VIII EDIZIONE

NEN PRECEPTORSHIP

LA PRATICA CLINICA NELLE NEOPLASIE NEUROENDOCRINE

16/17 Maggio 2019 | IEO, Istituto Europeo di Oncologia - Milano

NEN Preceptorship

IEO
Istituto Europeo di Oncologia

Approccio diagnostico-terapeutico al paziente con NET pancreatico

L'Oncologo

Carlo Carnaghi
Oncologia Bolzano

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NCCN Guidelines Ind
Table of Conter
Discussi

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019
Neuroendocrine Tumors of the Pancreas

MANAGEMENT OF LOCOREGIONAL ADVANCED DISEASE AND/OR DISTANT METASTASES[g]

EVALUATION

Abdominal/pelvic multiphasic[a] CT or MRI and chest CT (± contrast) as clinically indicated
Somatostatin receptor-based imaging (ie, ^{68}Ga-dotatate imaging preferred [PET/CT or PET/MRI][e] or somatostatin receptor scintigraphy)
Biochemical evaluation as clinically indicated (See NE-B)[c]
Consider tumor classification/ grade (See NE-A)[x]

TREATMENT

If complete resection possible[g,y] → Resect metastases + primary[aa] → See Surveillance (PanNET-6)

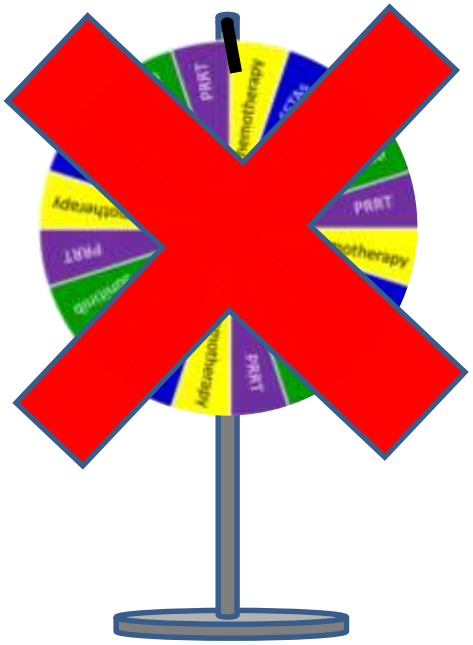
Asymptomatic, low tumor burden, and stable disease →
- Observe with markers and abdominal/pelvic multiphasic[a] CT or MRI every 3–12 mo and chest CT (± contrast) as clinically indicated
- Consider octreotide[k,bb] or lanreotide[k,bb]

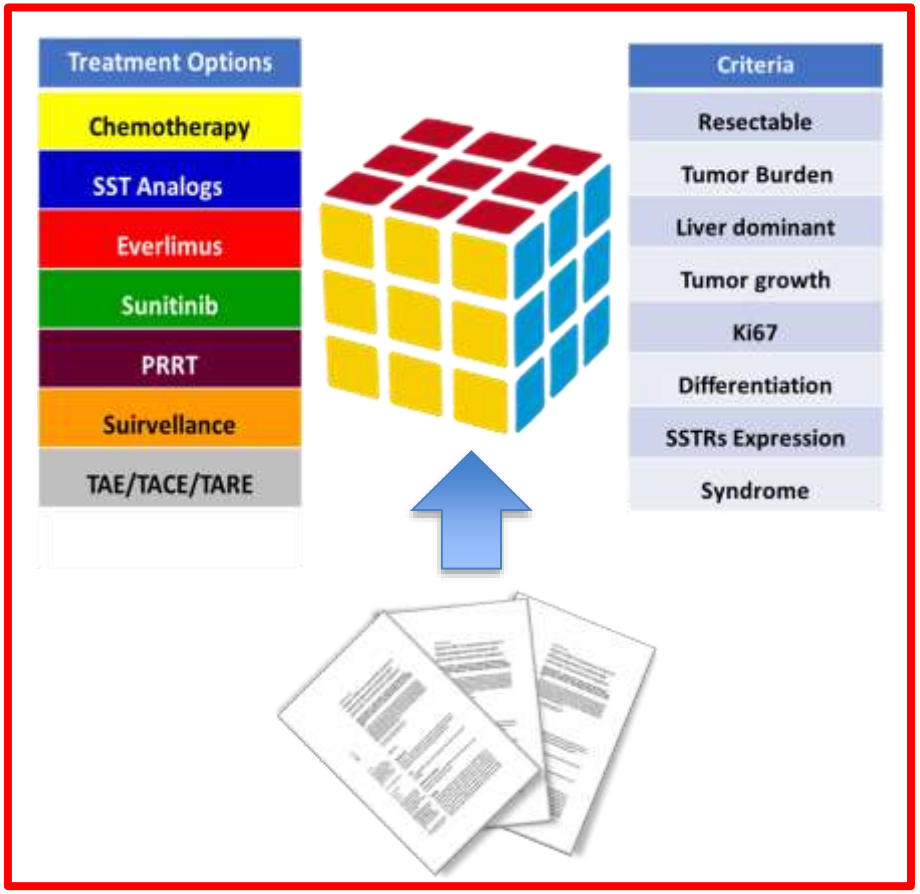
→ Clinically significant progressive disease, see below

