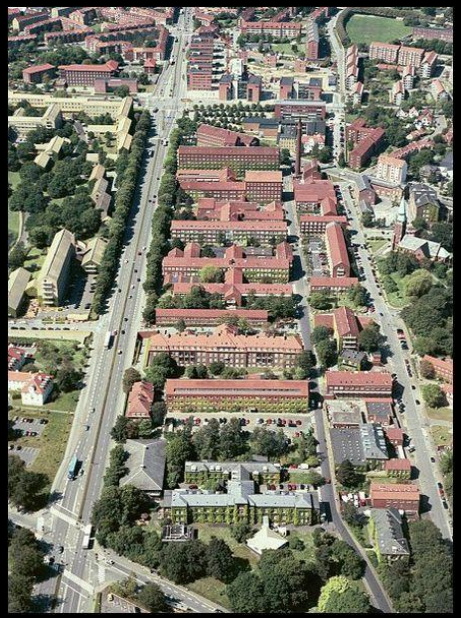
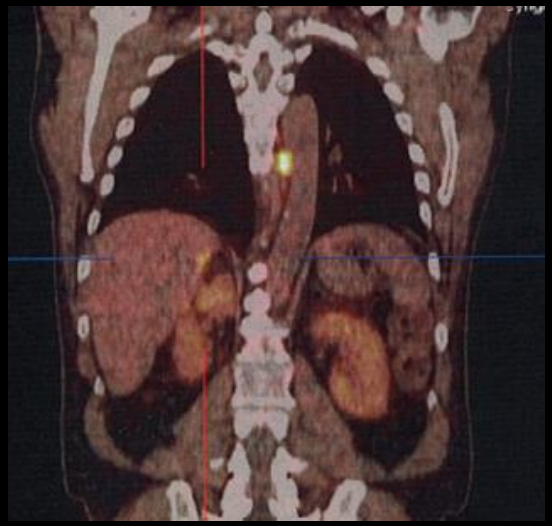
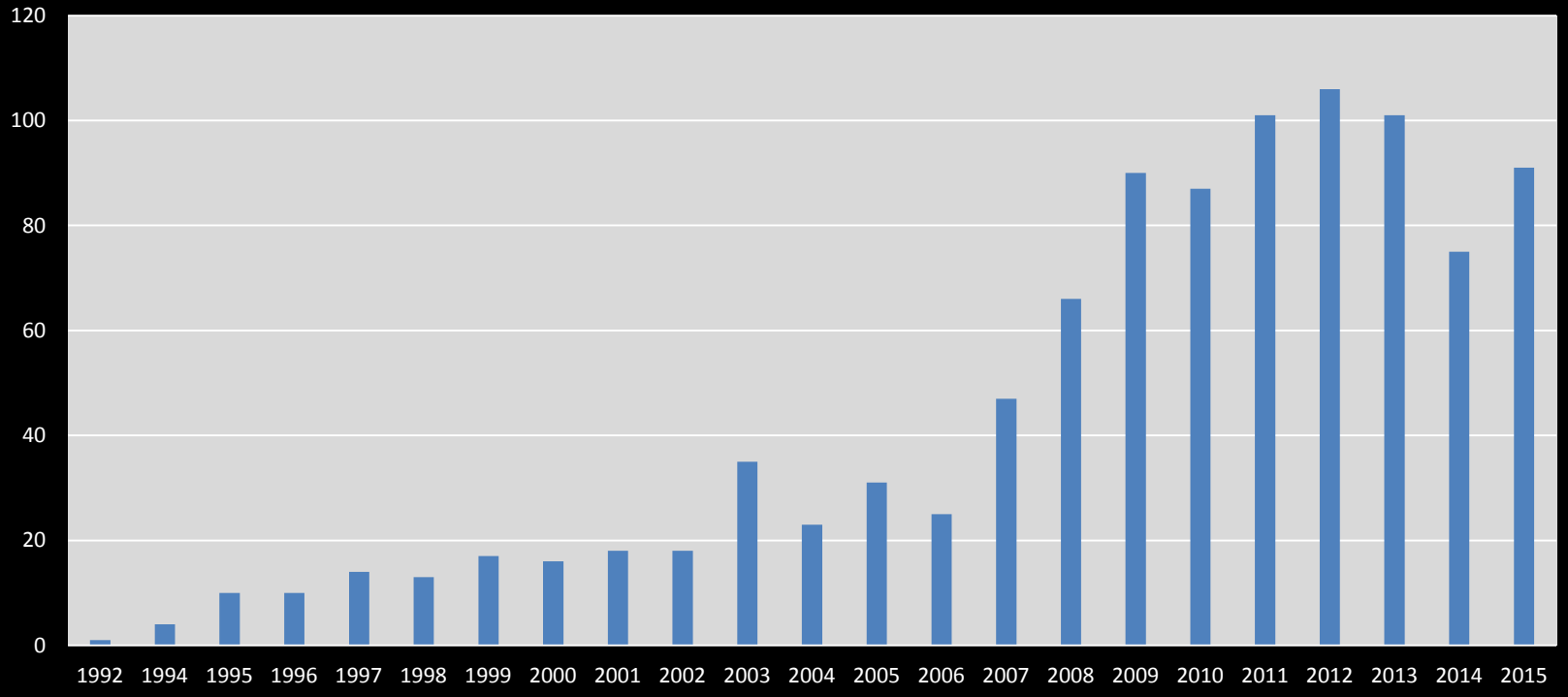
Medicinsk behandling af NET
25 år med NET i Aarhus

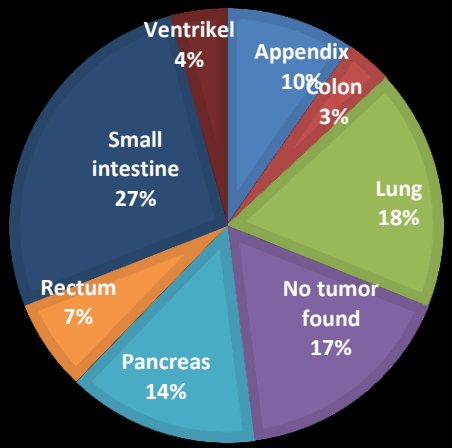


Henning Grønbæk, overlæge, Ph.D.
Medicinsk Afdeling V
Århus Universitetshospital



NET i Arhus


120
100
80
60
40
20
0
1992
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015

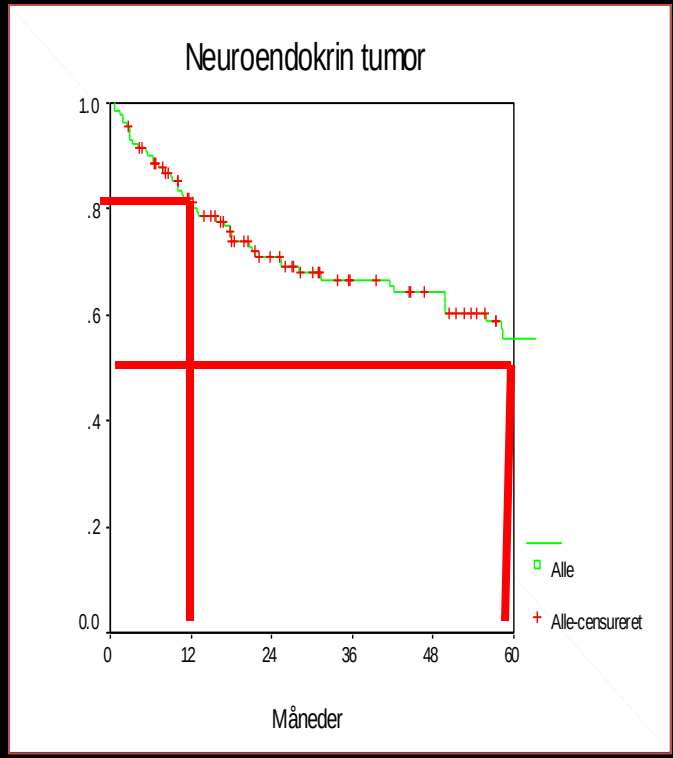

Ventrikel
4%
Appendix
10%
Colon
3%
Small
intestine
27%
Lung
18%
Rectum
7%
No tumor
found
17%
Pancreas
14%

Udvikling af lægemidler

- Den gode ide – nu optimeret og udviklet
- Dyrestudier
- Fase I – først i menneske, toksisk?
- Fase II – afprøvning i lille patient gruppe
  - Effekt (symptomer, tumor)
  - Bivirkninger
- Fase III – afprøvning i større patient gruppe
  - Langtids effekter (symptomer, tumor)
  - Bivirkninger

Behandlingsmål

- Symptom effekt
- Biokemisk effekt
- Tumor effekt
- 1-, 5-, 10-års overlevelse
- Middel overlevelse



