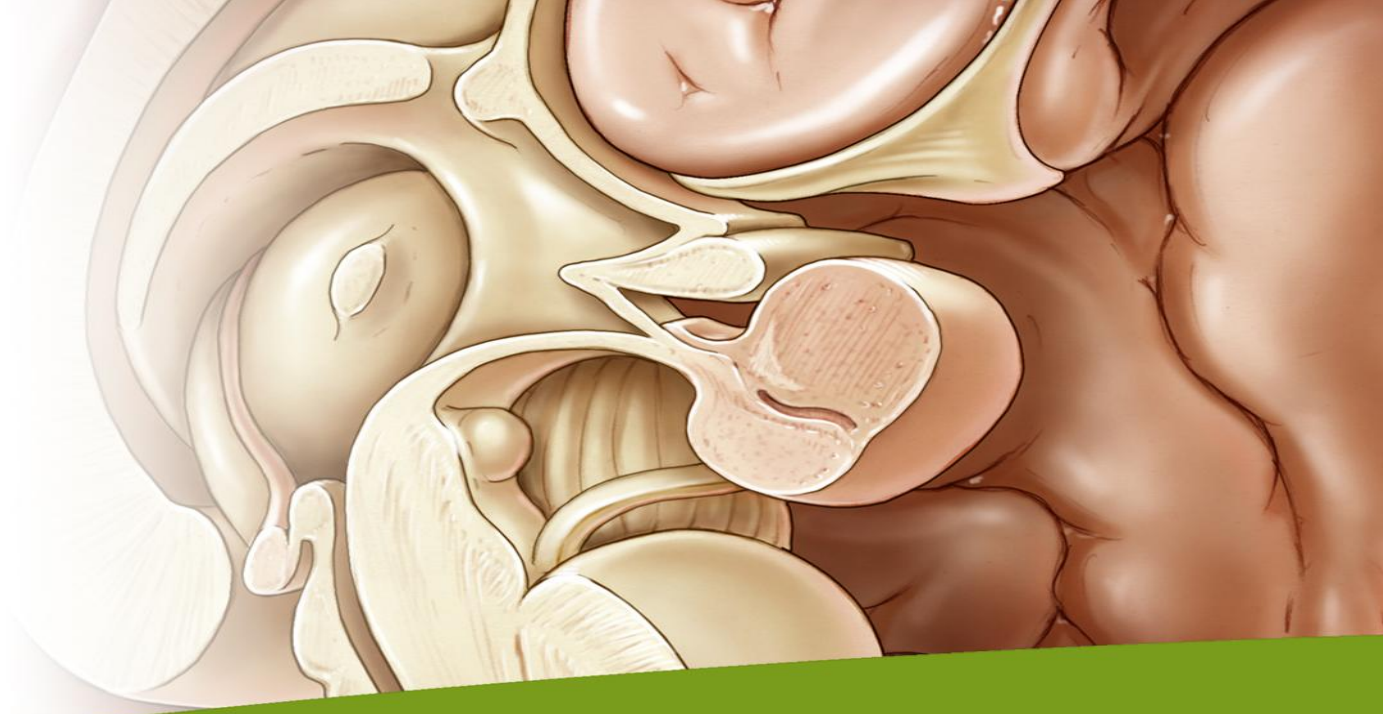


Novel adrenal steroidogenesis inhibitors in the medical treatment of Cushing's syndrome

Maria Fleseriu, MD, FACE

Professor Endocrinology and Neurosurgery

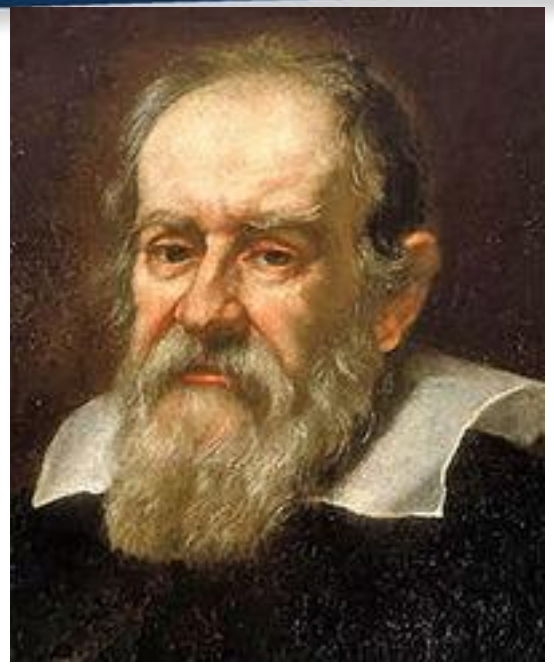
Director Pituitary Center

Oregon Health and Science University, Portland, OR

Disclosure

- **Novartis, Millendo, Strongbridge**
  - **PI, Research funding to OHSU**
- **Novartis, Strongbridge**
  - **Scientific consulting fee**

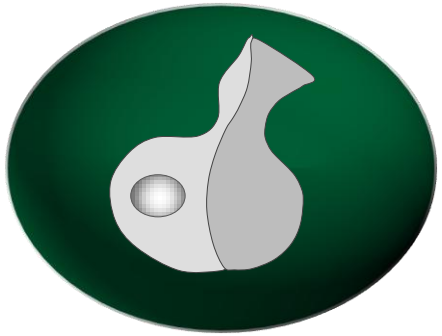
“ Measure what is measurable, and to make measurable what is not so”



