Post-Endo
Update NET and Pituitary

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NET Update - Debate

The house believes that following MEN-1 screening/surveillance guidelines can do more harm than good

PRO: Paul J. Newey (Dundee)

AGAINST: Gerloff D Valk (Utrech

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SPECIAL FEATURE

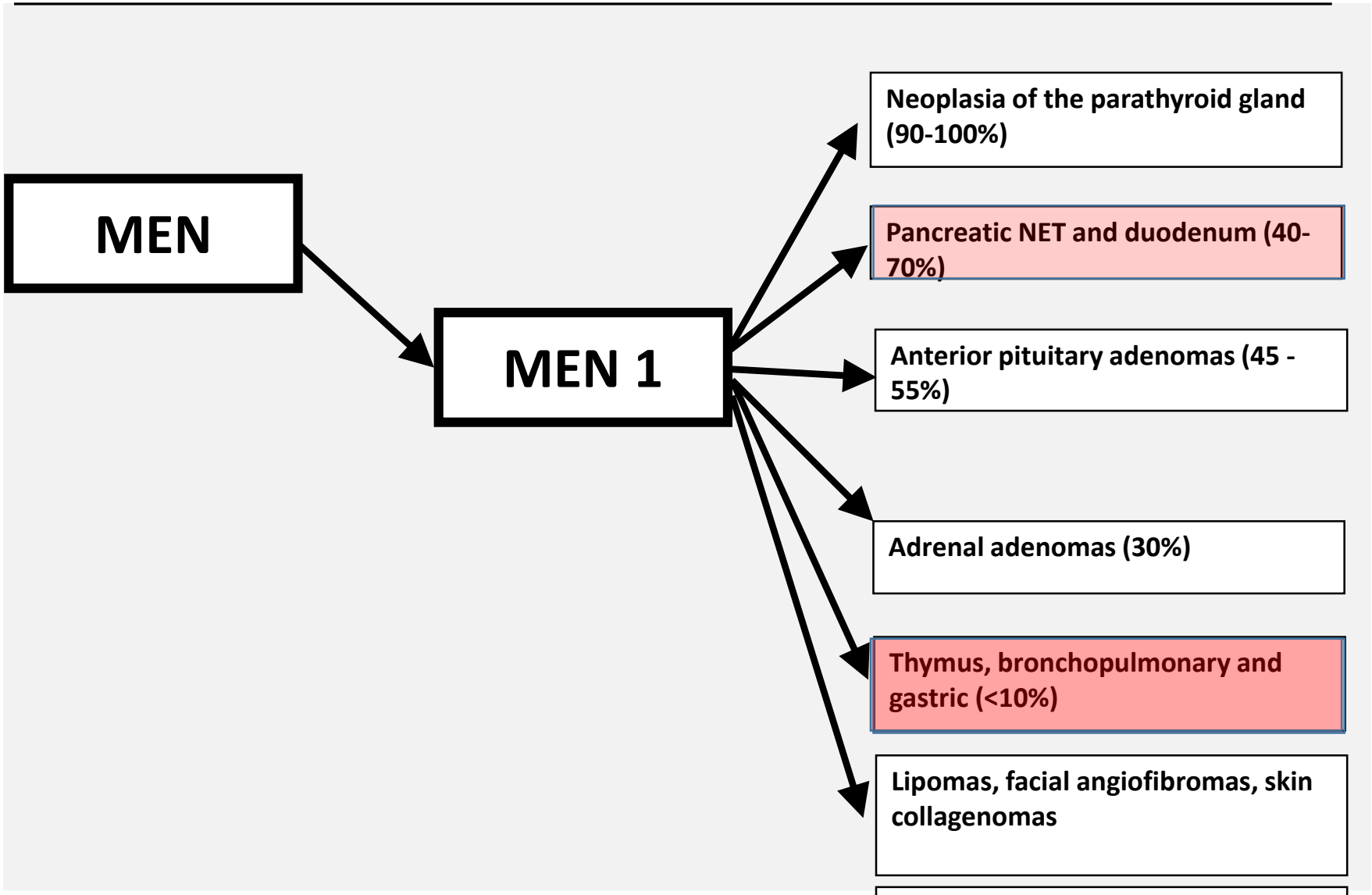
Clinical Practice Guideline

Clinical Practice Guidelines for Multiple Endocrine Neoplasia Type 1 (MEN1)

Rajesh V. Thakker, Paul J. Newey, Gerard V. Walls, John Bilezikian, Henning Dralle, Peter R. Ebeling, Shlomo Melmed, Akihiro Sakurai, Francesco Tonelli, and Maria Luisa Brandi

- What do the guidelines suggest with regard to screening and surveillance (2012)?

Tumors in MEN 1



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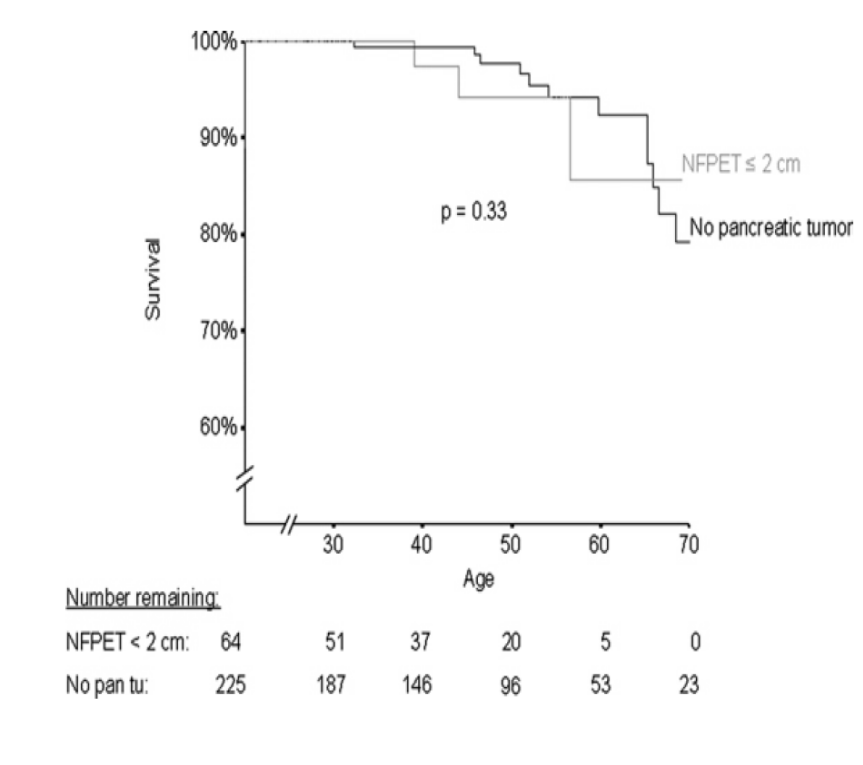
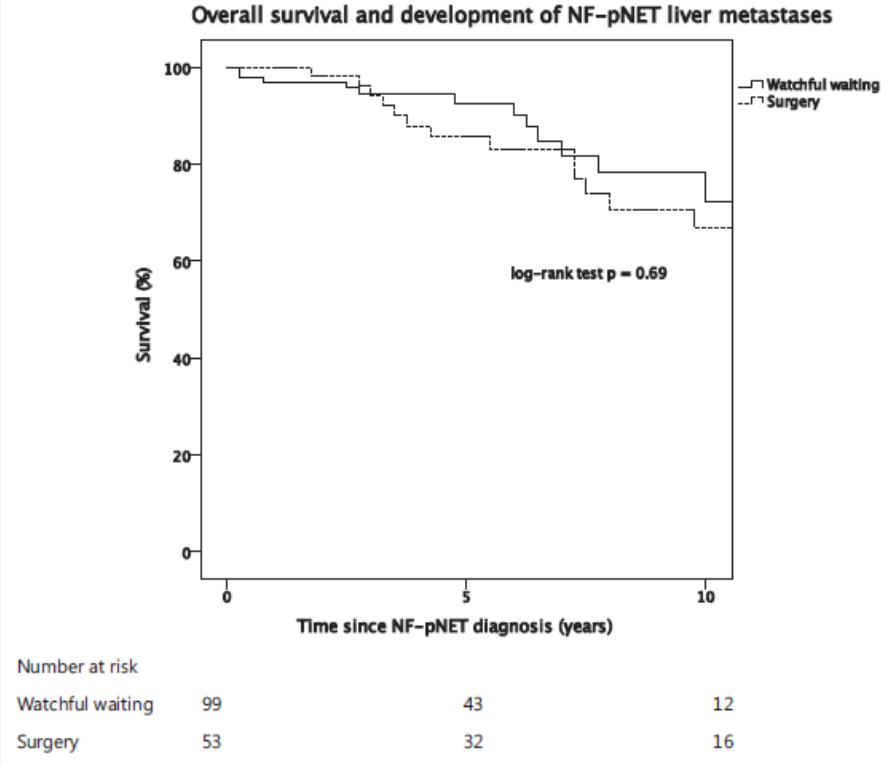
Survival of patients with non functioning pNET and MEN-1

Clinically relevant lesions?