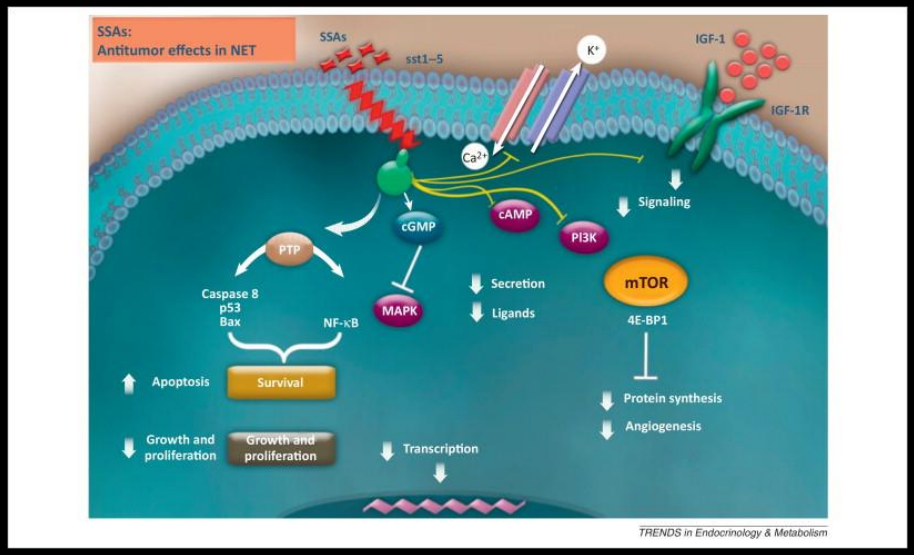
- **Klinisk kontrolleret studie:**
  - Sammenligner ny mod gammel eller ingen behandling

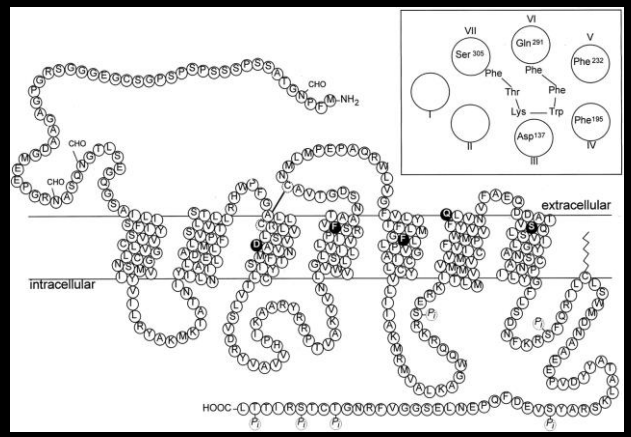
Kendte og nye behandlinger

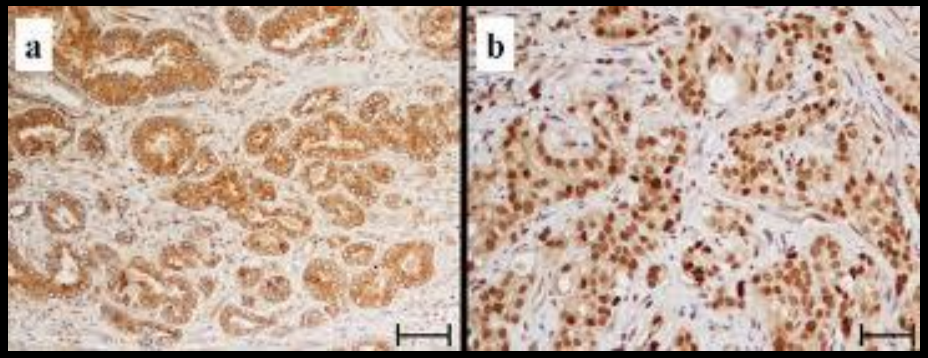
- Somatostatin analoger
  - Ipstyl (Lanreotid) og Sandostatin (Octreotid)
  - Pasireotid
- Interferon?
- Telotristat
- Temodal – xeloda
- Everolimus og sunitinib
- Radionuklidbehandling (PRRT), SIRT
- Kemoterapi
  - Streptozotocin 5FU
  - Carboplatin, etoposid

NET celler og somatostatin receptorer

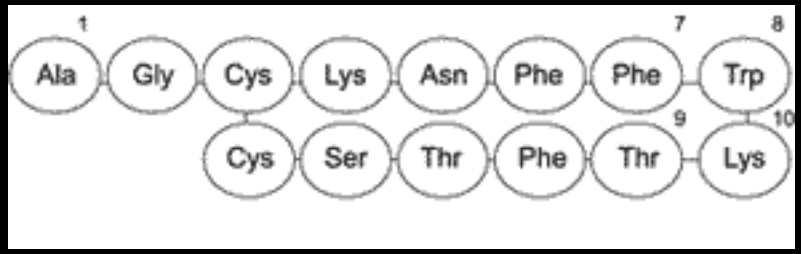
Celle vækst
Hormon sekretion



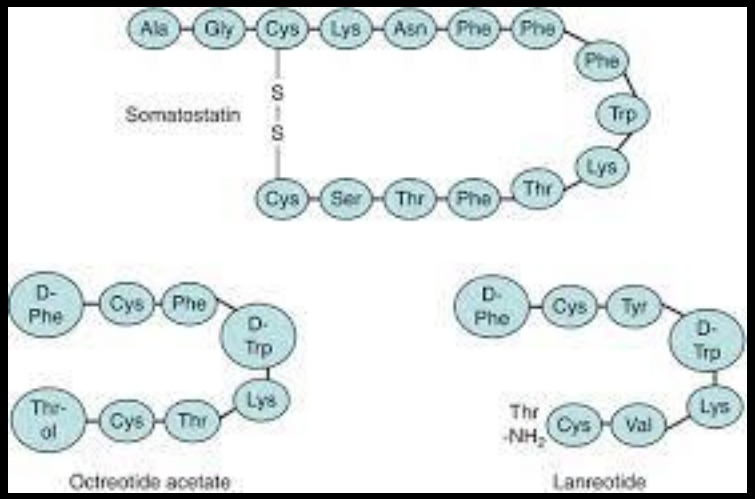


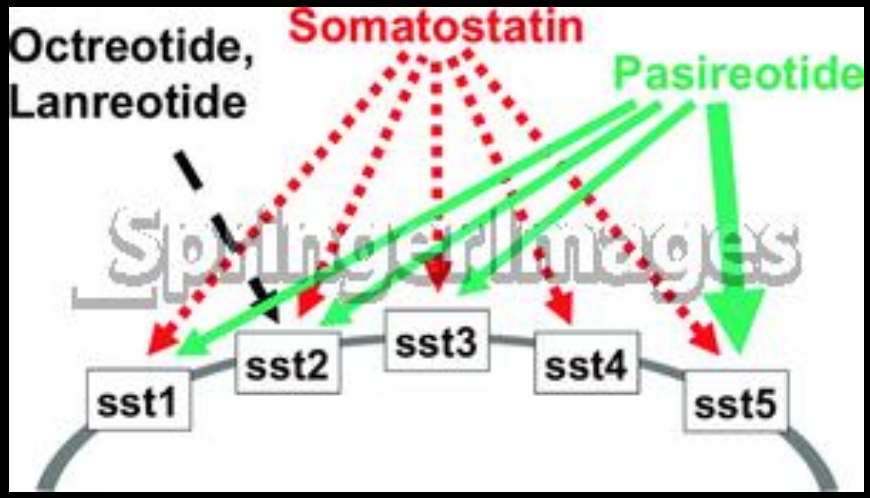


Somatostatin og analoger:



Kort halveringstid – 2-3 minutter



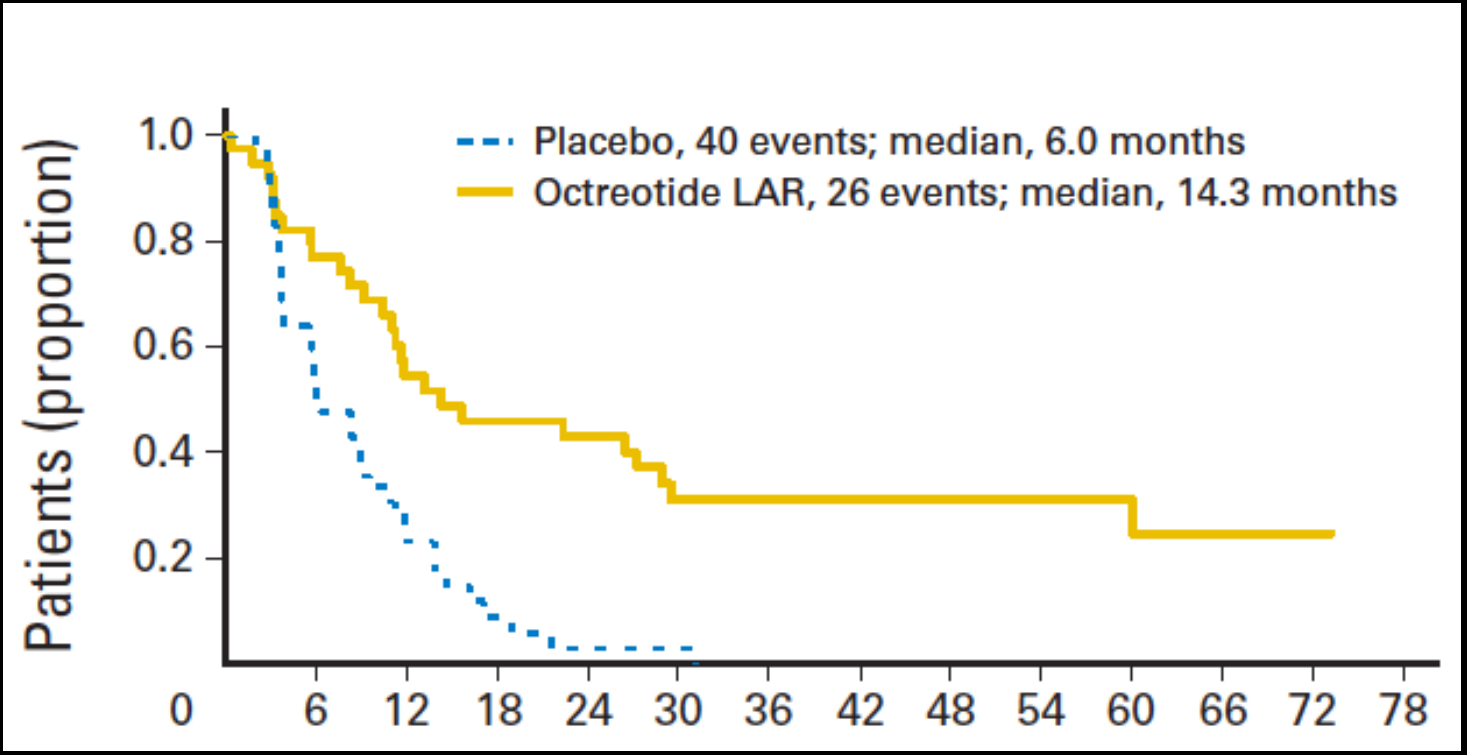


– Octreotid (Novartis), Lanreotid (Ipsen)
– Hæmmer frigivelse af hormoner og peptider
– Hæmmer celledeling

Medicinsk behandling

- ***Somatostatin analoger***:
  - ***Sandostatin*** *100 µg* (testdosis)
  - **Sandostatin LAR 30** mg/4. uge.
  - ***Lanreotid autogel 120*** *mg/4 uge.*
  - *Bivirkninger: Fedtdiare, Kreon*
  - *mavesmerter, galdesten*
  - ***SOM230 – en ny somatostatin analog***

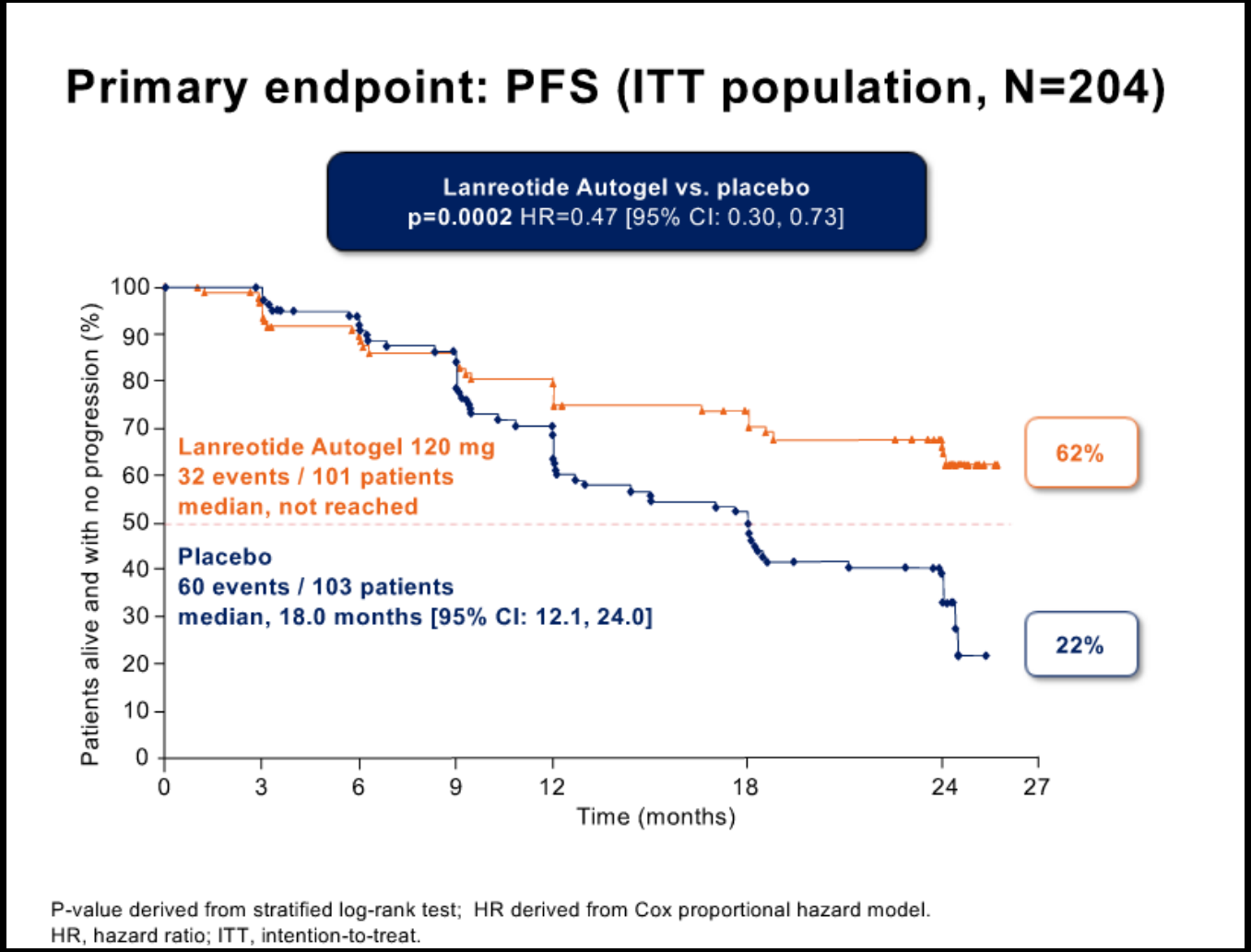
Sandostatin LAR vs. Placebo Tyndtarms NET



- Stabil sygdom 67% vs. 37% efter 6 måneder

FØRSTE STUDIE DER VISER EFFEKT AF SOMATOSTATIN ANALOG BEHANDLING

Lanreotid autogel 120 mg vs. Placebo
Tarm, bugspytkirtel, G1 og G2 tumorer (Ki67<10%)



Interferon NET studier

- Varierende doser og varighed af behandling
- Symptomatisk effekt: 62%
- Biokemisk effekt: 50%
- Tumor effekt:
  - Regression: 10%
  - Stabil sygdom: 65%
  - Progression: 23%

Investigator	
Öberg 1983	
Öberg 1986	Progresion 5/36 (14%)
Smith 1987	
Doberauer 1987	Progression: 5/14 (35%)
Hanssen 1989 (± embolisation)	
Nobin 1989	Progression: 1/13 (8%)
Öberg 1989	Progression: 1/17 (6%)
Mortel 1989	
Creutzfeldt 1991	Progression: 4/17 (23%)
Hanssen 1991 (± embolisation)	Progression: 7/36 (19%)
Öberg 1991	Progression: 21/111 (19%)
Doberauer 1991	Progression: 5/14 (36%)
Basser 1991	
Valimaki 1991	Progression: 4/8 (50%)
Biesma 1992	Progression: 2/24 (8%)
Veenhoff 1992	
Schober 1992	
Ahren 1992	Progression: 6/14 (43%)
Janson 1992 (vs. doxyrubicin)	Progression: 3/12 (25%)
Joensuu 1992	Progression: 5/14 (36%)
Schöber 1992	Progression: 4/25 (16%)
Janson 1993 (INFα/INFγ)	Progression: 4/25 (16%)
Di Bartholomeo 1993	
Bajetta 1993	
Jacobsen 1995	
Dirix 1996	Progression: 1/15 (7%)
Stuart 2004 (INFγ)	Progression: 15/25 (31%)

First-Line Chemotherapy With Capecitabine and Temozolomide in Patients With Metastatic Pancreatic Endocrine Carcinomas

Jonathan R. Strosberg, MD[1]; Robert L. Fine, MD[2]; Junsung Choi, MD[1]; Aejaz Nasir, MD[3]; Domenico Coppola, MD[3]; Dung-Tsa Chen, PhD[4]; James Helm, MD[1]; and Larry Kvols, MD[1]