Galileo Galileo 1564-1642

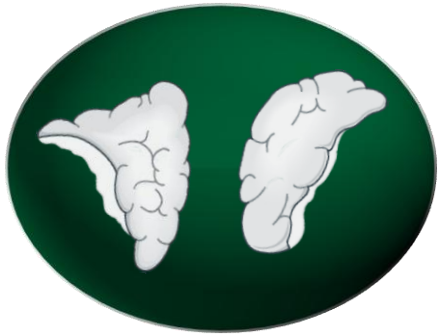
On the horizon for Cushing's syndrome
Levoketoconazole, phase III data published

Anterior pituitary



ACTH →

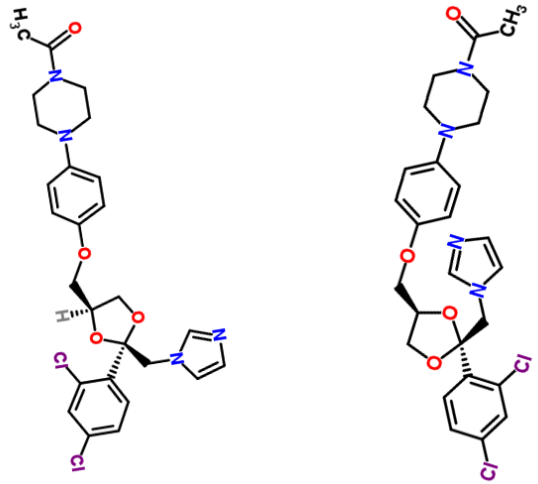
Adrenal glands



Cortisol →

Glucocorticoid receptor

Ketoconazole (racemic mixture)

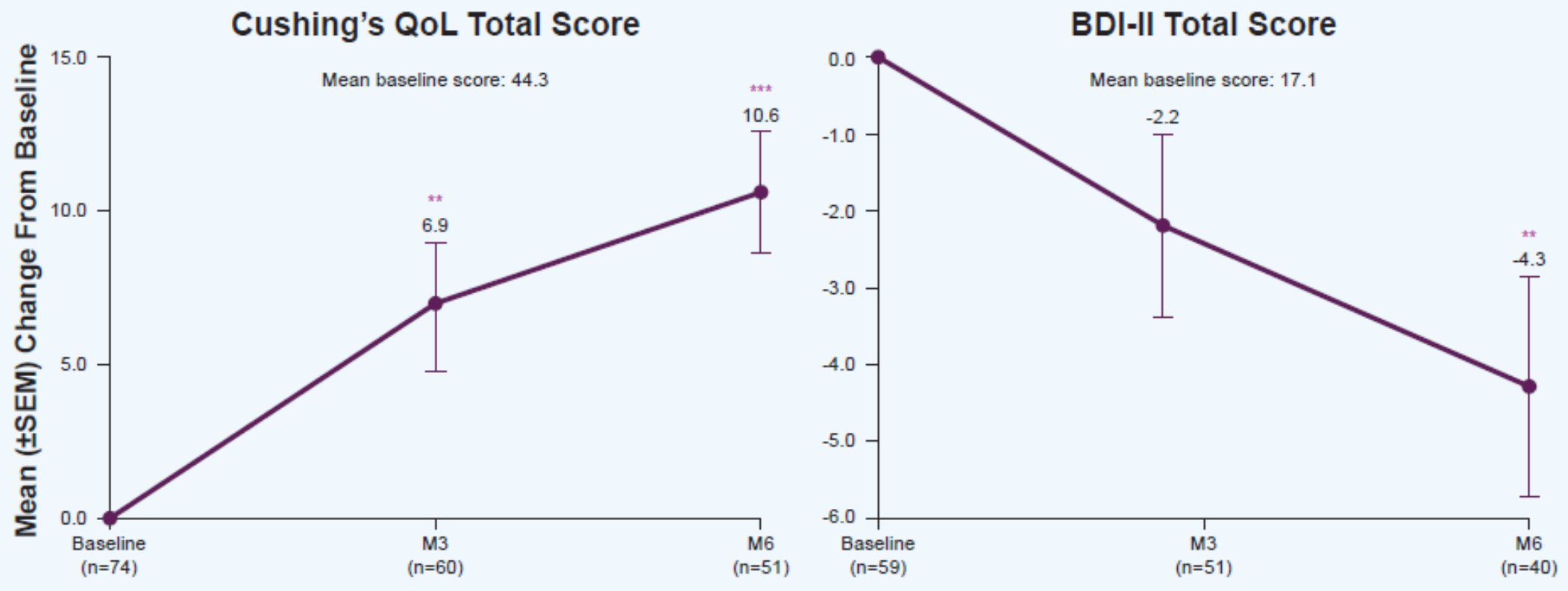


Levoketoconazole — **the 2S, 4R enantiomer**

Fleseriu M *et al. Pituitary* 2016

Fleseriu et al , Lancet Diabetes and Endocrinology, 2019

Significant improvements in quality of life and depression with levoketoconazole from baseline to end of maintenance



Fleseriu M *et al.* Presented at AACE 2019; abstract #497

***P*<0.01 versus baseline; ****P*<0.001 versus baseline

BDI-II, Beck Depression Inventory II; QoL, quality of life

On the horizon for Cushing's disease
Osilodrostat , phase III data available

Anterior pituitary → ACTH → *Adrenal glands* → Cortisol → *Glucocorticoid receptor*

