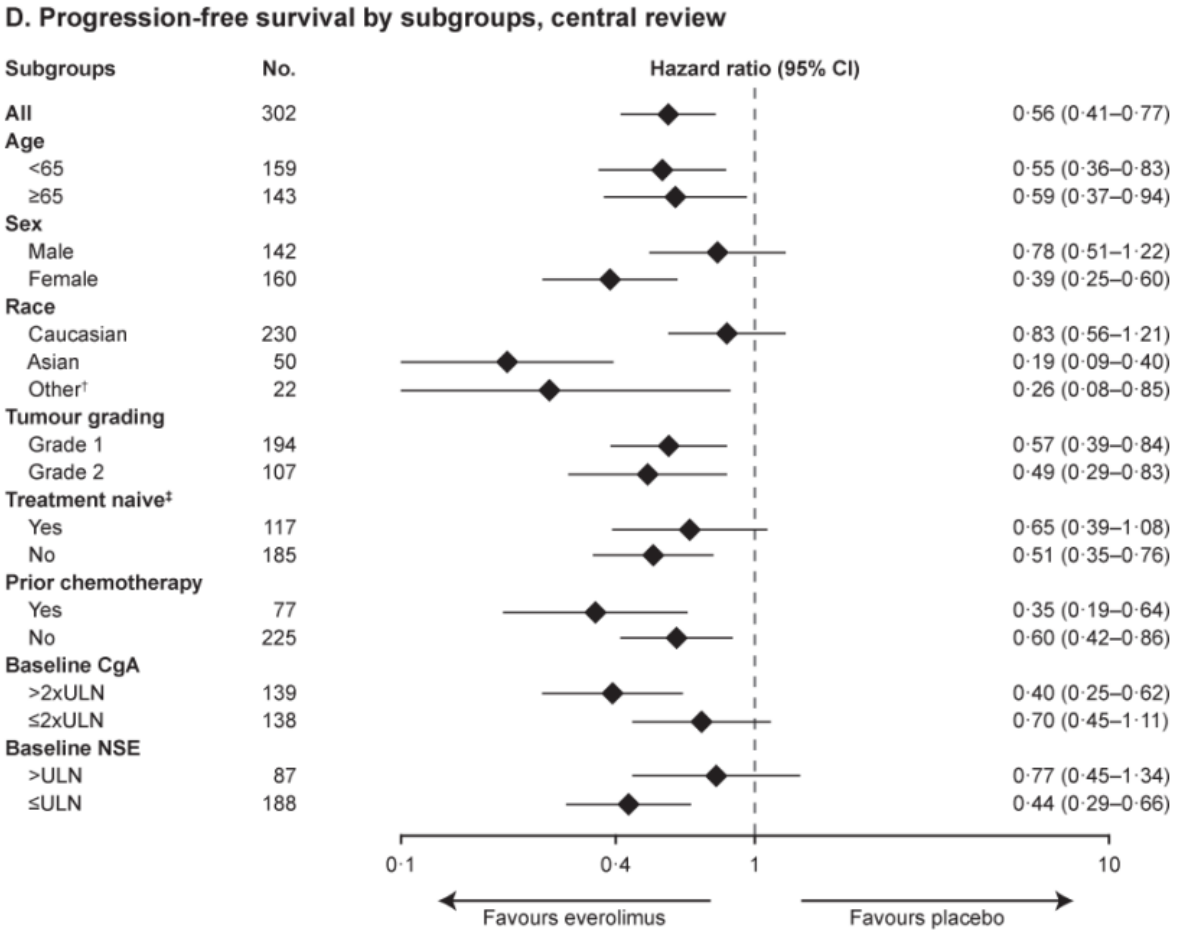
Radiant-4

	Everolimus (n=205)	Placebo (n=97)
Age, years	65 (22–86)	60 (24–83)
Sex		
Men	89 (43%)	53 (55%)
Women	116 (57%)	44 (45%)
WHO performance status*		
0	149 (73%)	73 (75%)
1	55 (27%)	24 (25%)
Primary tumour site		
Lung	63 (31%)	27 (28%)
Ileum	47 (23%)	24 (25%)
Rectum	25 (12%)	15 (16%)
Neuroendocrine tumour of unknown primary origin†	23 (11%)	13 (13%)
Jejunum	16 (8%)	6 (6%)
Stomach	7 (3%)	4 (4%)
Duodenum	8 (4%)	2 (2%)
Colon	5 (2%)	3 (3%)
Other‡	6 (3%)	2 (2%)
Caecum	4 (2%)	1 (1%)
Appendix	1 (1%)	0
Tumour grade§		
Grade 1	129 (63%)	65 (67%)
Grade 2	75 (37%)	32 (33%)

Radiant-4

Time from initial diagnosis to randomisation		
≤6 months	26 (13%)	12 (12%)
>6 months to ≤18 months	51 (25%)	25 (26%)
>18 months to ≤36 months	41 (20%)	22 (23%)
>36 months	87 (42%)	38 (39%)
Previous treatments¶		
Surgery	121 (59%)	70 (72%)
Chemotherapy	54 (26%)	23 (24%)
Radiotherapy including peptide receptor radionuclide therapy	44 (22%)	19 (20%)
Locoregional and ablative therapies	23 (11%)	10 (10%)
Somatostatin analogues	109 (53%)	54 (56%)