Symptomatic or Clinically significant tumor burden or Clinically significant progressive disease[z] →
Manage clinically significant symptoms as appropriate (PanNET-1, PanNET-2, PanNET-3, PanNET-4, and PanNET-5)
or
Consider alternative front-line therapy (see options for disease progression)[cc]

→ If disease progression, consider octreotide[k,bb] or lanreotide[k,bb] (if not already receiving)

→ If disease progression[z]:
Everolimus[k] (10 mg/d) (category 1 for progressive disease)
or
Sunitinib[k] (37.5 mg/d) (category 1 for progressive disease)
or
PRRT with 177Lu-dotatate, if somatostatin receptor-positive imaging and progression o octreotide or lanreotide[k,bd]
or
Cytotoxic chemotherapy: Capecitabine/ temozolomide, streptozocin-based or other options[k]
or
Consider a hepatic-directed therapy for hepatic-predominant disease:[ee]
- Arterial embolization, or
- Hepatic chemoembolization, or
- Hepatic radioembolization (category 2B), or
- Cytoreductive surgery/ablative therapy[g,ff] (category 2B)


PRRT
PRRT
PRRT


Treatment Options
Chemotherapy
SST Analogs
Everlimus
Sunitinib
PRRT
Suirvellance
TAE/TACE/TARE
Criteria
Resectable
Tumor Burden
Liver dominant
Tumor growth
Ki67
Differentiation
SSTRs Expression
Syndrome

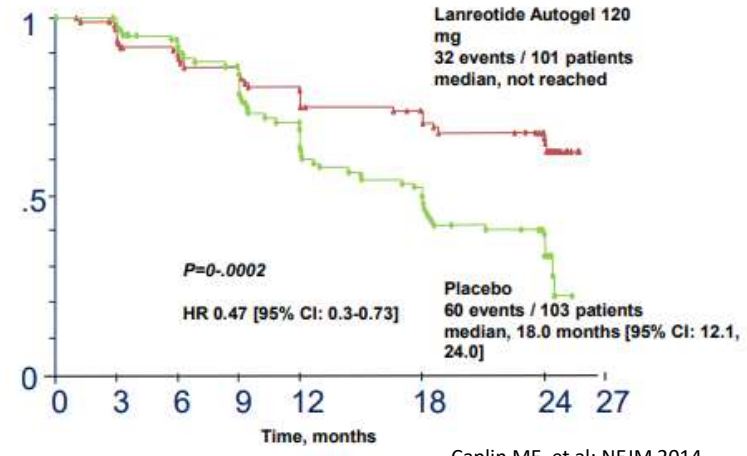
Criteria*			
Resectable	Yes		No
Tumor Burden	Low		High
Liver Dominant	Yes		No
Tumor Growth	SD		PD
Grade	G1	G2	G3
SSTRs Expression	Yes		No
Syndrome	Yes		No

*Not applicable to NEC

Criteria		
Resectable	Yes	No
Tumor Burden	Low	High
Liver dominant	Yes	No
Tumor growth	[illegible]	PD
Grade	G1 G2	G3
SSTRs Expression	Yes	No
Syndrome	Yes	No