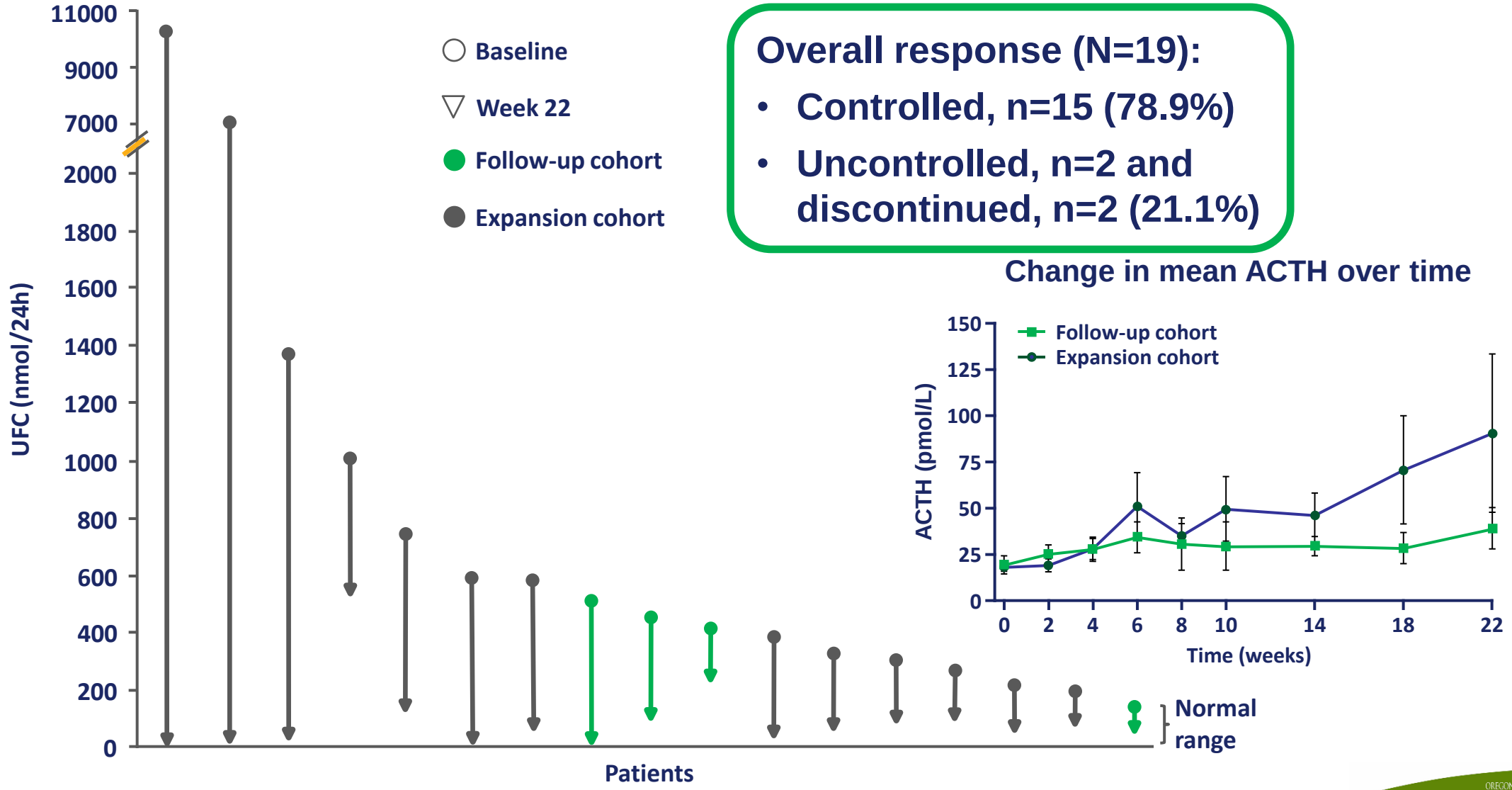
Osilodrostat (LCI699)

- Oral inhibitor of 11β-hydroxylase (responsible for catalysing final step of cortisol synthesis) ; also inhibits aldosterone synthesis

Fleseriu M *et al. Pituitary* 2016, Pivonello, Fleseriu et al , ICE 2018

Osilodrostat phase II study- 22 weeks

Potent inhibitor of 11β-hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2)



Overall response (N=19):

- **Controlled, n=15 (78.9%)**
- **Uncontrolled, n=2 and discontinued, n=2 (21.1%)**

Change in mean ACTH over time

Fleseriu M et al, Pituitary 2015

Osilodrostat in Cushing's disease (CD): Results from a Phase III, multicenter, double-blind, randomized withdrawal study (LINC 3)

Rosario Pivonello,[1] Maria Fleseriu,[2] John Newell-Price,[3] Xavier Bertagna,[4] James Findling,[5] Akira Shimatsu,[6] Feng Gu,[7] Richard Auchus,[8] Rattana Leelawattana,[9] Eun Jig Lee,[10] Jung Hee Kim,[11] Andre Lacroix,[12] Audrey Laplanche,[13] Paul O'Connell,[13] Libuse Tauchmanova,[13] Alberto M Pedroncelli[13] and Beverly MK Biller[14]

International Congress of Endocrinology, Cape Town, Oral presentation on Dec 1st 2018

	All patients N=137
Median age, years (range)	40.0 (19.0–70.0)
Female, n (%)	106 (77.4)
Median time since diagnosis, months (range)	47.2 (2.1–286.7)
Any previous pituitary surgery, n (%)	120 (87.6)
Any previous treatments for Cushing's disease, n (%)	131 (95.6)
Any previous pituitary irradiation, n (%)	22 (16.1)
Baseline UFC	
Mean, x ULN	7.3
Median, x ULN	3.5