Disease sites‖		
Liver	163 (80%)	76 (78%)
Lymph node or lymphatic system	85 (42%)	45 (46%)
Lung	45 (22%)	20 (21%)
Bone	42 (21%)	15 (16%)
Peritoneum	25 (12%)	8 (8%)
Liver tumour burden		
None	34 (17%)	14 (14%)
≤10%	119 (58%)	61 (63%)
>10% to 25%	29 (14%)	8 (8%)
>25%	21 (10%)	14 (14%)
Unknown	2 (1%)	0

Radiant-4

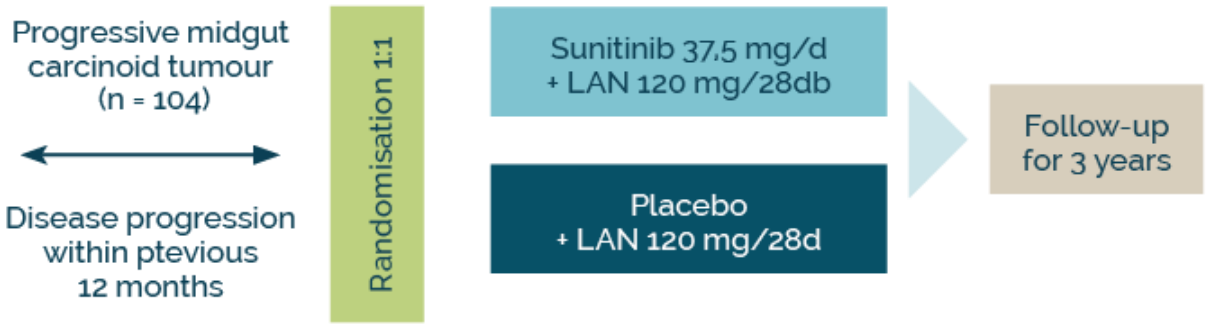

D. Progression-free survival by subgroups, central review
Subgroups
No.
Hazard ratio (95% CI)
All 302 0·56 (0·41–0·77)
Age
<65 159 0·55 (0·36–0·83)
≥65 143 0·59 (0·37–0·94)
Sex
Male 142 0·78 (0·51–1·22)
Female 160 0·39 (0·25–0·60)
Race
Caucasian 230 0·83 (0·56–1·21)
Asian 50 0·19 (0·09–0·40)
Other† 22 0·26 (0·08–0·85)
Tumour grading
Grade 1 194 0·57 (0·39–0·84)
Grade 2 107 0·49 (0·29–0·83)
Treatment naive‡
Yes 117 0·65 (0·39–1·08)
No 185 0·51 (0·35–0·76)
Prior chemotherapy
Yes 77 0·35 (0·19–0·64)
No 225 0·60 (0·42–0·86)
Baseline CgA
>2xULN 139 0·40 (0·25–0·62)
≤2xULN 138 0·70 (0·45–1·11)
Baseline NSE
>ULN 87 0·77 (0·45–1·34)
≤ULN 188 0·44 (0·29–0·66)
0·1
0·4
1
10
Favours everolimus
Favours placebo