Triponez, F., et. al 2006; Triponez F. et al 2018



Nell S. et al. 2018

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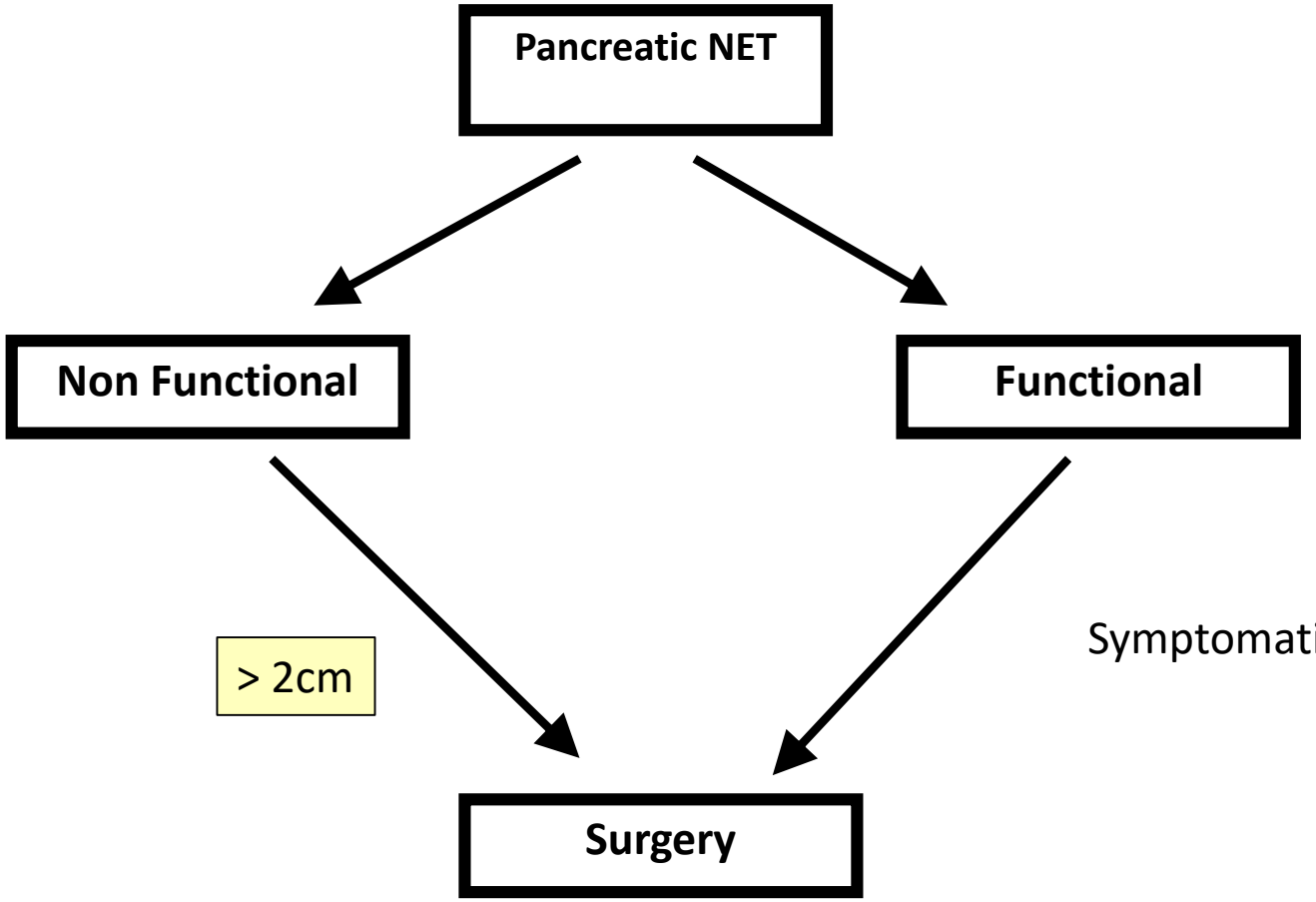
MEN 1 – pNET - Procedure



Symptomatic: any size

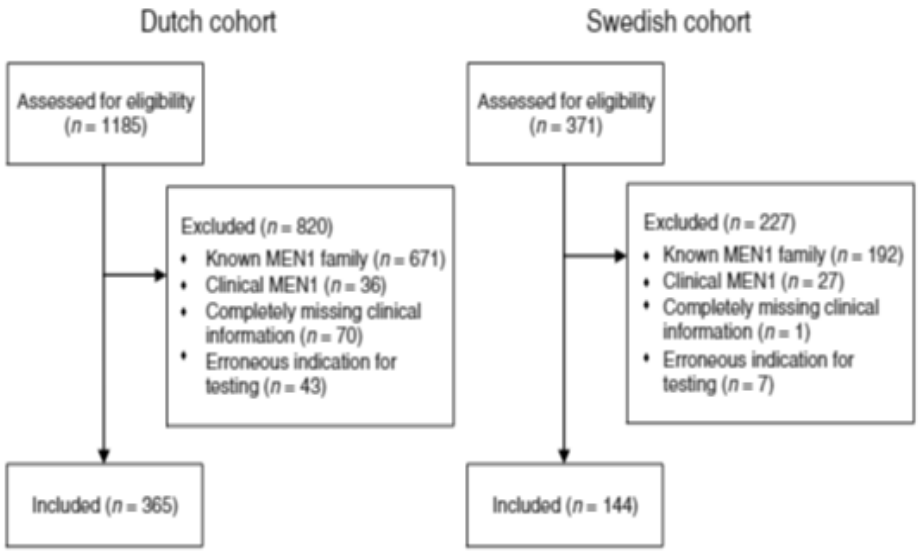
Triponez F. et al. 2018
Falconi M. et al. 2016
Partelli S et al 2016
Triponez F et al. 2006

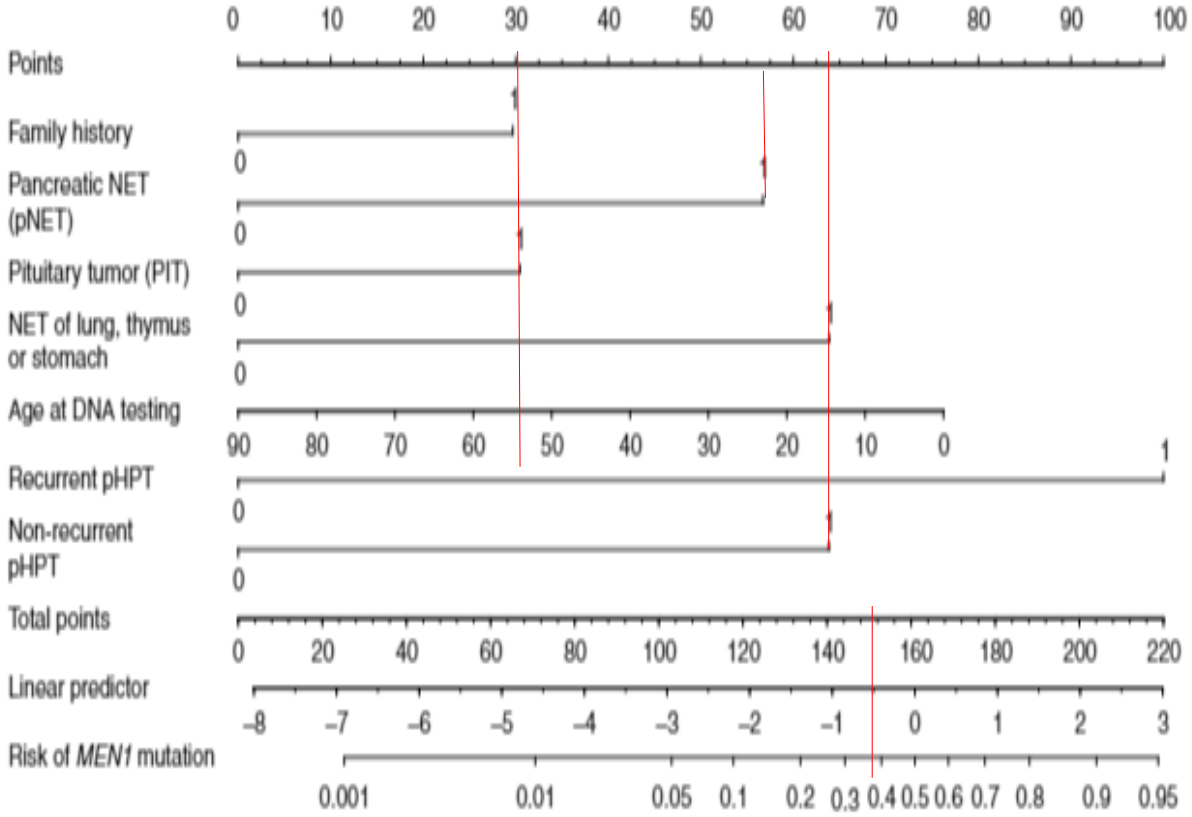
Who should be screened for MEN-1

- Index patient with lesions in ≥2 endocrine organs
- Polyglandular parathyroid disease and age <40 J
- Recurrence of a pHPT
- Gastrinom (mainly duodenal) or multiple pNET any age
- Positive FH; investigation of members of a family with a confirmed MEN-1 mutation