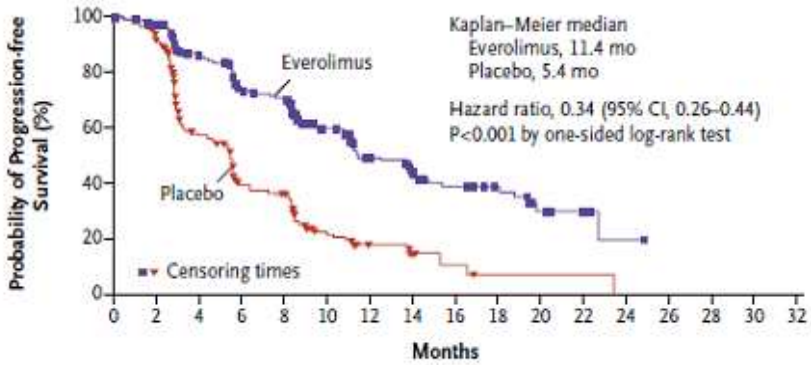
Target Therapies

CLARINET



Caplin ME, et al; NEJM 2014

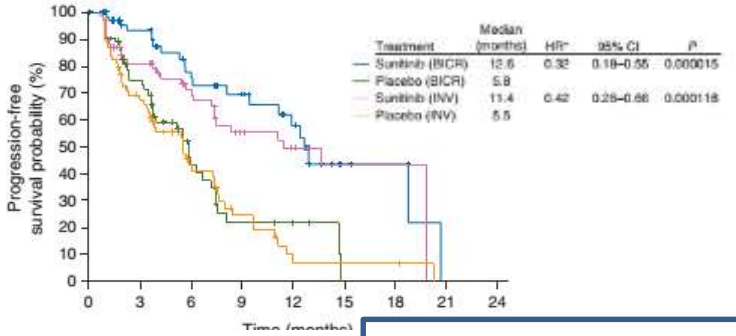
RADIANT-3

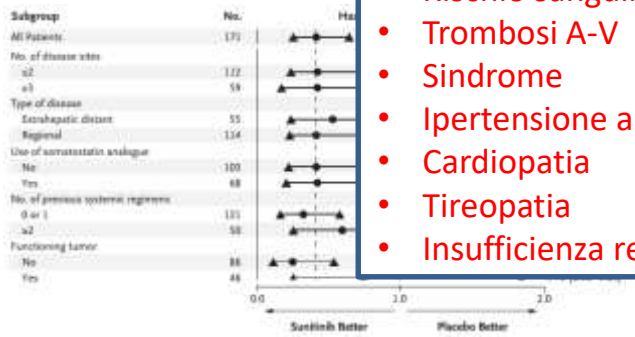


Yao JC, et al. JCO 2016

Target Therapies

Sunitinib





- Rischio sanguinamento
- Trombosi A-V
- Sindrome
- Ipertensione arteriosa
- Cardiopatia
- Tireopatia
- Insufficienza renale

Raymond E. et al. NEJM 2011

Sunitinib Drug Interactions

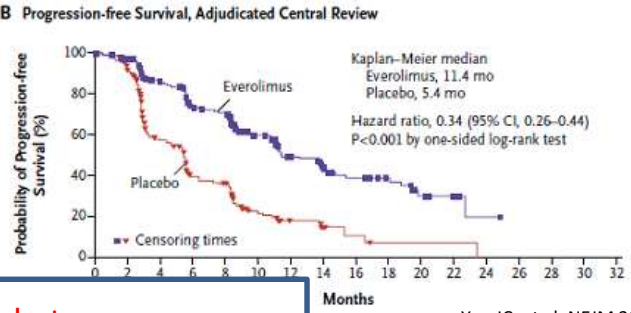
A total of **464 drugs** (1783 brand and generic names) are known to interact with sunitinib.

- 60 major drug interactions (160 brand and generic names)
- 398 moderate drug interactions (1587 brand and generic names)
- 6 minor drug interactions (36 brand and generic names)

www.drugs.com

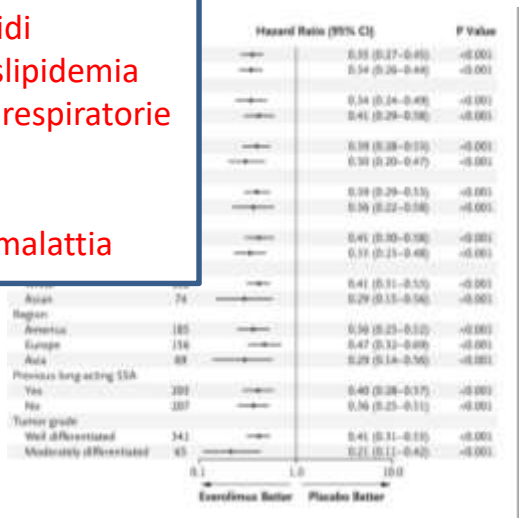
VS.