Sunitinib

06

Association de LAN + sunitinib dans le traitement des tumeurs carcinoïdes de l'intestin grêle progressives : étude SUNLAND

Design [53] :



53. https://clinicaltrials.gov/ct2/show/NCT01731925

Chimiothérapie

Type of study	Author, year (Ref)	Type of chemotherapy	Total number of patients	Number of chemotherapy-treated Wd GI non-pNETs	Line of therapy (previous treatments)	Tumour grade of differentiation	Assessment of response	Including patients with progressive disease (yes/no)	Overall-response rate (%)	Disease-stabilization rate (%)	Disease-control rate (%)	Median OS months (95% CI)	Median PFS months (95% CI)	Data for PR rate comparison non-pNETS vs. pNETs
Randomised phase III	Dahan et al. (2009) [121]	5-FU and streptozocin (vs. IFN)	64	24	Prior chemotherapy (13%). Concomitant SSA (19%)	Not specified	WHO	Yes	1/20 (5%)	Not reported	Not reported	Not reported	Not reported	Yes
Randomised phase II	Oberg et al. (1989) [122]	Streptozocin, 5-FU and IFN (vs. IFN)	20	10	Not specified	Not specified	WHO	Not specified	0/10 (0%)	5/10 (50%)	5/10 (50%)	Not reported	Not reported	No
	Janson et al. (1992) [123]	5-FU, doxorubicin and IFN (vs. IFN)	23	11	IFN (6 pts), SSA (2 pts), SSA + IFN (2 pts)	Not specified: "carcinoid tumours" only	Not specified	Not specified	0/10 (0%)	10/10 (100%)	10/10 (100%)	Not reported	Not reported	No

A. Lamarca et al. / Cancer Treatment Reviews 44 (2016)

Xeloda-Bevacizumab ESSAI BETTER

Summary of patient and disease characteristics intent to treat (ITT; $n = 49$).

Characteristic	*N*	%
Median age, years (range)	60 (41–82)	
Gender		
Men	26	53
Women	23	47
Eastern Cooperative Oncology Group (ECOG) performance status		
0	37	76
1	9	18
2	3	6
Primary tumour		
Small intestine	40	82
Rectum	4	8
Caecum	3	6
Stomach	2	4
Prior treatment for the disease	46	94
Median number of prior treatments	3 (0–9)	
Type of treatments		
Surgical and medical procedures	44	90
Locoregional treatment	43	88
Liver embolisation	15	31
Somatostatin analogues	28	57
Interferon	5	10

E. Mitry et al. / European Journal of Cancer (2014)

Xeloda-Bevacizumab ESSAI BETTER

Index of proliferation		
Missing	1	
Ki-67 ⩽ 2%	17	35
2 < Ki-67 < 5%	14	29
5 ⩽ Ki-67 < 10%	13	27
10 ⩽ Ki-67 < 15%	4	8
Carcinoid syndrome	29	59
Metastatic disease site (at least one)	49	100
Liver	46	94
Lymph node	24	49
Peritoneum	23	47
Lung	7	14
Bone	7	14
Other	5	10
Number of metastatic sites		
1	10	20
2	20	41
⩾3	19	39