AGGREEMENT

Validation study: Risk of MEN-1 for patients with apparently sporadic tumors





Laat JM et al 2012

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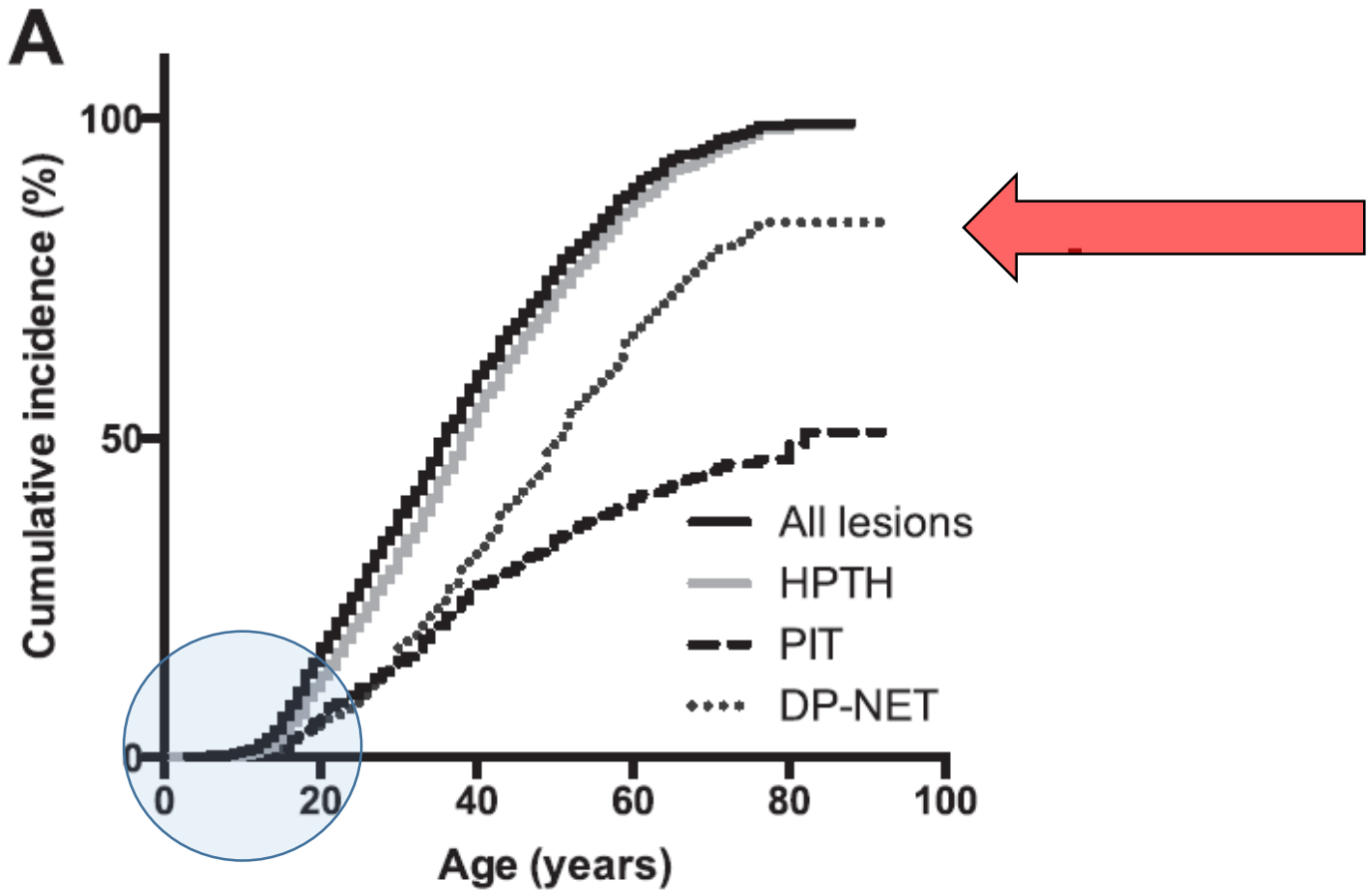
Incidence of major diseases during life span in MEN-1



Romanet P et al. 2019, JCEM

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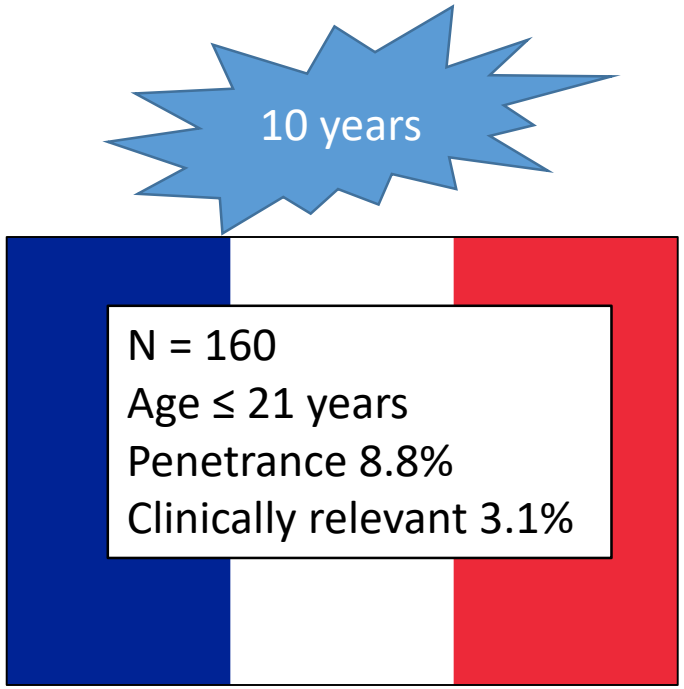
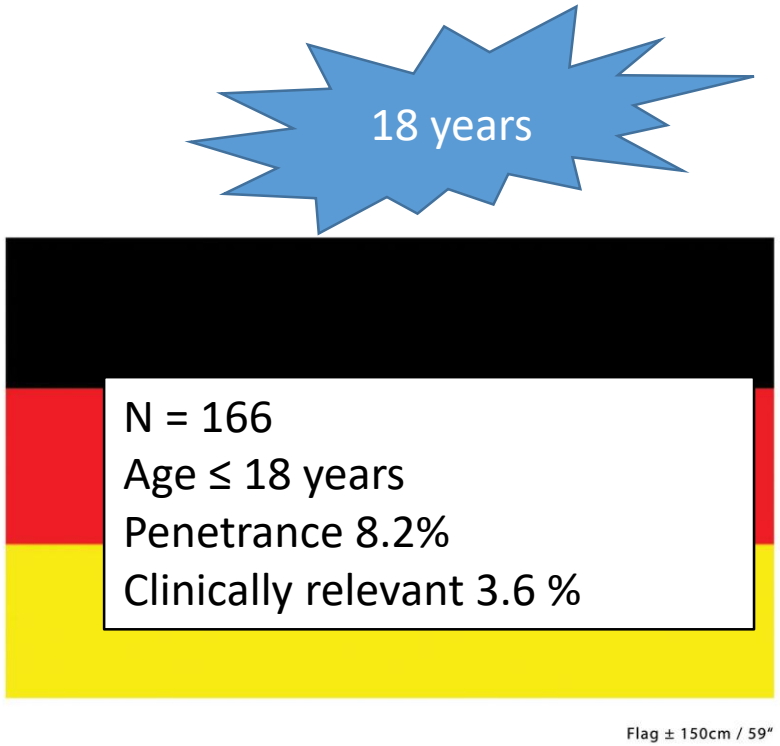
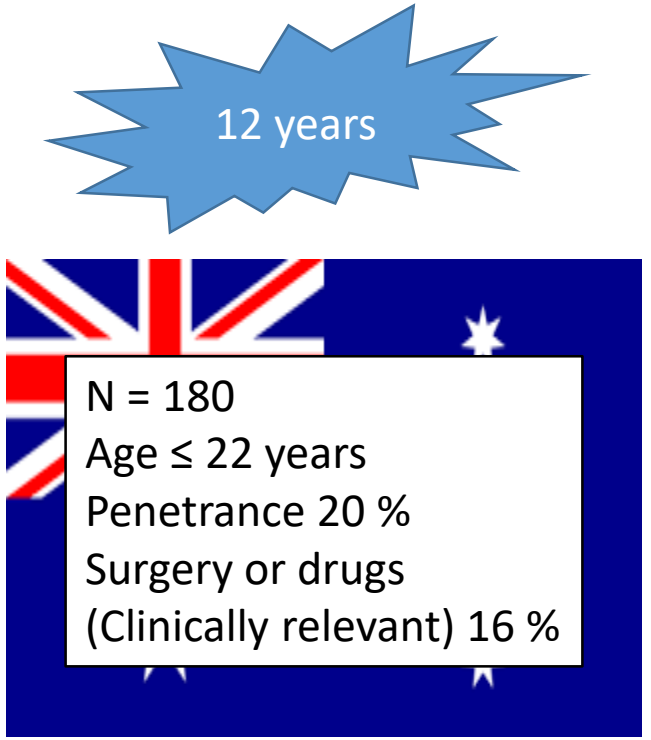
When (which age) should we should be screen for MEN-1



Goudet P. et al 2015



Manoharan J et al. 2017



Herath M et al. 2019

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- MEN1 germline mutation testing of asymptomatic relatives should be offered at the earliest opportunity because MEN1 manifestations may occur by the age of 5 yr (2QQEE)

MEN-1 Testing: points to ponder (PN and GV)

- At which age should genetic testing take place?
- What are the earlies ages of diagnosis of MEN-1 manifestations and the earliest ages of intervention?
- What can be done with the results
  - Poor geno-/phenotype correlations
  - Earlier diagnosis but no preventive care
- Does earlier diagnosis lead to better outcome?