Everolimus



Yao JC, et al. NEJM 2011

- Diabete
- Uso steroidi
- Severa dislipidemia
- Patologie respiratorie croniche
- Sintomi
- Carico di malattia



Yao JC, et al. JCO 2016

Criteria		
Resectable	Yes	No
Tumor Burden	Low	High
Liver dominant	Yes	No
Tumor growth	SD	PD
Grade	G1	G2
SSTRs Expression	Yes	No
Syndrome	Yes	No

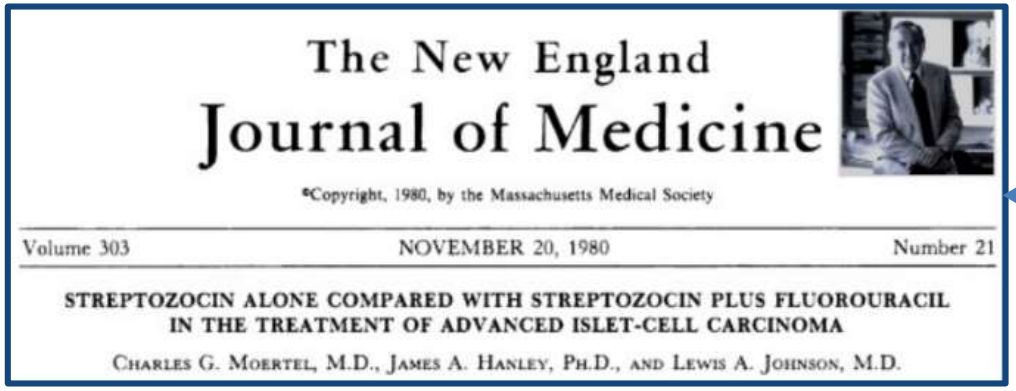
Chemotherapy

Strengths:
- High response rates
- Temozolomide is generally tolerable
- Convenient oral administration

Weaknesses:
- Unpredictable grade 3-4 cytopenias (~15% of patients)
- No clear validated predictive markers

Most appropriate for: Patients with **pancreatic NETs**, aggressive disease, high tumor burden, or tumor-related symptoms