Temodal
Xeloda

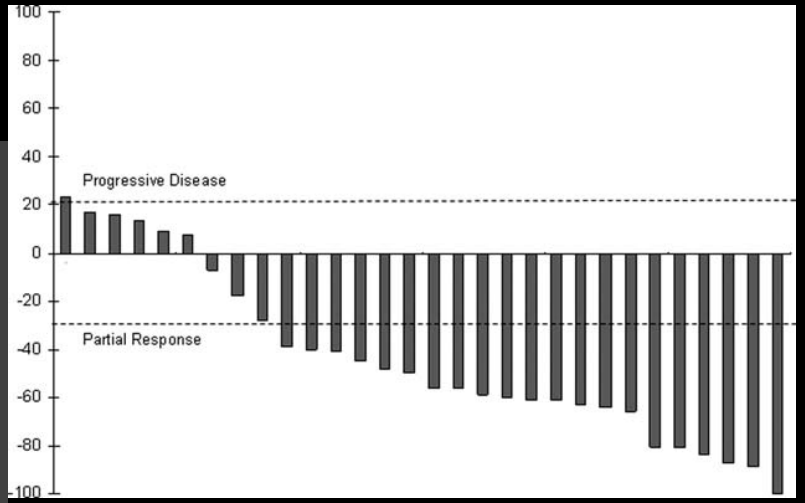
Tabletter:

Capecitabine, 750 mg/m^2 x 2 dgl (dag 1-14)

Temozolomide 200 mg/m^2 x 1 dgl. (dag 10-14)

Hver 28. dag

Kvalmestillende medicin



30 patienter

21 (70%) tumor effekt

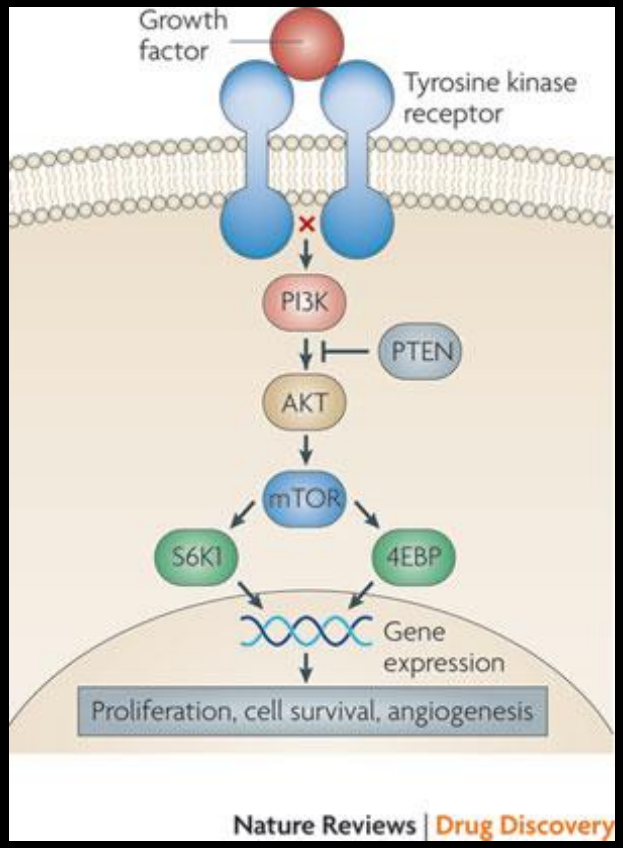
Progressions-fri overlevelse 18 mdr.

2-års overlevelse: 92%

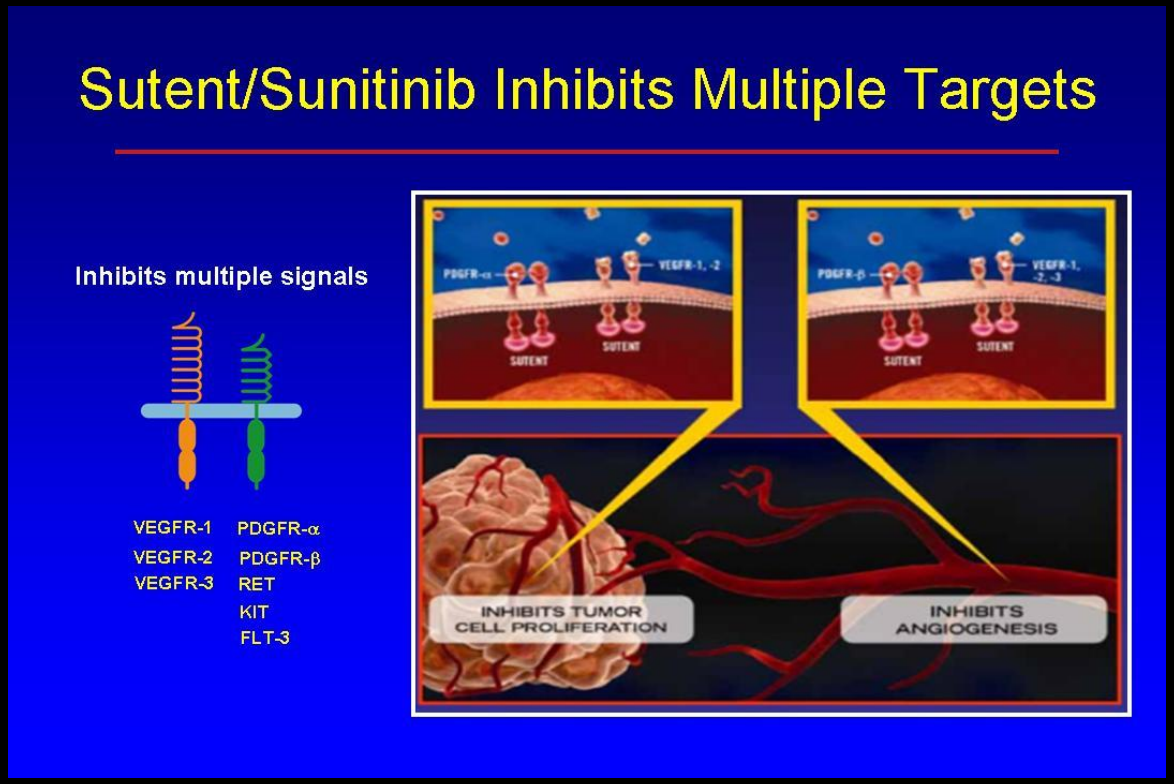
4 patienter (12%) grad 3/4 bivirkninger

”Målrettet” behandling

Everolimus



Sunitinib



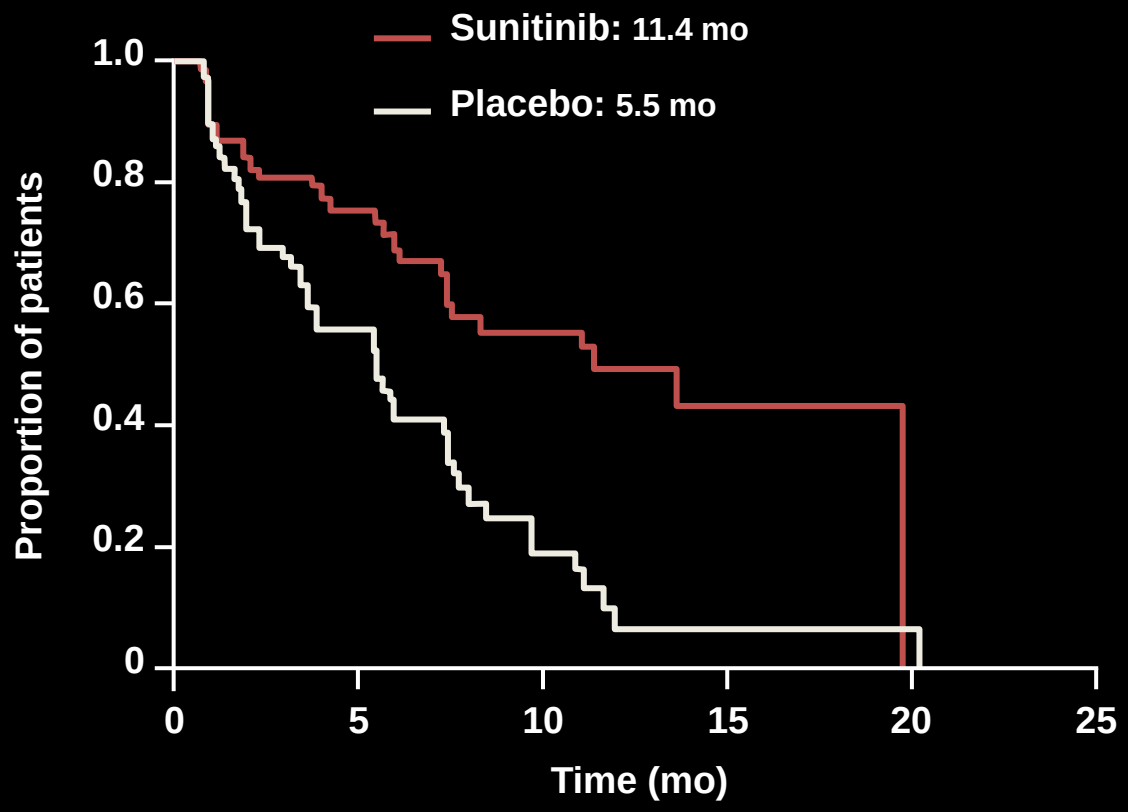
Sunitinib til pancreas NET - 2011

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 10, 2011 VOL. 364 NO. 6

Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors

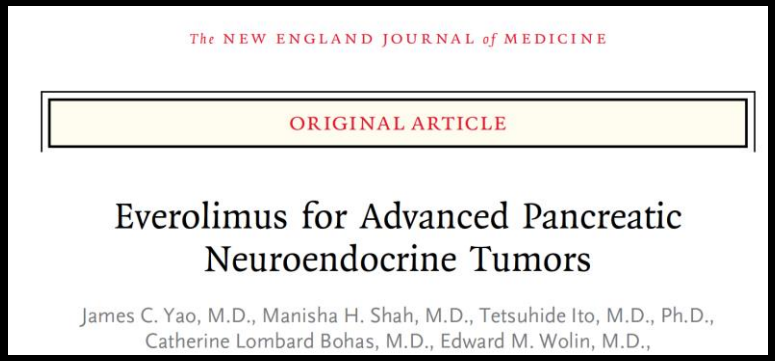
Eric Raymond, M.D., Ph.D., Laetitia Dahan, M.D., Ph.D., Jean-Luc Raoul, M.D., Ph.D., Yung-Jue Bang, M.D.,