ULN for mUFC is 138 nmol/24 h

Summary: Cushing's Disease treatment

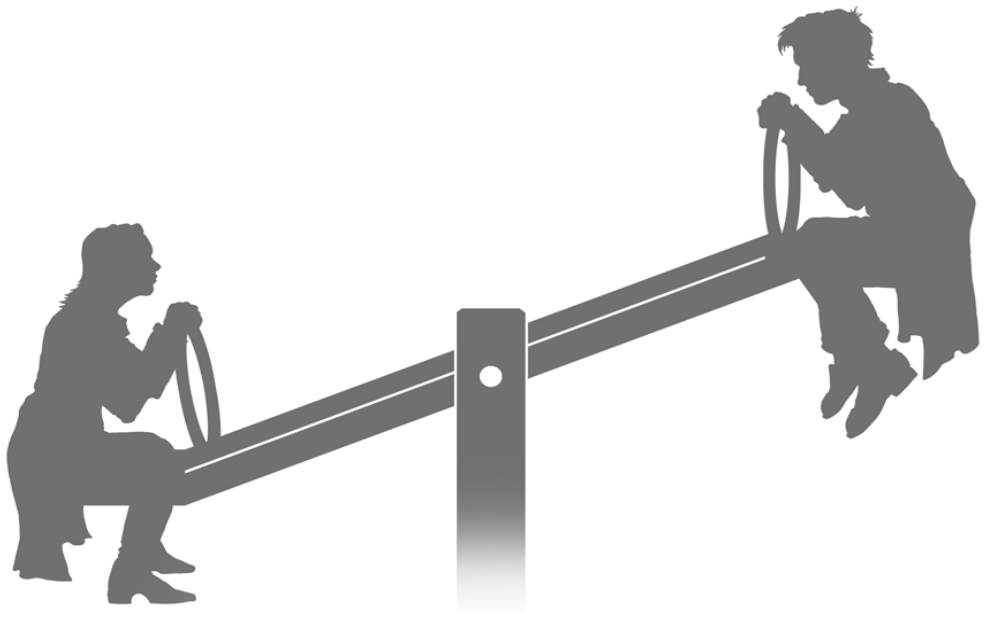
- Surgery is first-line treatment, but is associated with high recurrence rates and is not a viable option in some patients
- Repeat pituitary surgery, bilateral adrenalectomy and radiotherapy can result in control of hypercortisolism, but they are associated with variable response rates and significant risks
- **Medical therapy** plays an increasing role

PROS	CONS
Agents with different actions	
Rapid & sustained effects	Long- term
Treatment adjustable & reversible	Costs
Tumor shrinkage	AEs

Individualized therapy!

Which drug/target?

Single or combination?




Thank you!
Questions?

Cushing's disease: tumor directed medical therapy

Eliza B. Geer, M.D.