E. Mitry et al. / European Journal of Cancer (2014)

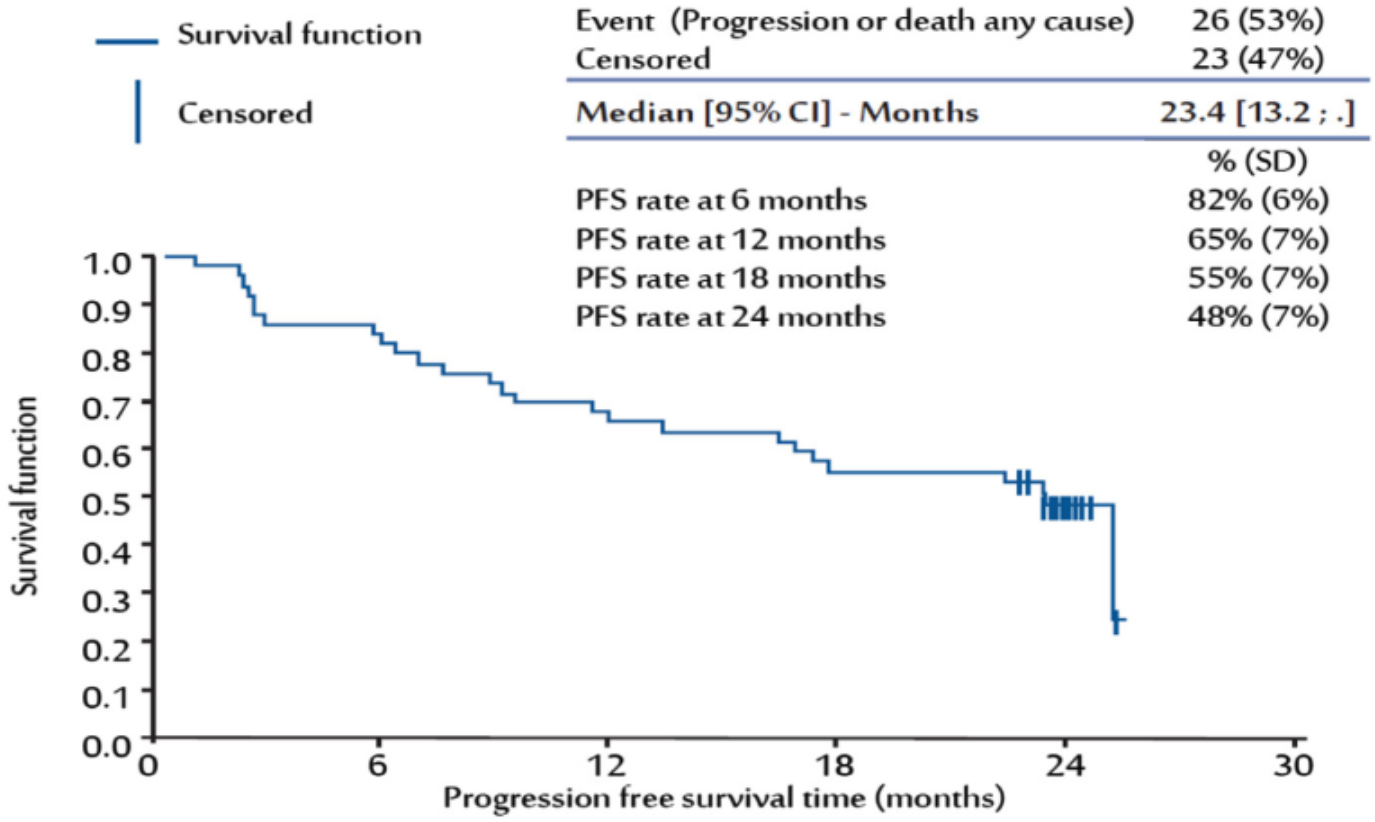
Xeloda-Bevacizumab
ESSAI BETTER

Progression-free survival (PFS) and response rates (ITT; $n = 49$).

	Investigator assessment		Expert radiologist assessment	
	N (%)	[95% confidence interval (CI)]	*N* (%)	[95% CI]
Disease progression or death	26 (53%)		16 (35%)	
Median PFS, months	23.3	[13.2; nr]	25.2	[24.3 ; nr]
Overall disease control rate	43 (88%)		45 (94%)	
Partial response	9 (18%)	[7%; 29%]	6 (12%)	[3%; 22%]
Stabilisation	34 (70%)	[56%; 82%]	39 (81%)	[70%; 92%]
Progression	4 (8%)	[0.5%; 16%]	0	
Not evaluable	2 (4%)	[0%; 10%]	3 (6%)	[0%; 13%]
Missing data			1*	