Number at risk

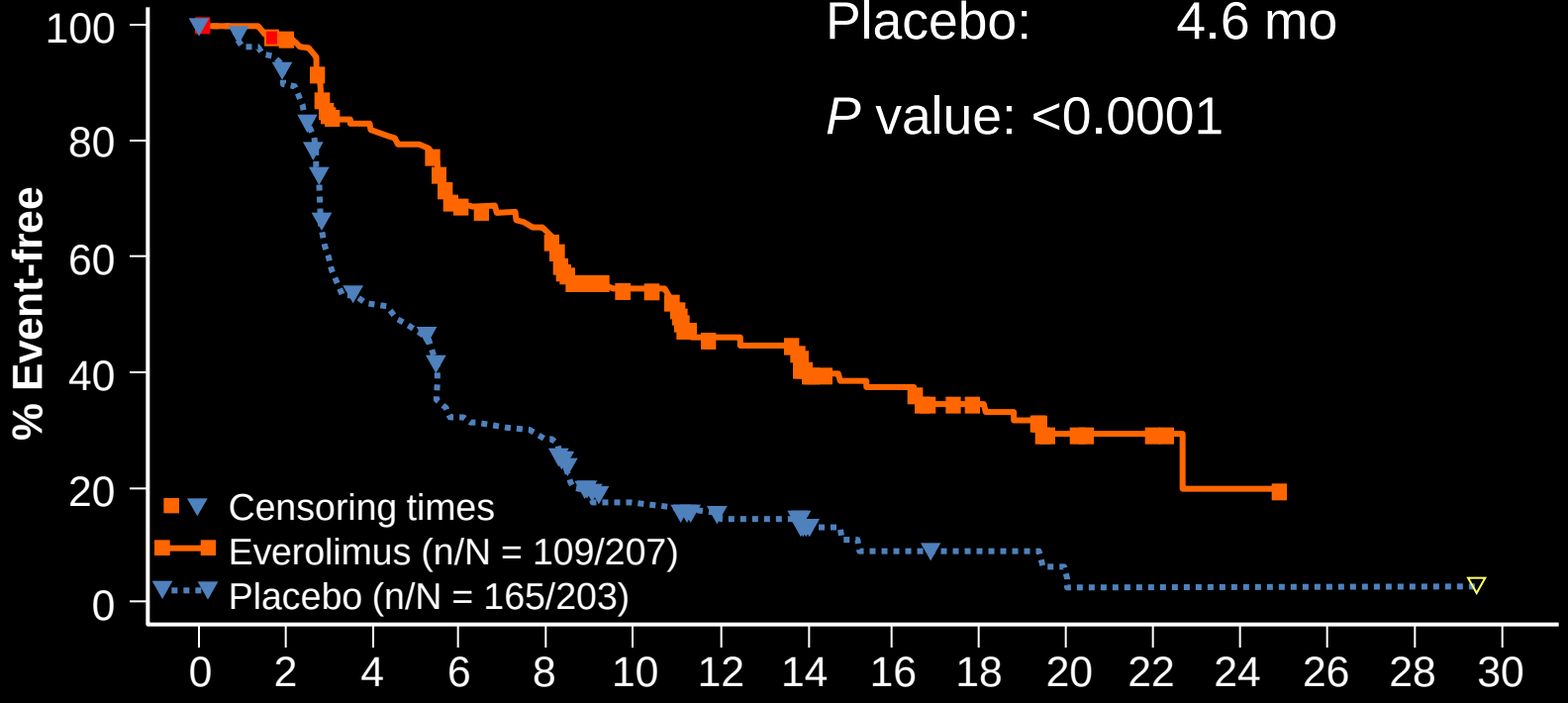
Sunitinib	86	39	19	4	0	0
Placebo	85	28	7	2	1	0

Everolimus til pancreas NET - 2011



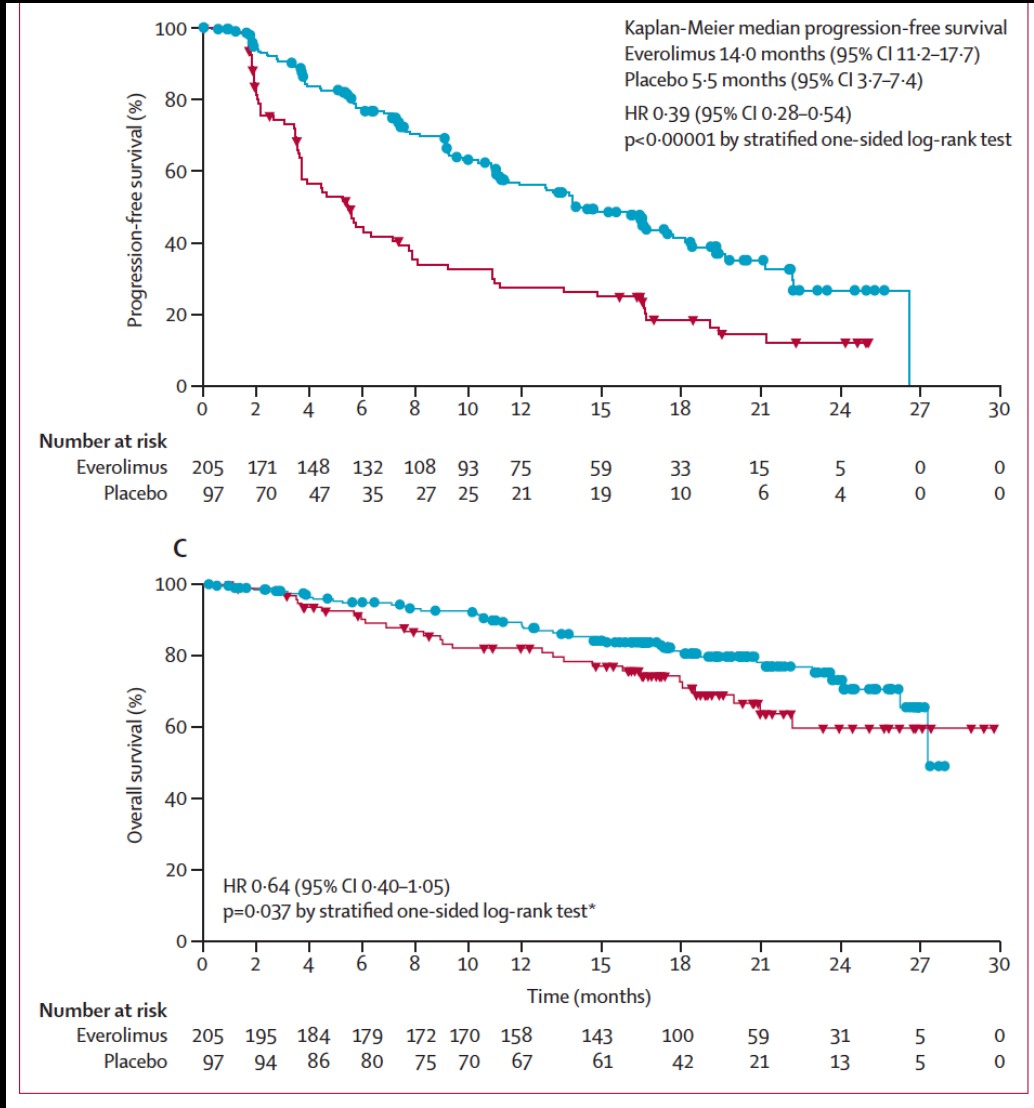
Progressionsfri overlevelse
Everolimus: 11.0 mo
Placebo: 4.6 mo