CSRF conference

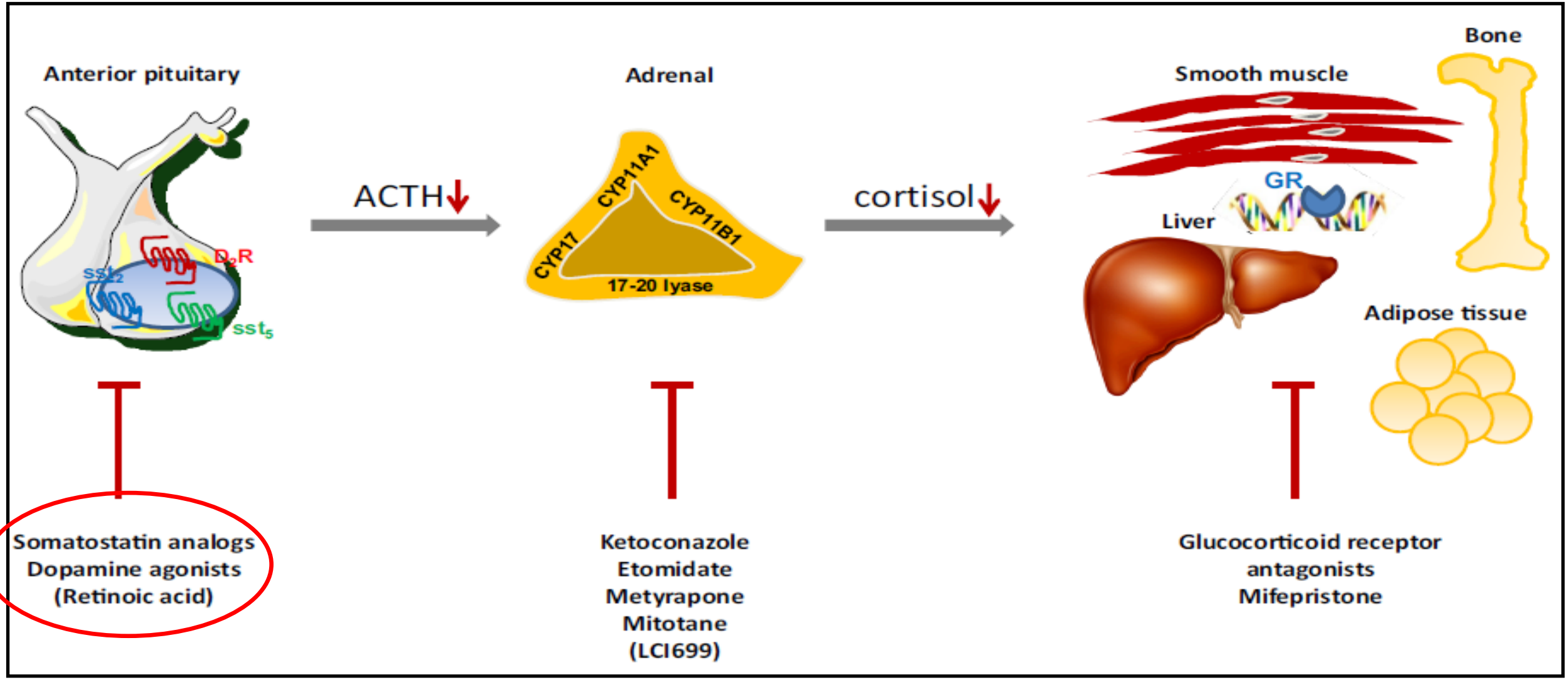
October 4-6th, 2019

Memorial Sloan Kettering Cancer Center

Financial relationships

Commercial Interest(s)	Nature of Relationship
Novartis	Institution-directed research support for clinical trial participation
Strongbridge	Institution-directed research support for clinical trial participation; medical advisory board
Chiasma	Institution-directed research support for clinical trial participation
Ionis	Institution-directed research support for clinical trial participation
Bristol-Myers Squibb	Research grant for a phase II trial investigating ipilimumab and nivolumab in the treatment of aggressive pituitary tumors.

Drug targets for Cushing's disease



R Feelders J Clin Endocrinol Metab 98(2): 425-438, 2103

cabergoline for CD

Table 1 Review of literature.

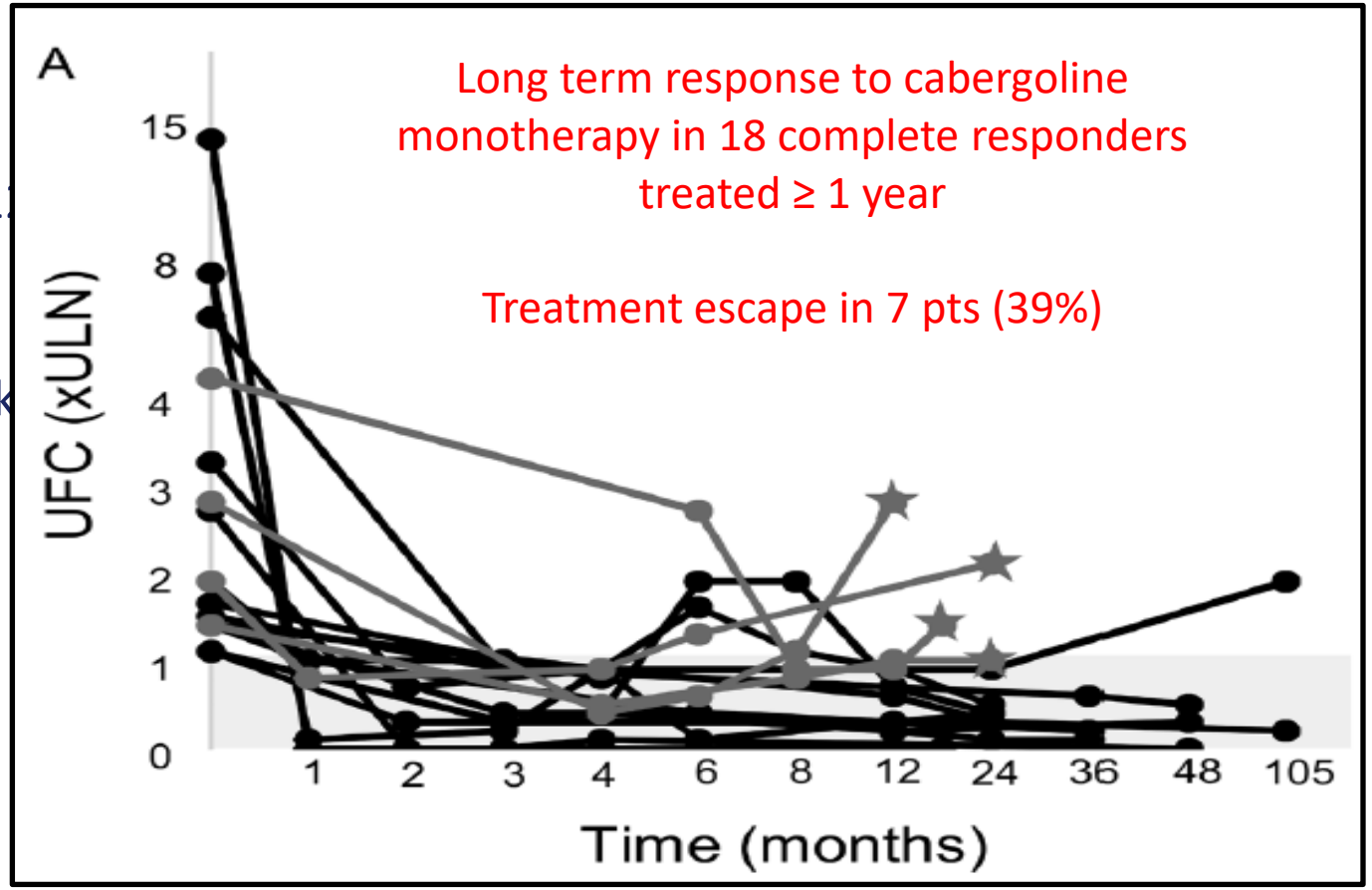
Study	Design	*n*	Dose (mg/week)	Response criteria	Patients with controlled hypercortisolism (%)	Maximal duration of treatment
Pivonello (2004) (4)	Retrospective, multicenter, monotherapy	10	2.2 (1.0–3.0)	UFC	40	3 months
Pivonello (2009) (6)	Prospective, multicenter, monotherapy	20	3.5 (1.0–7.0)	UFC	35 (short term) 40 (long term)	2 years
Lila (2010) (17)	Prospective, multicenter, monotherapy	20	3.6 (1.0–5.0)	Midnight cortisol and/or LDDST	28	12 months
Godbout (2010) (7)	Retrospective, multicenter, monotherapy	30	2.1 (0.5–4.0)	UFC	37 (short term) 30 (long term)	3 years
Vilar (2010) (8)	Prospective, monocenter, bitherapy	12	2.5 (1.0–3.0)	UFC	25	6 months
Barbot (2014) (9)	Prospective, monocenter, bitherapy	14	2.3 (0.5–3.0)	UFC	33 (short term, monotherapy) 100 (long term, bitherapy)	12 months
Burman (2016) (10)	Prospective, monocenter, monotherapy	20	4.7 (2.5–5.0)	UFC	0	6 weeks