The longest time spent waiting for a randomized trial…

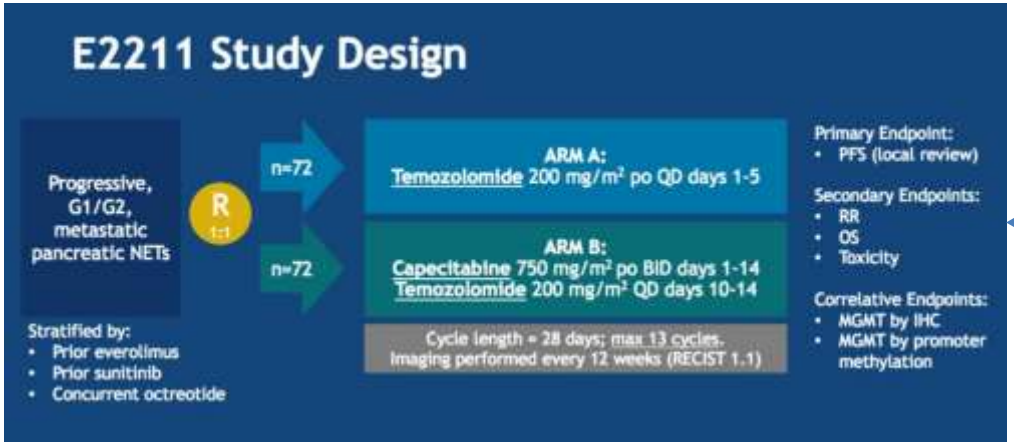


The New England
Journal of Medicine

Volume 303 NOVEMBER 20, 1980 Number 21

STREPTOZOCIN ALONE COMPARED WITH STREPTOZOCIN PLUS FLUOROURACIL IN THE TREATMENT OF ADVANCED ISLET-CELL CARCINOMA

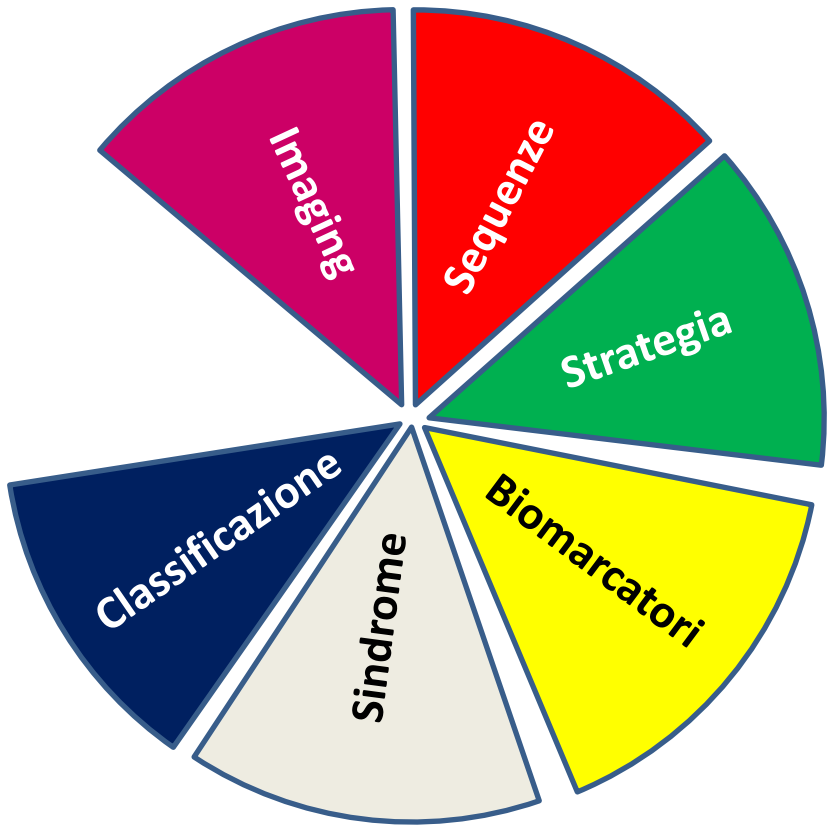
CHARLES G. MOERTEL, M.D., JAMES A. HANLEY, PH.D., AND LEWIS A. JOHNSON, M.D.



28 YEARS ANNIVERSARY

Criteria			
Resectable		Yes	
Tumor Burden	Low		No
Liver Dominant		Yes	
Tumor Growth	SD		No
Grade	G1	G2	PD
SSTRs Expression		Yes	
Syndrome	Yes		No

Criteri Generali



2° domanda: cosa fareste adesso?

1. PET/TC con FDG	**Filice**
2. Terapia medica	**Carnaghi**
3. Ulteriore imaging radiologico	**Funicelli**
4. Indagini genetiche	**Lania**

Criteria		
Resectable	Yes	No
Tumor Burden	Low	High
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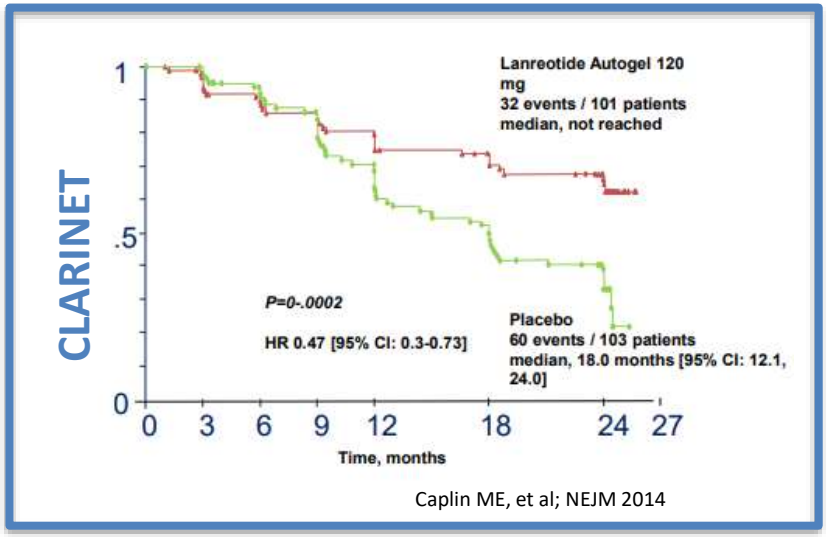
SSTRs Expression	Yes	No
Syndrome	Yes	No

Somatostatin Analogs



Caplin ME, et al; NEJM 2014

Symptom	Number effected (rating 1-10/10)	Percentage (%) affected (rating 1-10/10)	% effected on Sandostatin LAR Studies	% effected on Somatuline Autogel Studies
Constipation	150	85.22%	≥ 10%	0.1-9.99%
Steatorrhoea	148	84.09%	0.1-9.99%	0.1-9.99%
Diarrhoea	139	78.97%	≥ 10%	≥ 10%
Feeling burden of treatment	119	67.61%	No data	No data
Vitamin B12 deficiency	110	62.50%	No data	No data
Hair thinning	101	57.38%	0.1-9.99%	0.1-9.99%
Nausea	93	52.84%	≥ 10%	0.1-9.99%
Vit A,D,E,K deficiency	91	51.70%	No data	No data
Weight loss	76	43.18%	No data	0.1-9.99%
Low glucose	75	42.61%	0.1-9.99%	0.1-9.99%
Gallstones	29	16.47%	≥ 10%	≥ 10%

Table 1. Self-reported symptoms/side effects after commencing SSA's.