MEN-1: presymptomatic screening

- Assumption (but no clear evidence) that an earlier diagnosis and treatment will help to reduce morbidity and mortality

BUT

- Earlier identification of asymptomatic disease may potentially lead to premature and unnecessary treatment that may have a negative long-term impact
- Years of episodic testing may have psychosocial (and financial) consequences

PN: Genetic screening in case of clinical signs and symptoms

GV: Genetic screening according to the wish of patients/family


LISTENING
FRIENDLINESS
OPEN MINDEDNESS
Essential Communication Skills for Your Career
FEEDBACK
CONFIDENCE
NON-VERBAL COMMUNICATION
the balance

Which kind of surveillance sould be performed in asymptomatic patients with MEN-1

As a minimum, an annual plasma biochemical evaluation of a fasting gastrointestinal tract hormone profile that includes measurement of gastrin, glucagon, vasointestinal polypeptide, pancreatic polypeptide, chromogranin A, and insulin with an associated fasting glucose level
(2QQEE).

A consensus for optimum radiological screening has not been established and will depend on local resources, clinical judgment, and patient preferences. A suggested minimum imaging protocol includes annual pancreatic and duodenal visualization with magnetic resonance imaging (MRI), computed tomography (CT), or endoscopic ultrasound (2QQEE).

PN: Start surveillance in case of clinical signs and symptoms, no regular hormone screening

GV: Start surveillance according to the wish of patients/family

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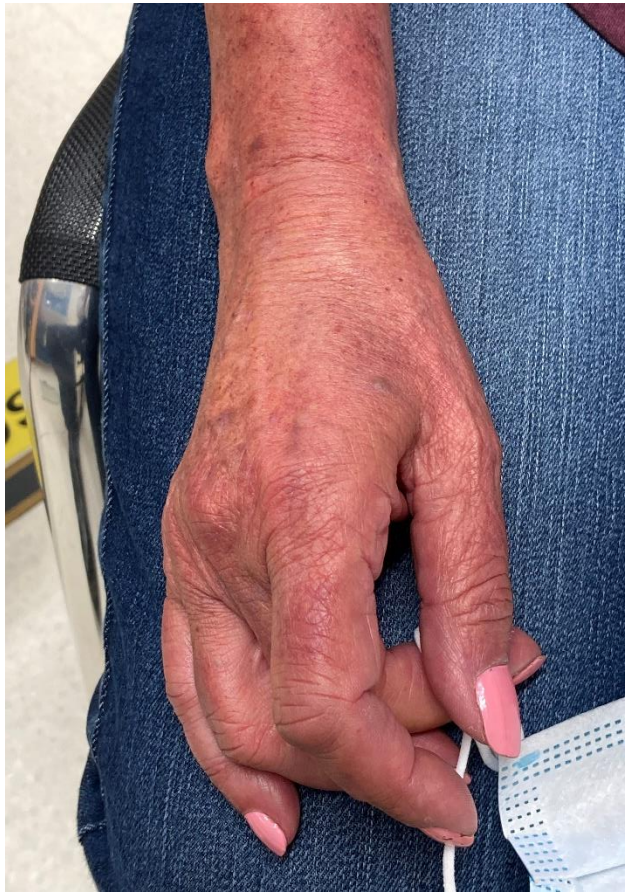
CONSEQUENCE

NEED FOR NEW GUIDELINES
(Prognostic markers? Not only size of lesions?
Regular hormonal screening necessary?
Individual time point for genetic testing?)



NET Update - Carcinoid Crisis

MTP and Symposium: Electron Kebebew, MD (Stanford University)

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Definition – Aetiology – Risk factors

- Flushing, Diarrhoe
- Hypotension, tachyarrhythmia
- +/- Cardiac valvular disease
- +/- Bronchospasm

- Metastastic small bowel NEN
- Rarely Lung-NET or other NET with access to central venous circulation

- Surgical intervention, anaesthesia
- Rarely: PRRT (tumor load !), biopsy
- Spontaneously
- Drugs: Amitryptiline

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Common symptoms and frequency

Symptoms	Putative Substances	Frequency, %
Flushing	Histamine, tachykinins, kallikrein, bradykinin	>90
Diarrhea	Serotonin, substance P, motilin, prostaglandins	70-85
Cardiac valvular disease	Serotonin, 5-hydroxyindoleacetic acid, neurokinin A, substance P	~40-60
Telangiectasias	Serotonin, bradykinin, prostaglandins	25
Bronchospasm	Serotonin, bradykinin	15-19
Pellagra (dermatitis, diarrhea, dementia)	Niacin deficiency due to excess tryptophan metabolism	5-7

THERAPY

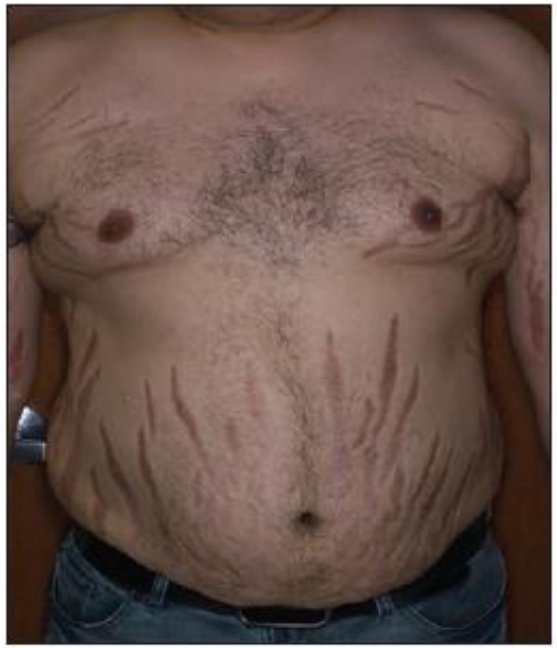
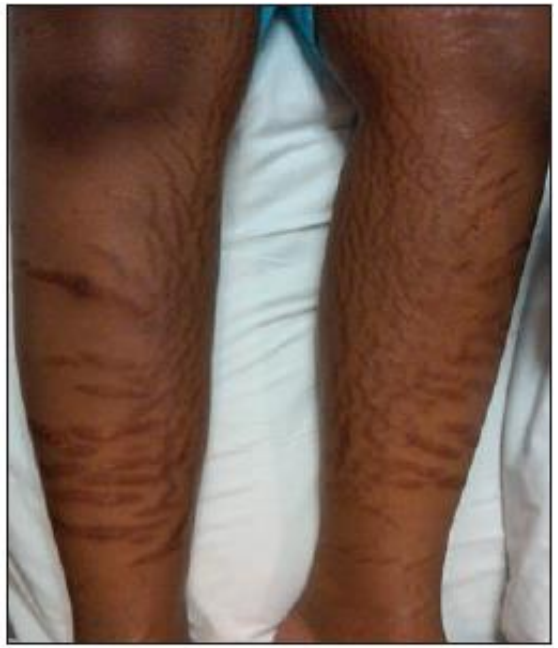
- Octreotide should be available in case of an intervention
- Prevention: (no real data)
  - Octreotide sc. 3x100 – 3x200, if necessary more
  - Somatuline Autogel/ Sandostatin LAR once stabilized
  - (ev. Anti-H2)

  - Increased risk (big tumor load): 50 ug i.v. followed by 50ug/h continuous intravenous infusion

Pituitary Update - Cushing's

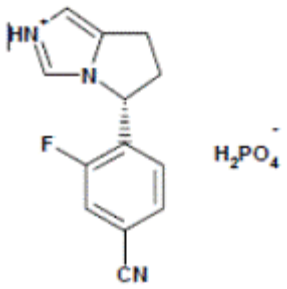
MTP and Oral presentations (M Gadhela, Brazil et al.)