n, number of patients; UFC, urinary free cortisol; LDDST, low-dose dexamethasone suppression test.

Ferriere A Eur J Endo 2017

Summary of cabergoline for CD

- No clinical trials; only small, observational, mostly short term studies
- 24 hr UFC control in 25-40% of patients treated > 1 months
- Modest response due to low doses used? (2 mg/wk range 0.5-6 mg)
- No clear predictive factors
- Variable time to control, lag of 3 months in some
- Treatment escape/intolerance in 40%



Ferriere A Eur J Endo 2017

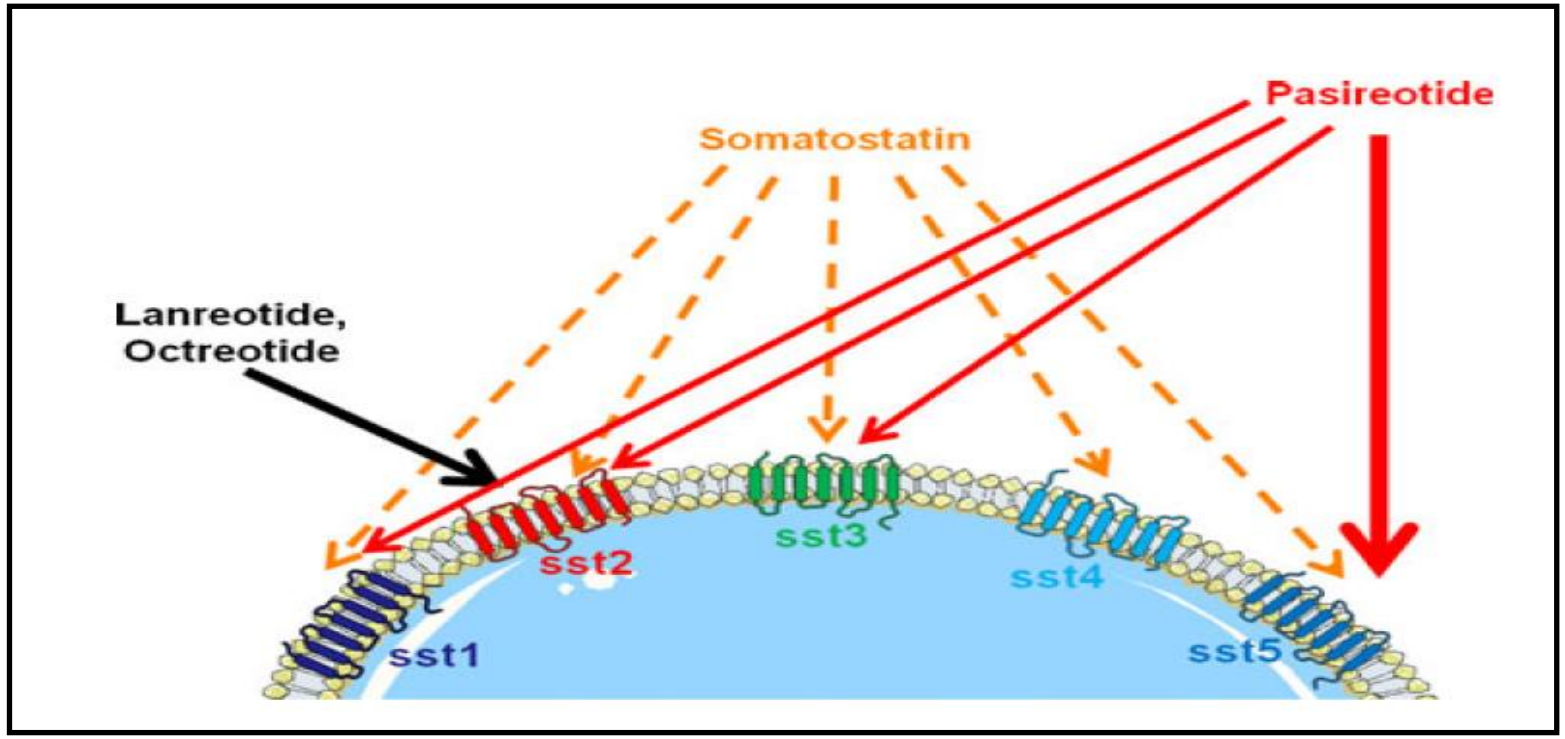
Memorial Sloan Kettering Cancer Center

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A 12-Month Phase 3 Study of Pasireotide in Cushing's Disease