E. Mitry et al. / European Journal of Cancer (2014)

Xeloda-Bevacizumab ESSAI BETTER



E. Mitry et al. / European Journal of Cancer (2014)

Xeloda-Bevacizumab
ESSAI BETTER

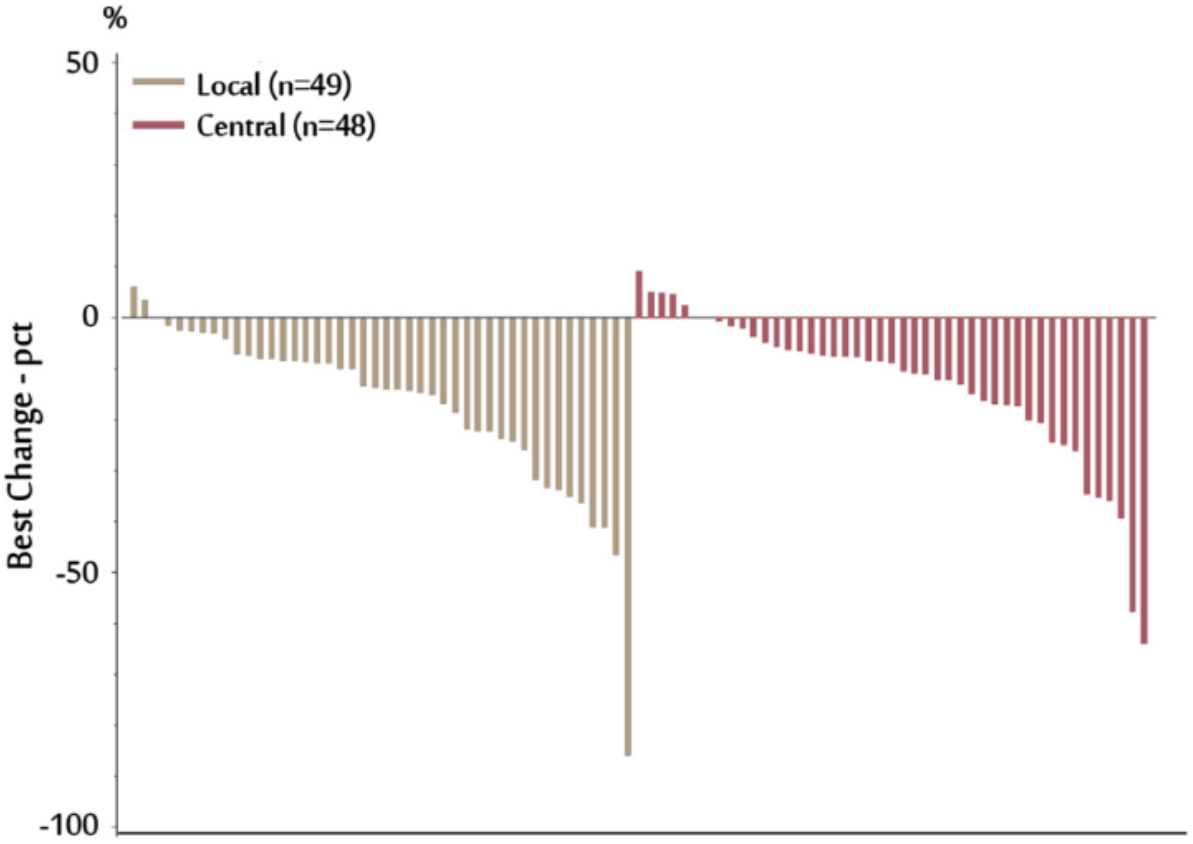


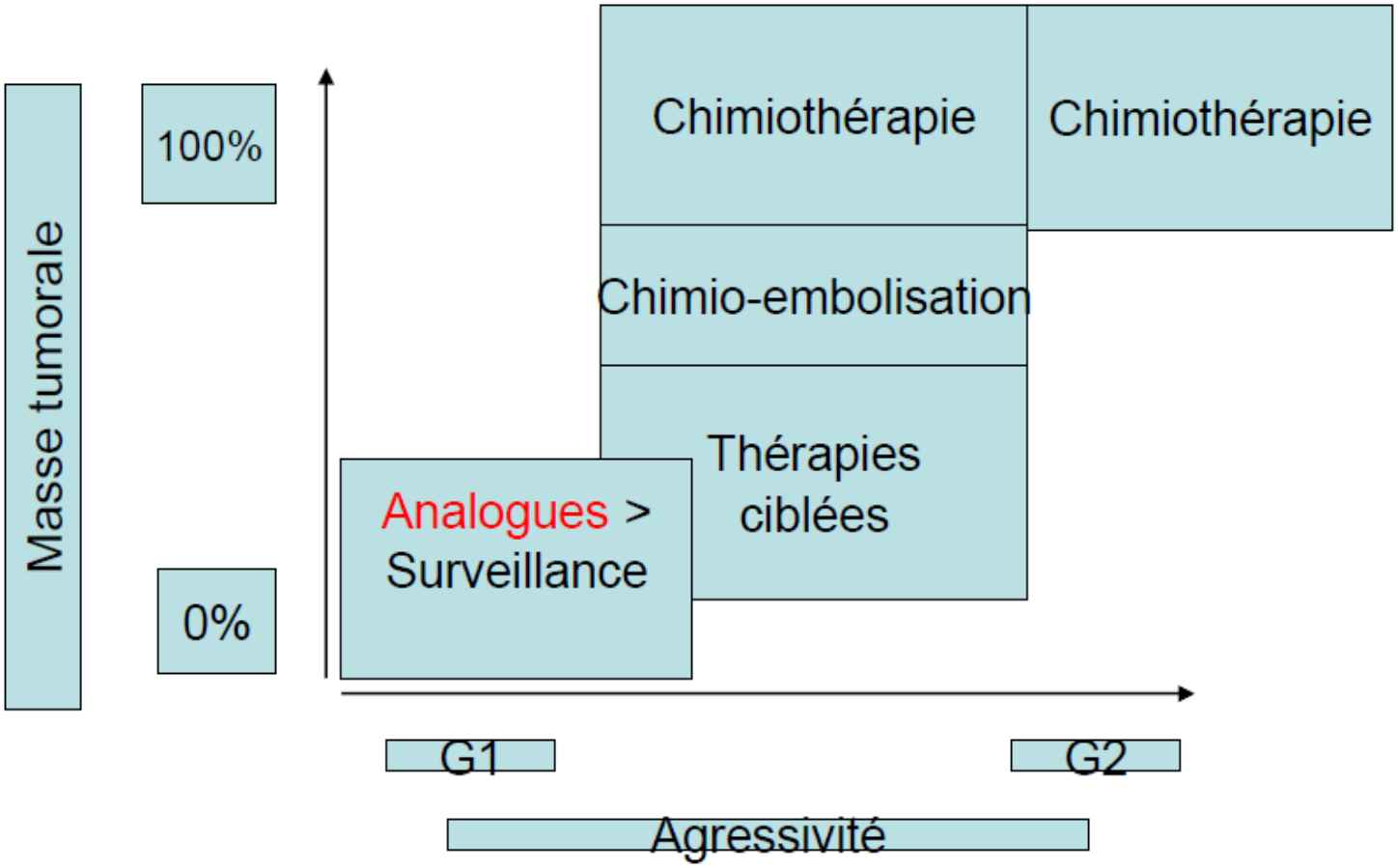
Fig. 2. Best response to treatment – Waterfall plot (ITT; $n = 49$).

E. Mitry et al. / European Journal of Cancer (2014)

Chimiothérapie vs ITK ?

- Volume tumoral
- Sites métastatiques (carcinose?)
- Pente évolutive (6 mois/ 1 an)
- KI67 (> ou < 10%?)
- Données de l'imagerie fonctionnelle (Mauvais pronostic, agressivité, hyperfixation au Tep FDG, pas de fixation au Dotatoc)

Stratégie antitumorale en pratique



➔ RCP RENATEN

➔ Essais thérapeutiques