Update Cushing: Drug therapy

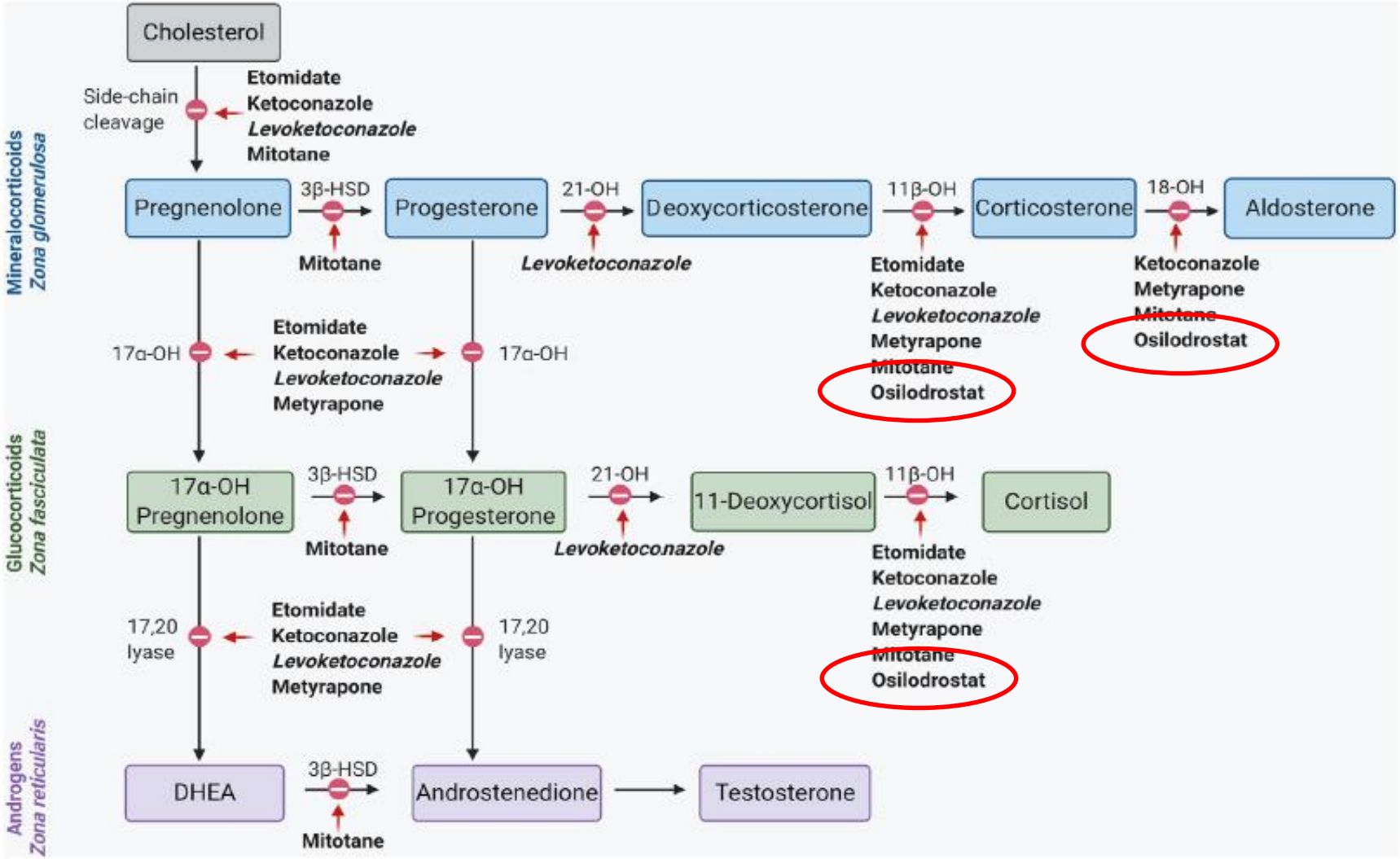




- Myopathy
- Skin

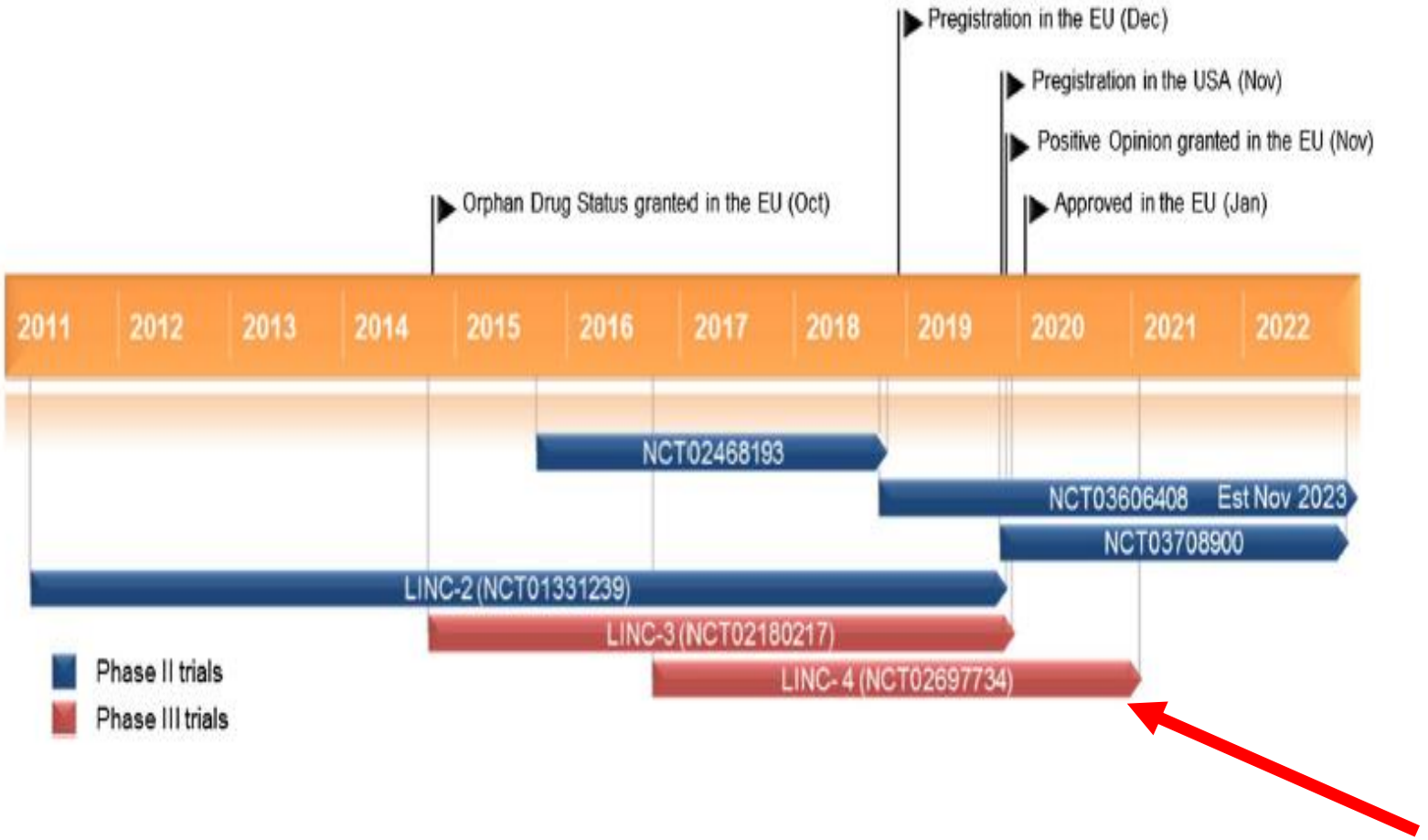
Medical therapy in Cushing's disease



OSILODROSTAT

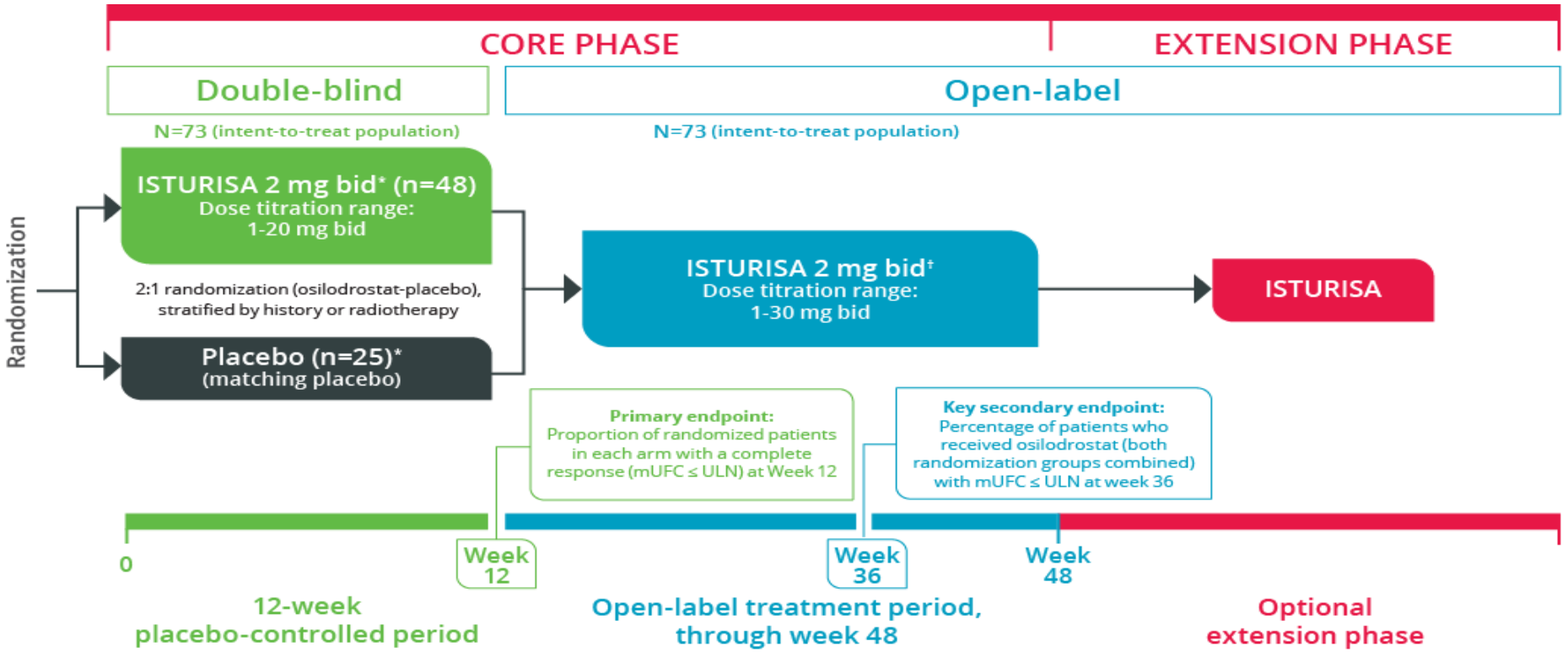


Trials with Osilodrostat



S Duggan 2021

Efficacy and safety of osilodrostat/Isturia© in patients with Cushing's disease (LINC 4)



Maria Gadhela et al 2021

Inclusion

- UFC > 1.3 ULR (mean of 3 meaurements)
- Adults (18-75), surgical candidate
- No prolongation of QT interval
- No local or systemic risk during 12 weeks placebo
- Confirmed pituitary disease
  - ACTH dependant AND/OR