Annamaria Colao, M.D., Ph.D., Stephan Petersenn, M.D., John Newell-Price, M.D., Ph.D., James W. Findling, M.D., Feng Gu, M.D., Mario Maldonado, M.D., Ulrike Schoenherr, Dipl.-Biol., David Mills, M.Sc., Luiz Roberto Salgado, M.D., and Beverly M.K. Biller, M.D., for the Pasireotide B2305 Study Group*



NEJM 2018 2012

Pasireotide treatment for Cushing's disease

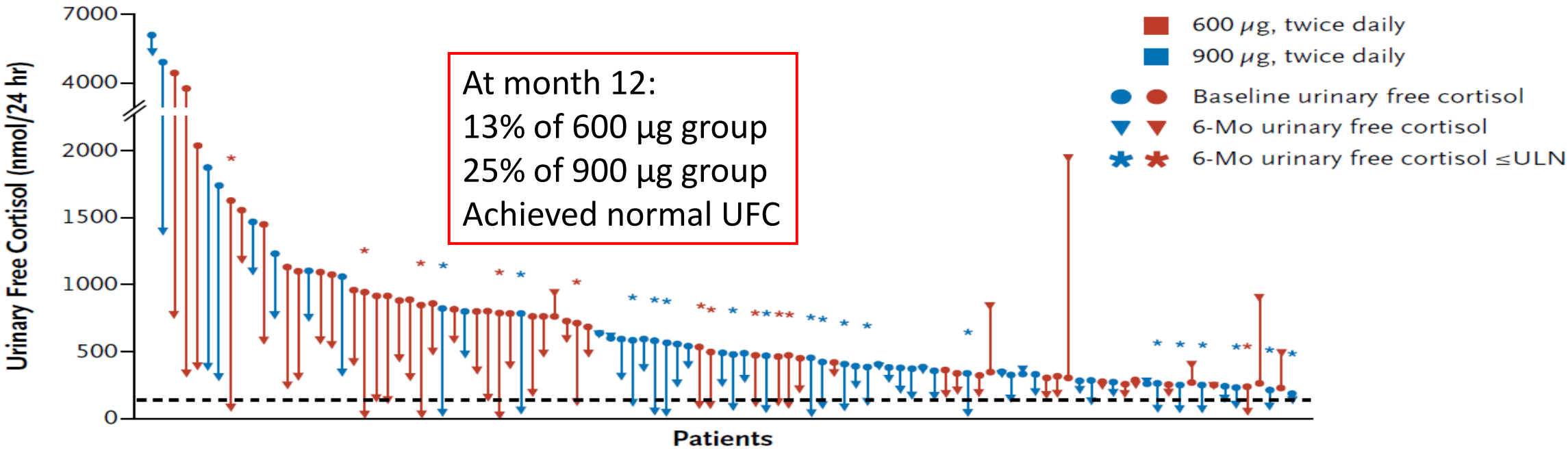


Figure 1. Absolute Change in Urinary Free Cortisol Levels from Baseline to Month 6.

Urinary free cortisol was available at baseline and at month 6 in a total of 103 patients; 61 patients had a reduction of at least 50% in urinary free cortisol levels 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]).

N ENGL J MED 366;10 NEJM.ORG MARCH 8, 2012

SC Pasireotide treatment for Cushing's disease

- Blood pressure, cholesterol, weight, and QoL improved
- Tumor volume decreased by 44% in 75 patients with a lesion in MRI in the 900 mcg group
- Safety profile:
  - Gastrointestinal side effects
  - 73% elevated glucose; 43% became prediabetic, 34% became diabetic
- Predictors? 50% response in mild Cushing's; 90% of nonresponders at 2 months did not normalize later