P value: <0.0001



Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study

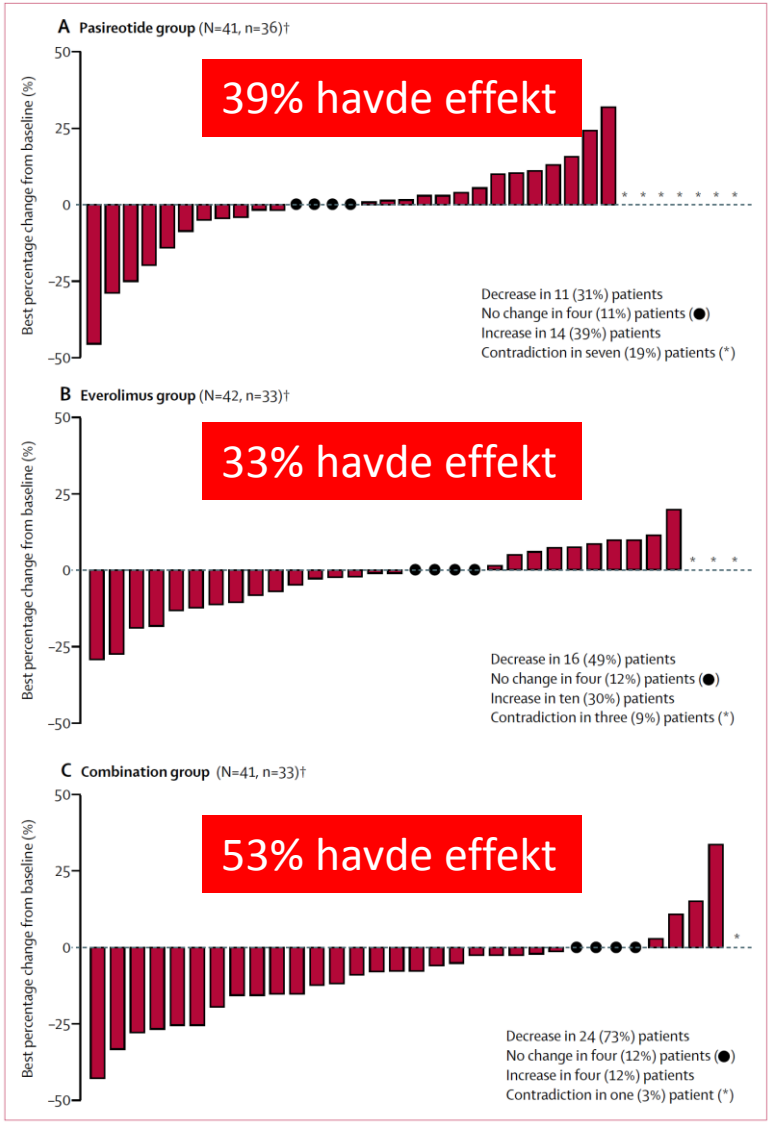
*James C Yao, Nicola Fazio, Simron Singh, Roberto Buzzoni, Carlo Carnaghi, Edward Wolin, Jiri Tomasek, Markus Raderer, Harald Lahner, Maurizio Voi, Lida Bubuteishvili Pacaud, Nicolas Rouyrre, Carolin Sachs, Juan W Valle, Gianfranco Delle Fave, Eric Van Cutsem, Margot Tesselaar, Yasuhiro Shimada, Do-Youn Oh, Jonathan Strosberg, Matthew H Kulke, Marianne E Pavel, for the RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial (RADIANT-4) Study Group**



Ingen effekt ved tyndtarms NET

Efficacy and safety of long-acting pasireotide or everolimus alone or in combination in patients with advanced carcinoids of the lung and thymus (LUNA): an open-label, multicentre, randomised, phase 2 trial

tine Do Cao, Hervé Léna, Alfredo Berruti, Vincenzo Damiano,
ohé, Vincenzo Minotti, Marcello Tiseo, Javier De Castro,
ric Baudin



Bivirkninger kombinationsbehandling

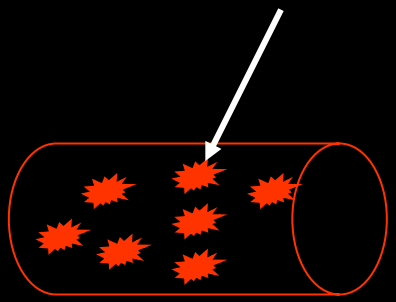
- Sukkersyge 66%
- Diare 46%
- Træthed 20%

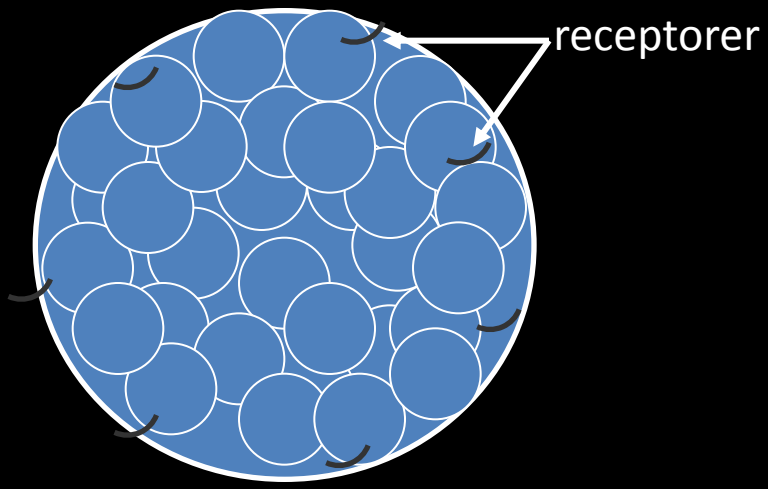
Radionuklid behandling
Yttrium-Dotatoc, Lutetium-Dotanoc

”Crossfire-effect”

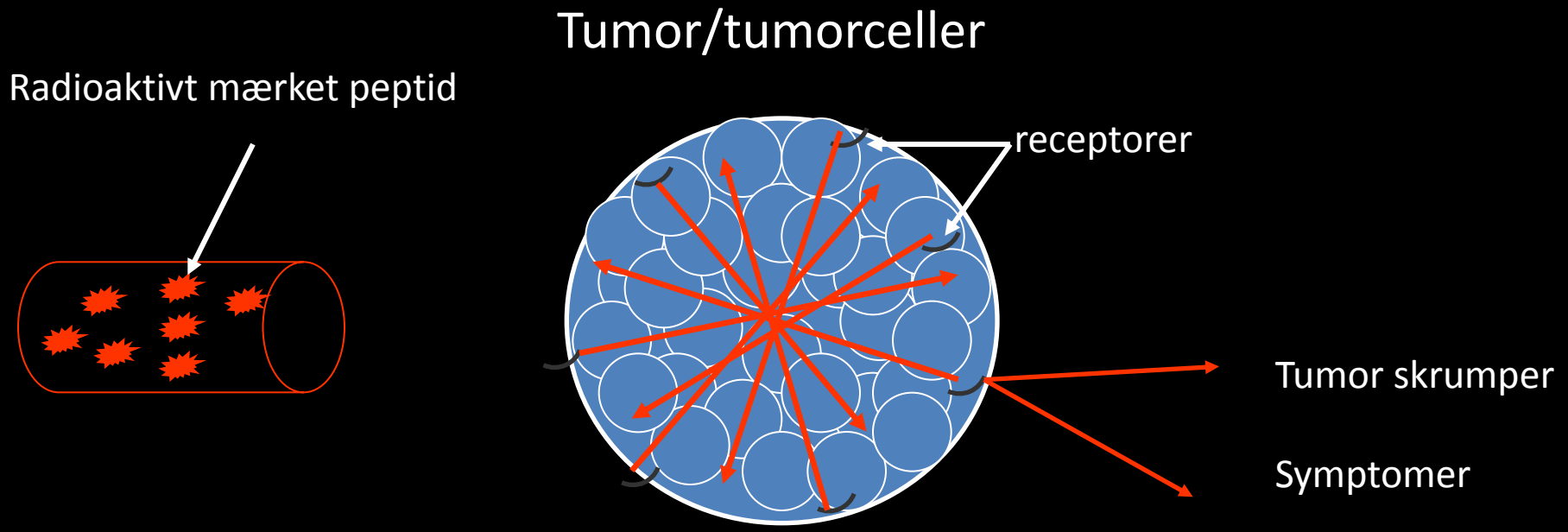
Tumor/tumorceller

Radioaktivt mærket peptid





”Crossfire-effect”



Progressiv sygdom før radionucleid behandling: 35-100%

- **Komplet respons: 0-3%**
- **Partiel respons: 5-35%**
- **Stabil sygdom: 40-85%**
- **Progressiv sygdom: 5-35%**