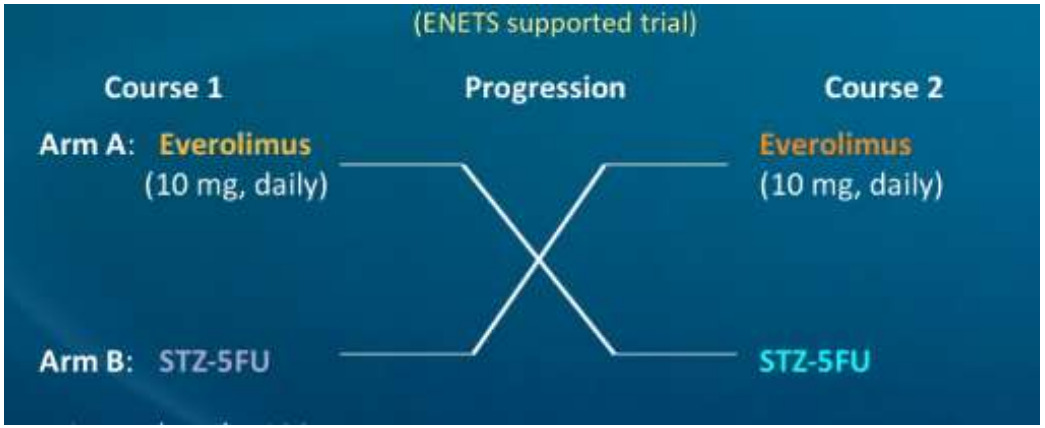
Whyand T, et al. Abstract ENETS 2018

3° domanda: cosa fareste?

1. Definizione di strategia terapeutica in ambito MDT	**Spada**
2. Inclusione in studi clinici	**Carnaghi**
3. EUS pancreatica + FNA	**Ravizza**
4. Ristadiazione radiologica e decisione conseguente	**Fazio**