  - Histology (after surgery)
  - Adenoma > 6 mm
  - Petrosus sampling

- USA, South-America, Europe, China; n = 73

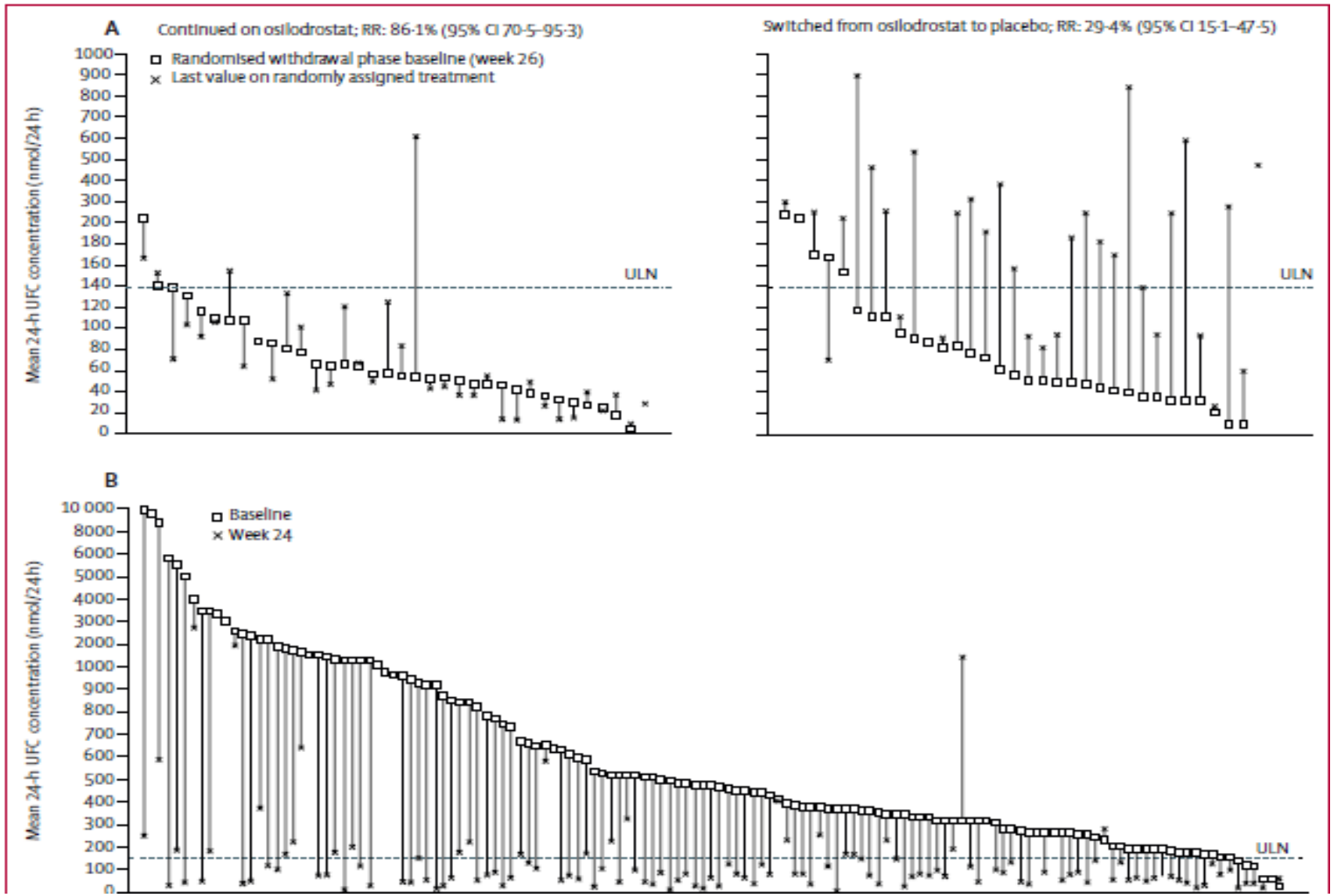
Results

1er ENDPOINT (12 week)

2nd ENDPOINTS

- **81% of ISTURISA patients had mUFC ≤ ULN[1†] after 24 weeks (2:1 randomization)**
- **Metabolic parameters (HbA1C, Glucose, Lipids, BP, weight, waist and QoL) improved**

Pro Memoria: Results (LINC 3)



Rosario Pivonello et al 2020

Pro memoria: Pasireotide in Cushing's

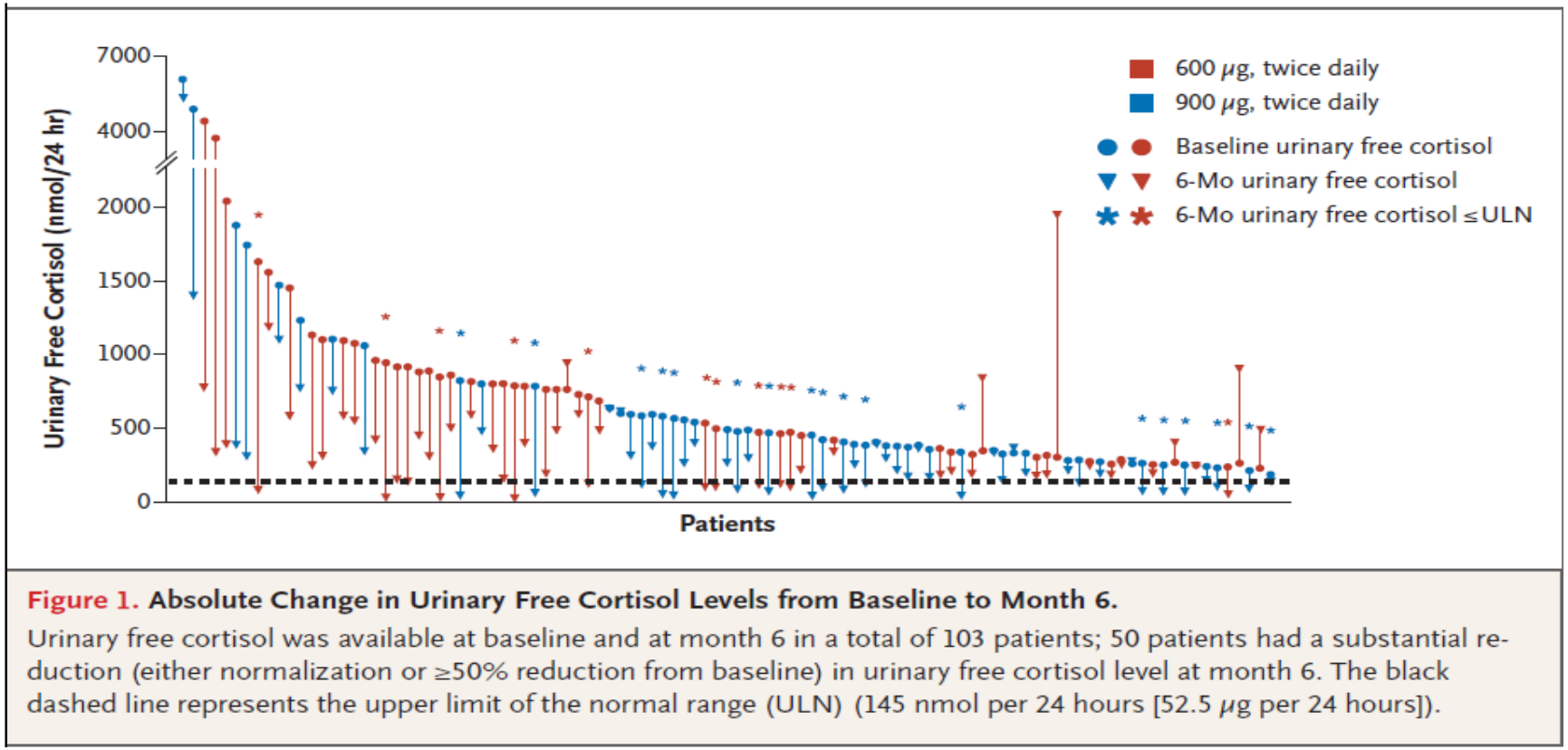


Figure 1. Absolute Change in Urinary Free Cortisol Levels from Baseline to Month 6.