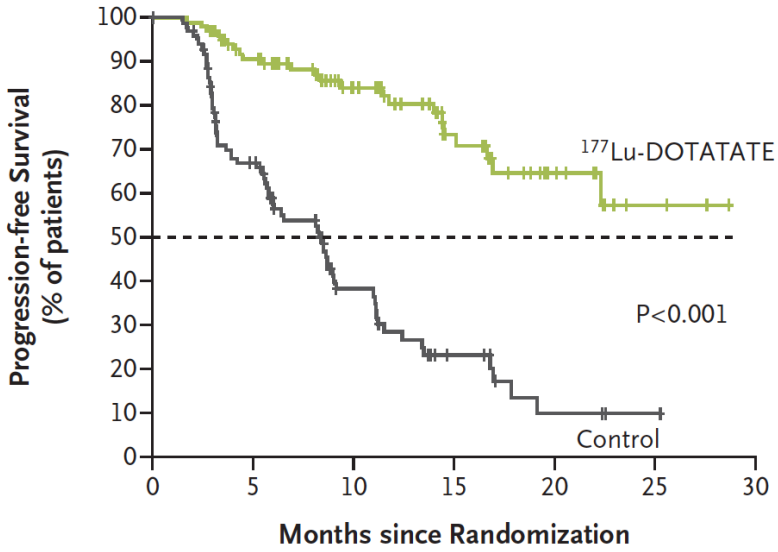
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra,

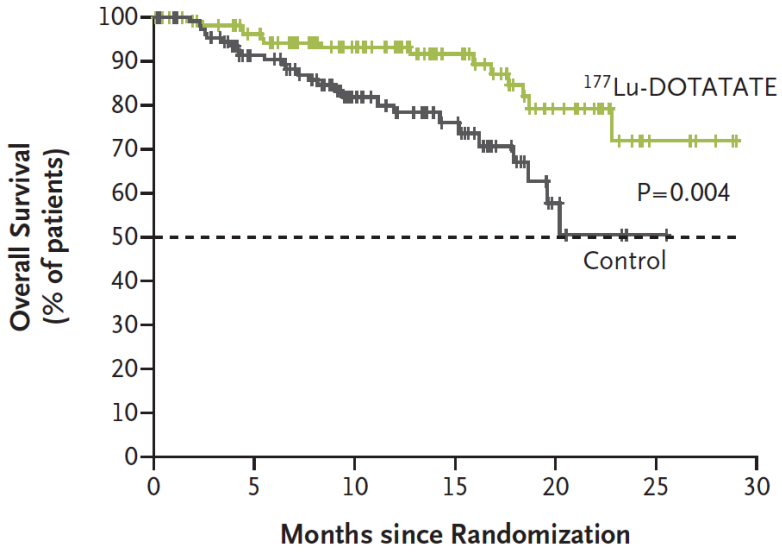
A Progression-free Survival



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

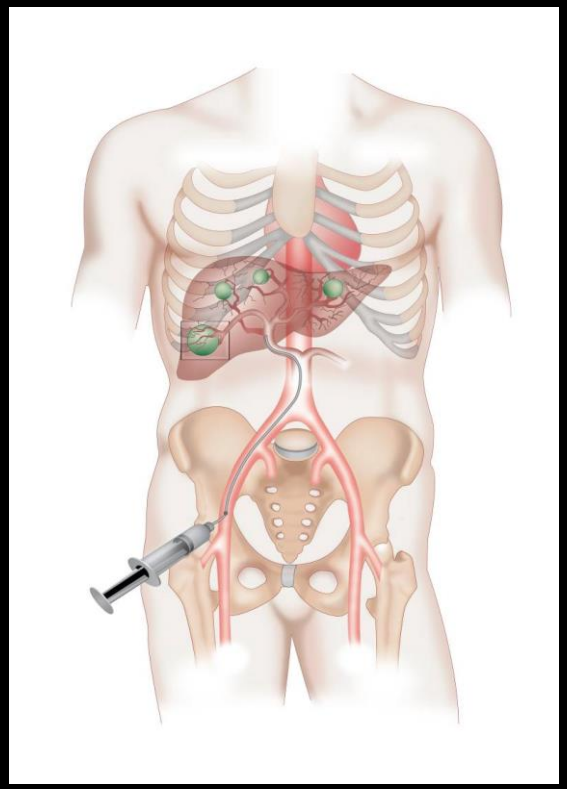
B Overall Survival (Interim Analysis)

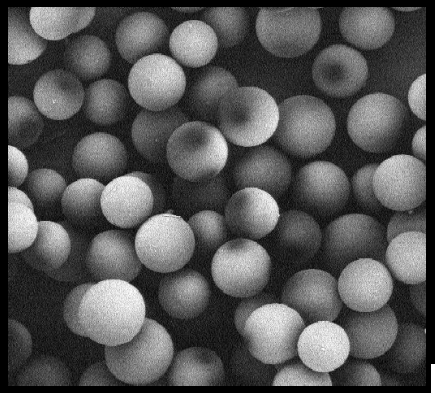


No. at Risk

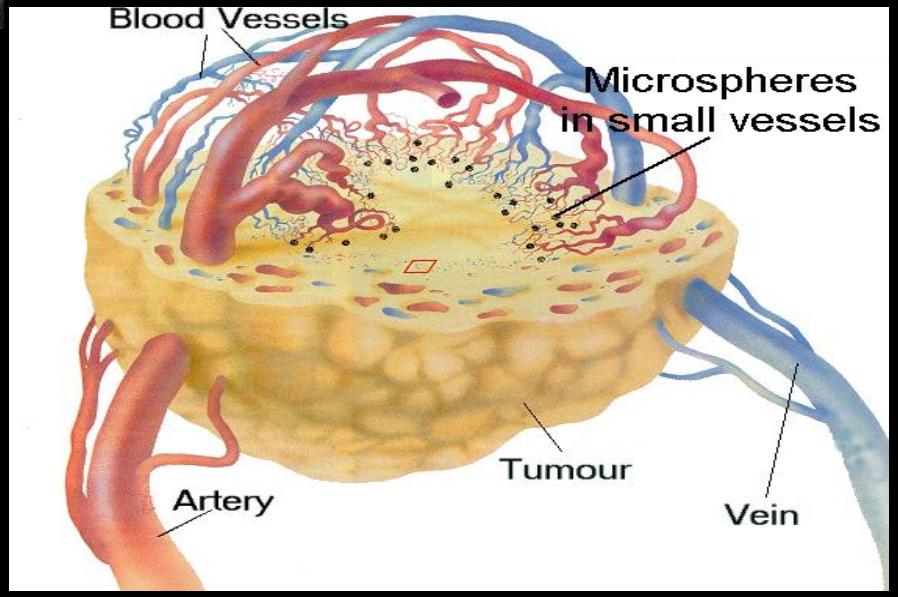
^{177}Lu-DOTATATE group	116	108	96	79	64	47	31	21	8	3	0
Control group	113	103	83	64	41	32	17	5	1	0	0

Selektiv Intern Radio-Terapi (SIRT)
Aarhus Universitetshospital





Yttrium – beta stråler
Bundet til resin eller microglasperler



Kemoterapi

Streptozotocin 5FU

– Neuroendokrine karcinomer
– G2 tumorer
– Ki67 indeks 10-20%

Carboplatin, etoposid

– Neuroendokrine karcinomer
– G3 tumorer
– Ki67>20%

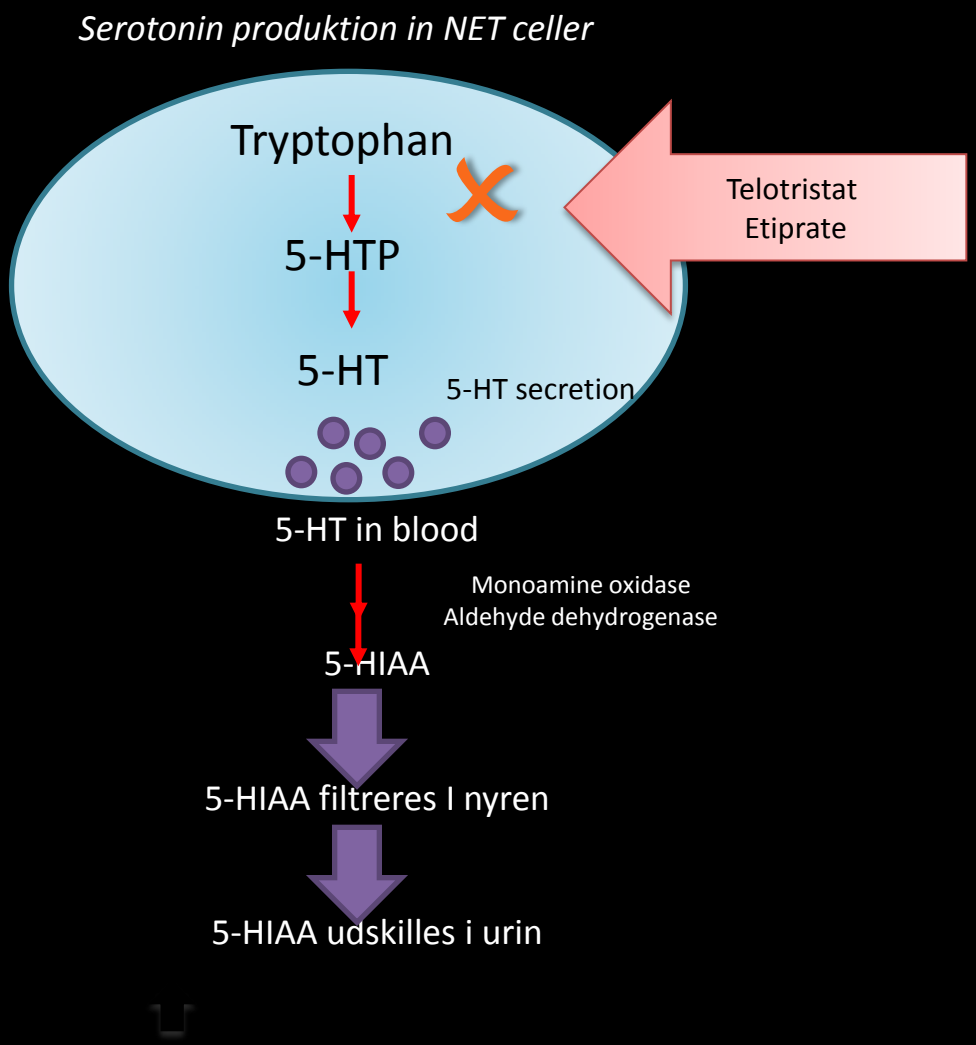
Behandling af carcinoid syndrom flushing og diare