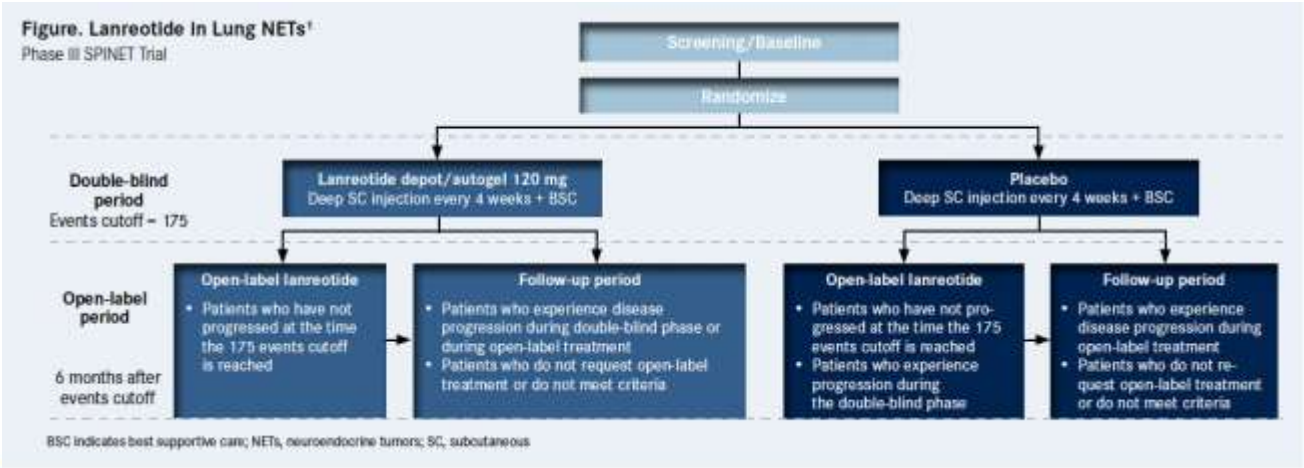
Inclusione in studi clinici

SEQTOR



Unmet Needs

SPINET



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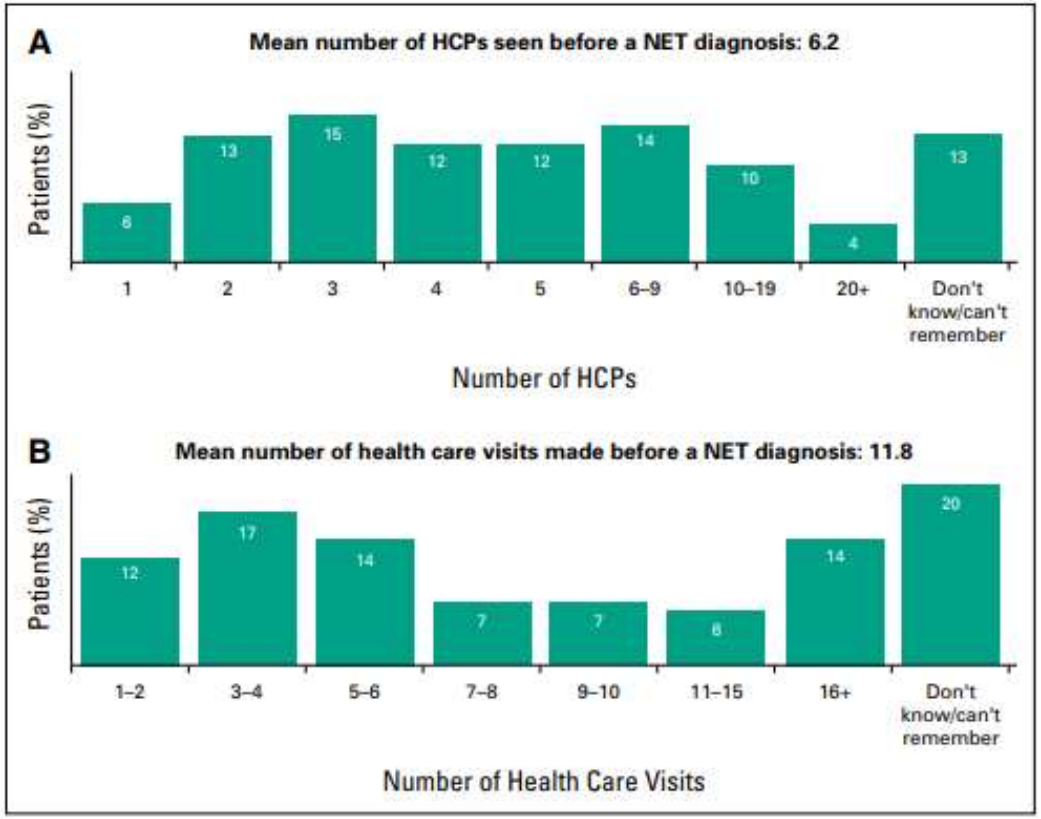
European ENETS Neuroendocrine Tumor Society

It.a.net

Centers of Excellence (CoE) Interactive Map

European ENETS Neuroendocrine Tumor Society

Centers of Excellence (CoE) Interactive Map

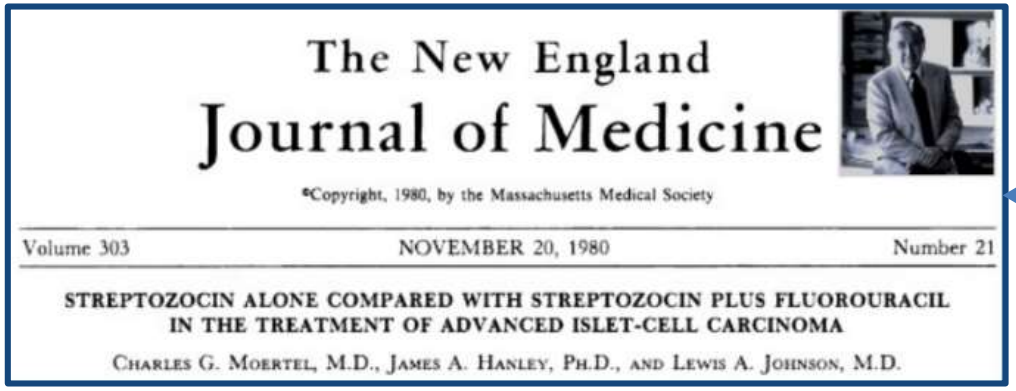


Singh S, et al. Journal of Global Oncology 2017

5° domanda: quale terapia sistemica fareste a scopo citoriduttivo?