Urinary free cortisol was available at baseline and at month 6 in a total of 103 patients; 50 patients had a substantial reduction (either normalization or ≥50% reduction from baseline) in urinary free cortisol level at month 6. The black dashed line represents the upper limit of the normal range (ULN) (145 nmol per 24 hours [52.5 μg per 24 hours]).

A Colao et al 2012

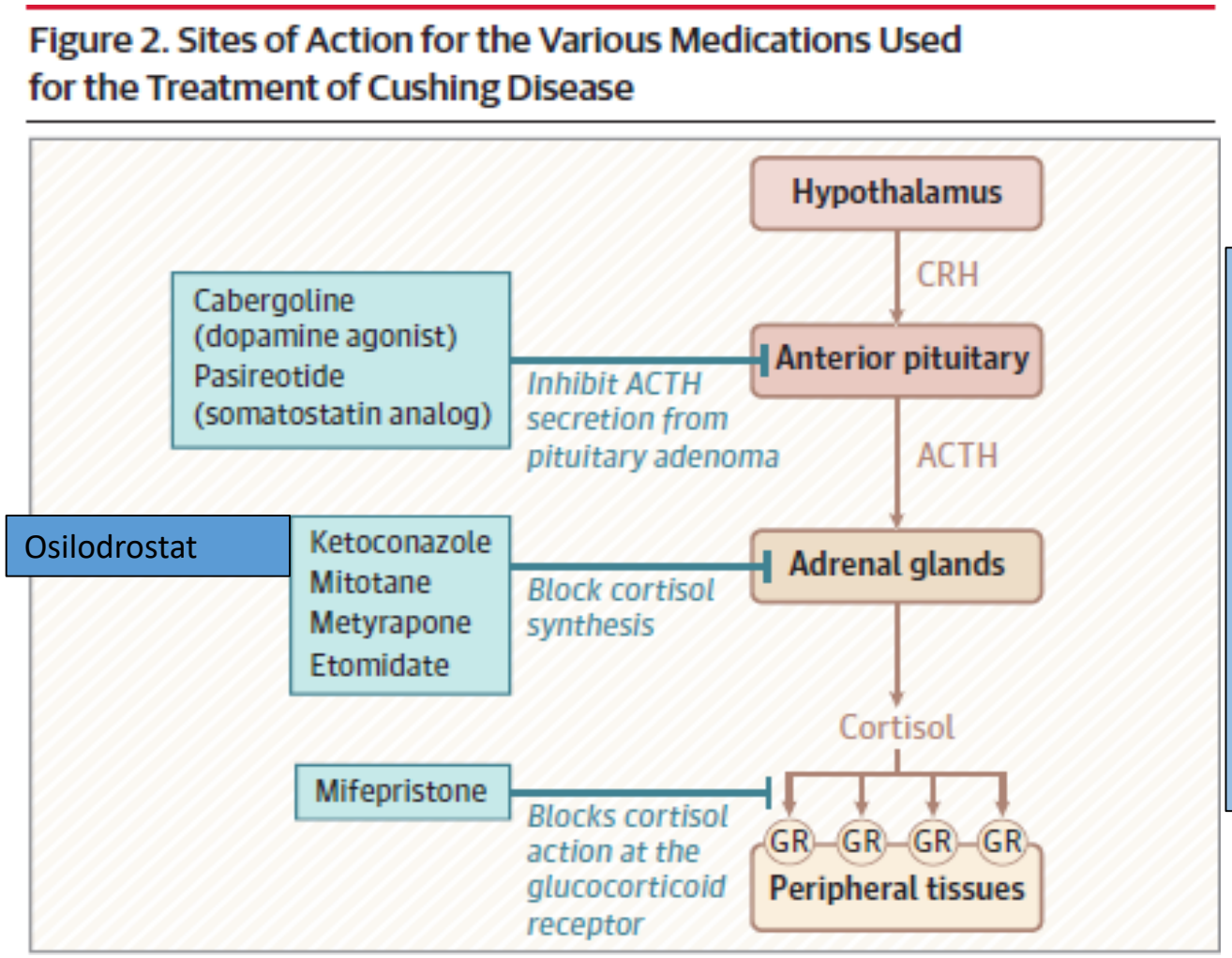
Side effects - Osilodrostat

AE	Frequency (%)
Arthralgia	45
Decreased appetite	45
Fatigue	38
Nausea	37
Headache	33

AE	Frequency (%)
Cortison related	45

AE grade 3-4 very rare,
dose reduction, no interruption of therapy required

Therapeutical Possibilities – what is next – unmet need



Pre-operative TT
Which TT?
Combination TT?

Co-morbidities TT
+/- Bactrim
+/- Heparin
+/- anti-hypertensive TT
+/- anti-diabetic TT
+/- Osteoporosis TT

Primary Polydypsia and GLP-1 agonists

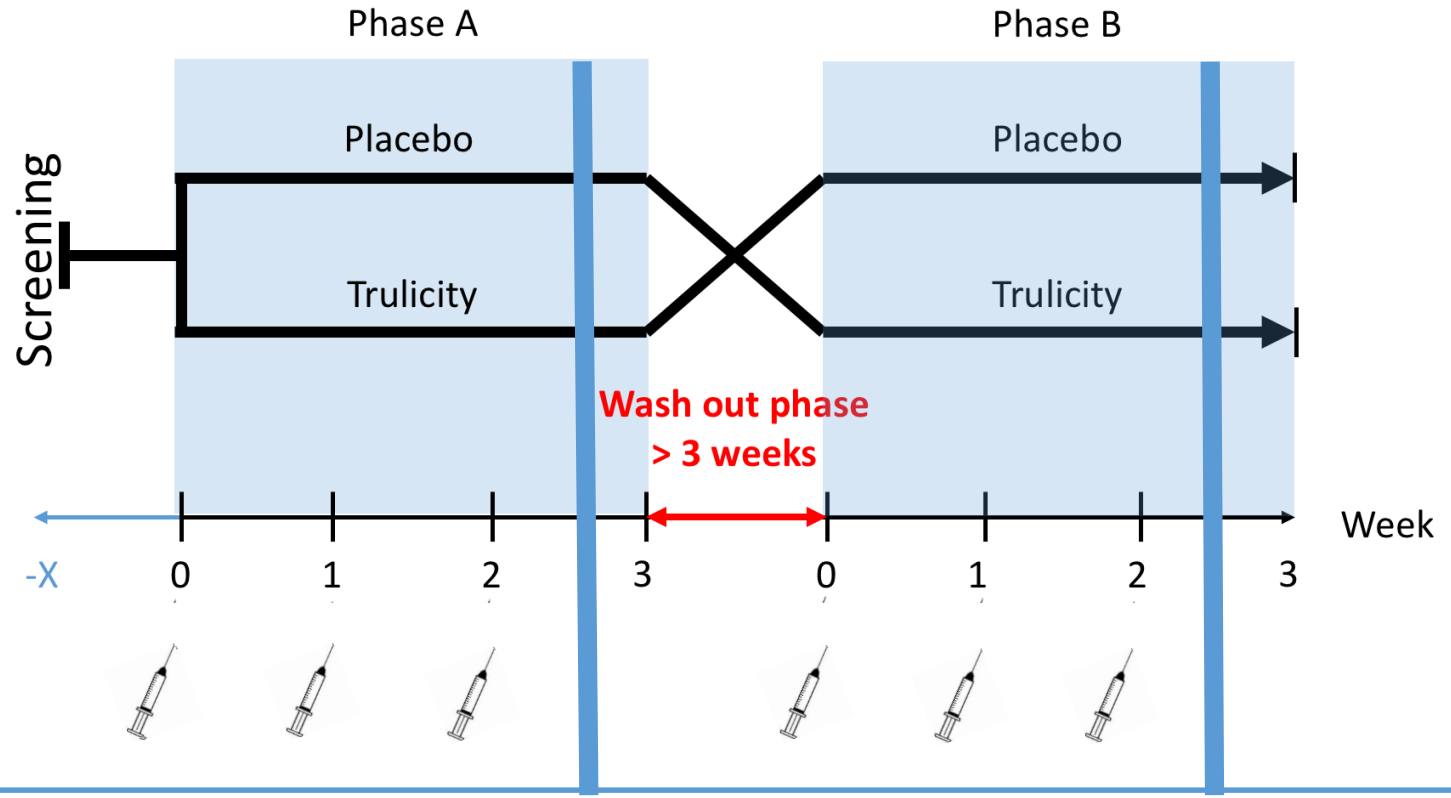
↑Satiety
↓Appetite
↓Food intake

↓ Fluid intake?