- Somatostatin analoger – super god effekt >85%
- Interferon – god effekt, bivirkninger, 65%
- PRRT og SIRT – god effekt, tumorbyrde
- Emboliseringer – god effekt, tumorbyrde
- Kirurgi – god effekt, tumorbyrde

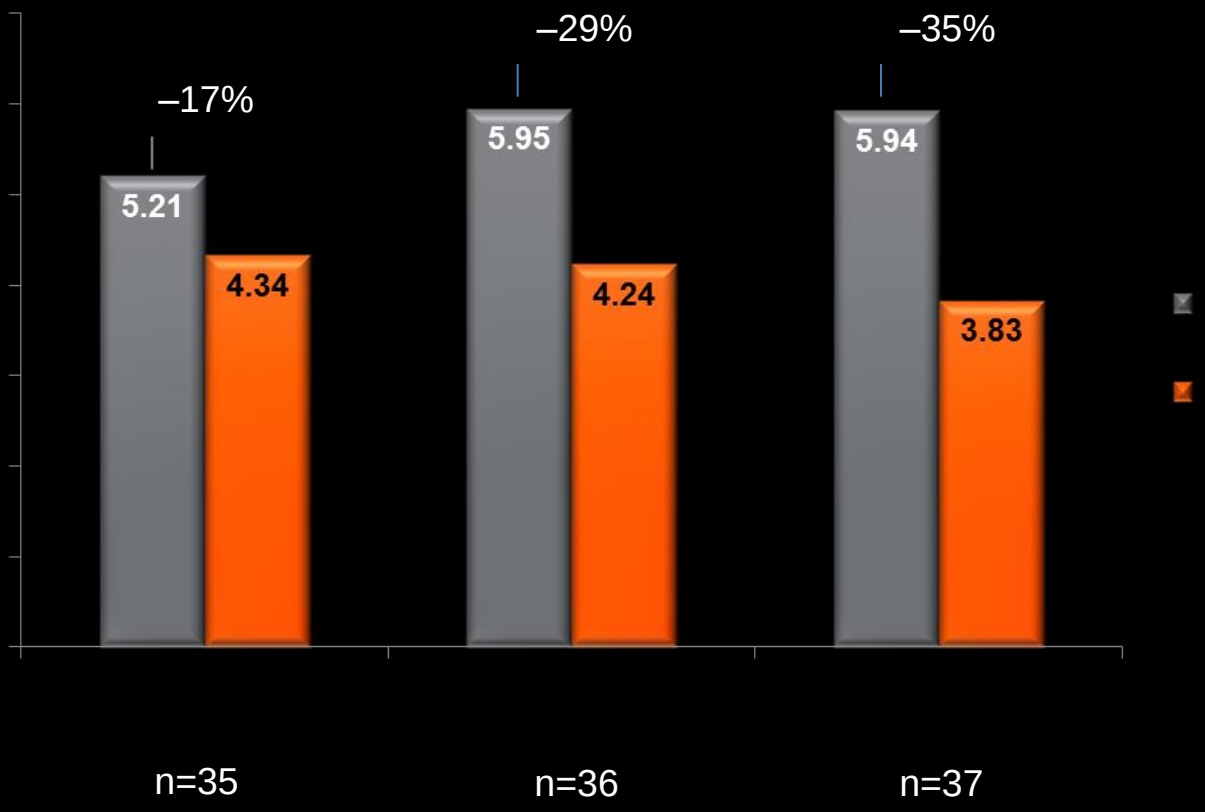
- TELOTRISTAT

Telotristat Etiprate

Hæmmer serotonin produktionen



Reduktion i antal afføringer fra start til uge 12



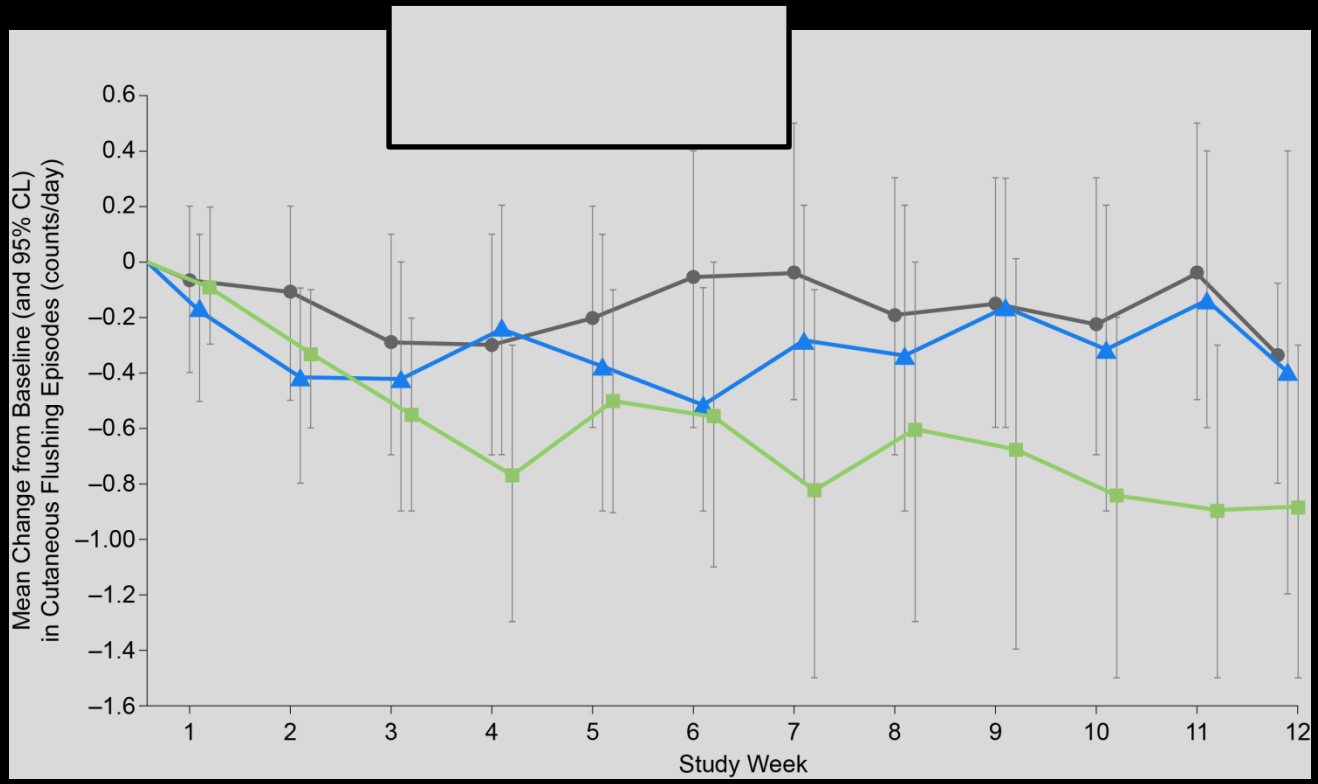
All patients continue SSA therapy throughout study period. Data include only patients for whom both baseline and Week 12 assessments were available.

SSA, somatostatin analog.

Flushing episoder per dag

Placebo n=45
Telotristat etiprate 250 mg n=45
Telotristat etiprate 500 mg n=45

All patients continue SSA therapy throughout study period



Telotristat

- Effekt?
- Bivirkninger?
- Pris?

- Far 6 til 4 afføringer/dg
- Ingen effekt på flushing
- Depression pga serotonin?
- Endnu ukendt – men dyr?

Forskning gør os bedre til at behandle NET

- Explain og ONEST – nye tumormarkører?
- Smerter v NET – Marie Madsen
- Ernæring v NET – Mette Borre
- Nyreskade v PRRT og NET - Tobias Lau
- Cirkulerende tumor celler og DNA v NET
  - Stine Karlsen og Jens Kelsen
- SEQTOR, NordicNEC

- Patientinddragelse - undervisning

NET BEHANDLING I FREMTIDEN

TAK FOR OPMÆRKSOMHENDEN!