1. Chemioterapia	**Carnaghi**
2. Terapia radiorecettoriale	**Filice**
3. Sunitinib	**Spada**
4. Everolimus	**Everolimus**

The longest time spent waiting for a randomized trial…



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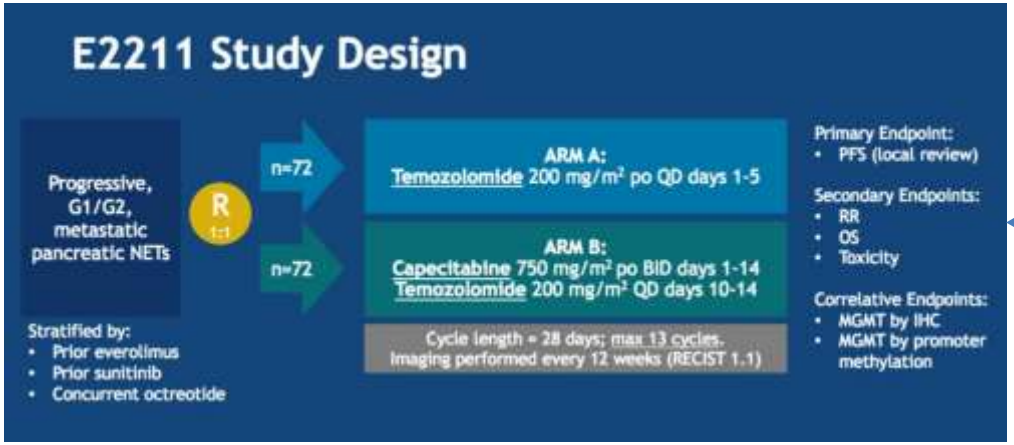


28 YEARS ANNIVERSARY

E2211 Study Design

Progressive, G1/G2, metastatic pancreatic NETs

R 1:1

n=72 — ARM A: Temozolomide 200 mg/m² po QD days 1-5

n=72 — ARM B: Capecitabine 750 mg/m² po BID days 1-14, Temozolomide 200 mg/m² QD days 10-14

Cycle length = 28 days; max 13 cycles. Imaging performed every 12 weeks (RECIST 1.1)

Stratified by:
- Prior everolimus
- Prior sunitinib
- Concurrent octreotide

Primary Endpoint:
- PFS (local review)

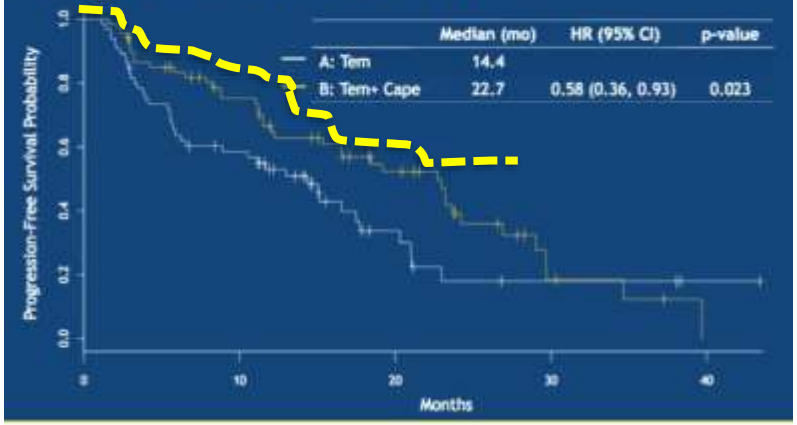
Secondary Endpoints:
- RR
- OS
- Toxicity

Correlative Endpoints:
- MGMT by IHC
- MGMT by promoter methylation

Response Rates

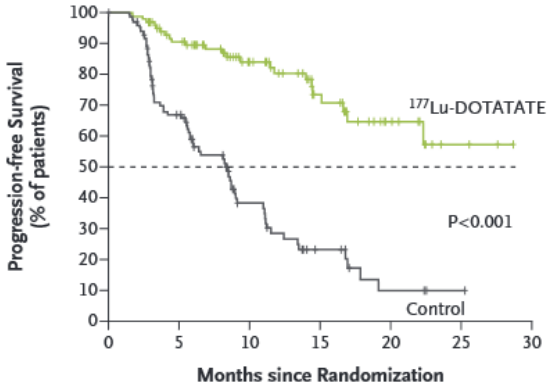
	Temozolomide (N=72)	Temozolomide + Capecitabine (N=72)	p-value
Complete response	2.8%	0	
Partial response	25.0%	33.3%	
Stable disease	40.3%	48.6%	
Progressive disease	19.4%	13.9%	
Unevaluable	12.5%	4.2%	
Objective Response Rate (CR+PR)	27.8%	33.3%	0.47
Disease Control Rate (CR+PR+SD)	68.1%	81.9%	
Response Duration (median)	9.7 mo	12.1 mo	

Progression Free Survival



2018 ASCO ANNUAL MEETING

A Progression-free Survival



No. at Risk

^{177}Lu-DOTATATE group	116	97	76	59	42	28	19	12	3	2	0
Control group	113	80	47	28	17	10	4	3	1	0	0

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