Methods / Outcomes

Study medication

Dulaglutide (Trulicity®) 1.5 mg s.c. / week



Evaluation visit 8-16h: 2 standardized meals, water ad libitum

Outcomes:

1) Total fluid intake (ml) during evaluation visit
2) Thirst perception, reported average daily fluid intake, voiding frequency, nocturia, AEs

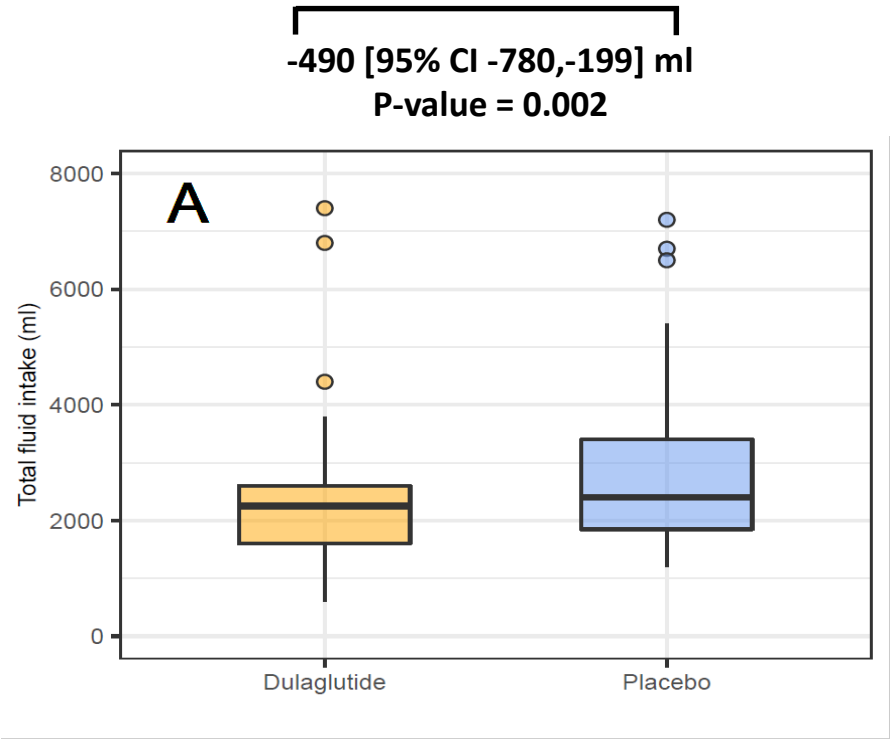
Gold-study – Results

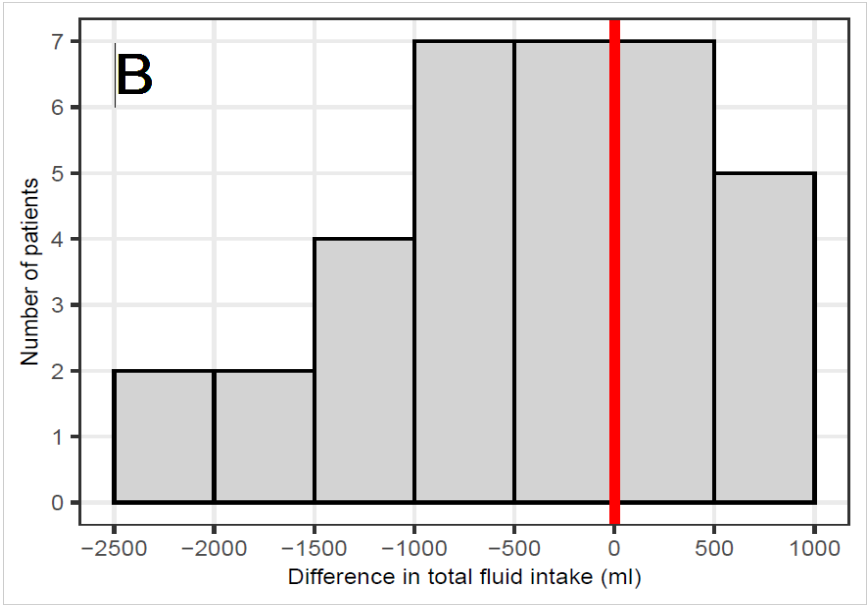
34 patients with primary polydipsia

Age, median (IQR)	29.5 (26.0, 38.8)
Male gender, n (%)	11 (32.4)
BMI, median (IQR)	23.1 (20.7, 25.5)
Psychiatric disease, n (%)	20 (58.8)
Other comorbidities, n (%)	14 (41.2)
Smoking, n (%)	14 (41.2)
Reported daily fluid intake, ml, median (IQR)	4500 (3600, 5000)
24h urine output, ml, median (IQR)	4700 (3900, 5600)

Courtesy of Winzeler B et al., JCI 2021

Study - Results



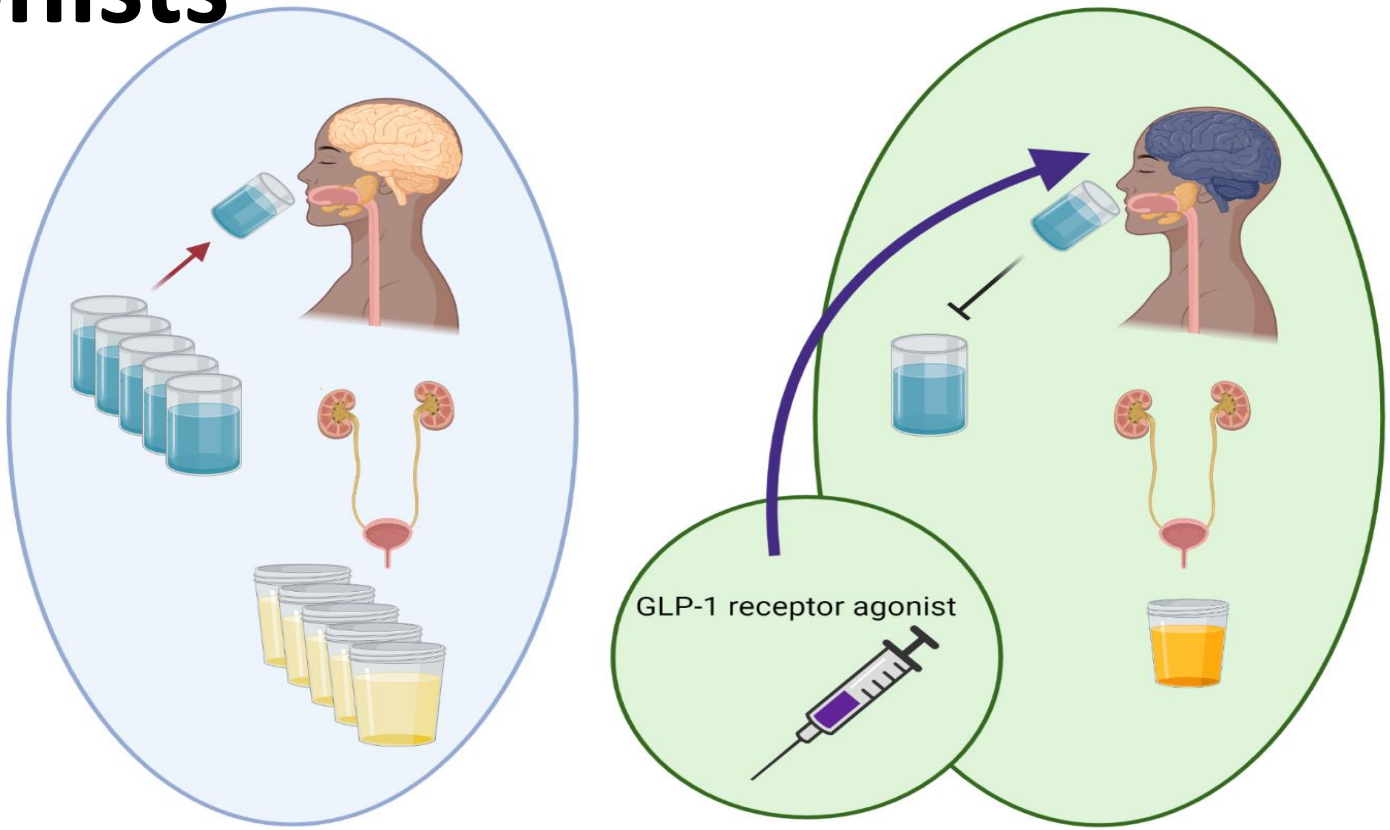


Courtesy of Winzeler B et al., JCI 2021

Primary Polydypsia and GLP-1 agonists

↑Satiety
↓Appetite
↓Food intake

↓ Fluid intake? YES



Courtesy of Winzeler B et al., JCI 2021

Take home message

- NET was not the primary interest of the POC
- NEW: Interdisciplinary topics (help of…)
- NEW: Inclusion of patients in presentations

- THANK YOU for your attention