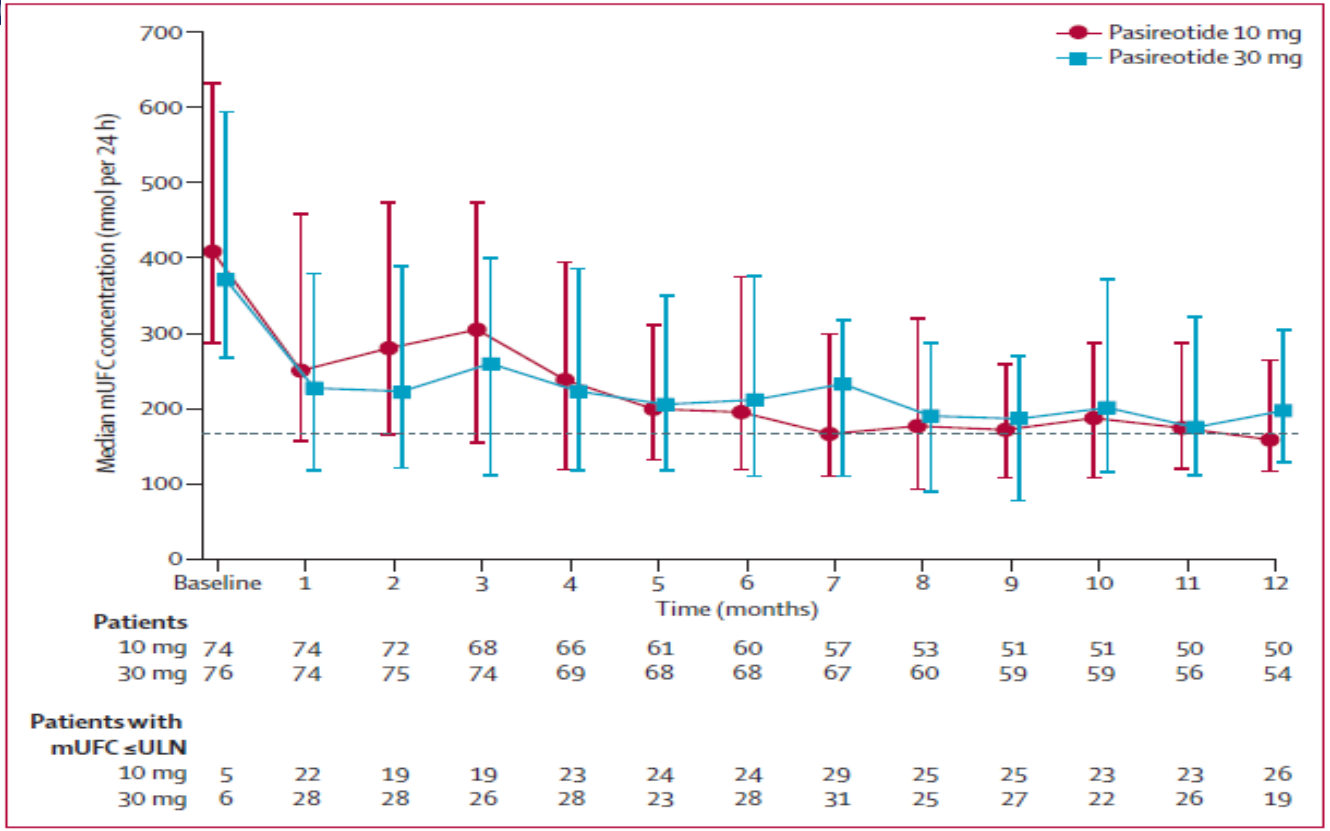
FDA approved for CD in December, 2012

N ENGL J MED 366;10 NEJM.ORG MARCH 8, 2012

Efficacy and safety of once-monthly pasireotide in Cushing's disease: a 12 month clinical trial

*André Lacroix, Feng Gu, Wilson Gallardo, Rosario Pivonello, Yerong Yu, Przemysław Witek, Marco Boscaro, Roberto Salvatori, Masanobu Yamada, Libuse Tauchmanova, Michael Roughton, Shoba Ravichandran, Stephan Petersenn, Beverly M K Biller, John Newell-Price, for the Pasireotide G2304 Study Group**

- 150 patients randomized to pasireotide LAR 10 or 30 mg monthly
- 40% achieved normal 24 hr. UFC
- Side effects: high glucose/diabetes, nausea, diarrhea, gallstones
- Patients had milder CD than in SC pasireotide trial could explain higher proportion that achieved remission



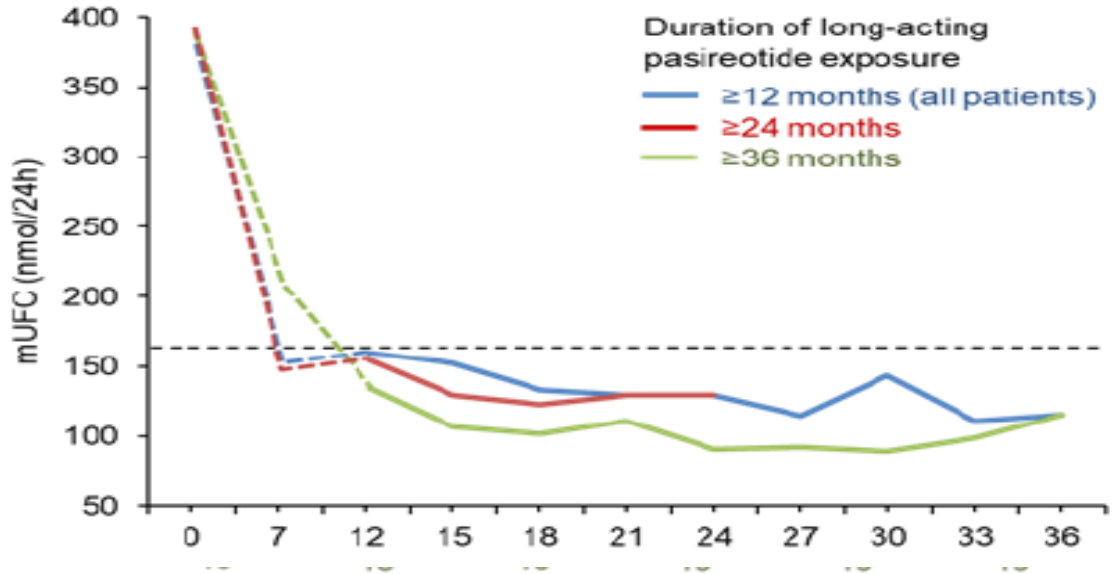
Patients	Baseline	1	2	3	4	5	6	7	8	9	10	11	12
10 mg	74	74	72	68	66	61	60	57	53	51	51	50	50
30 mg	76	74	75	74	69	68	68	67	60	59	59	56	54

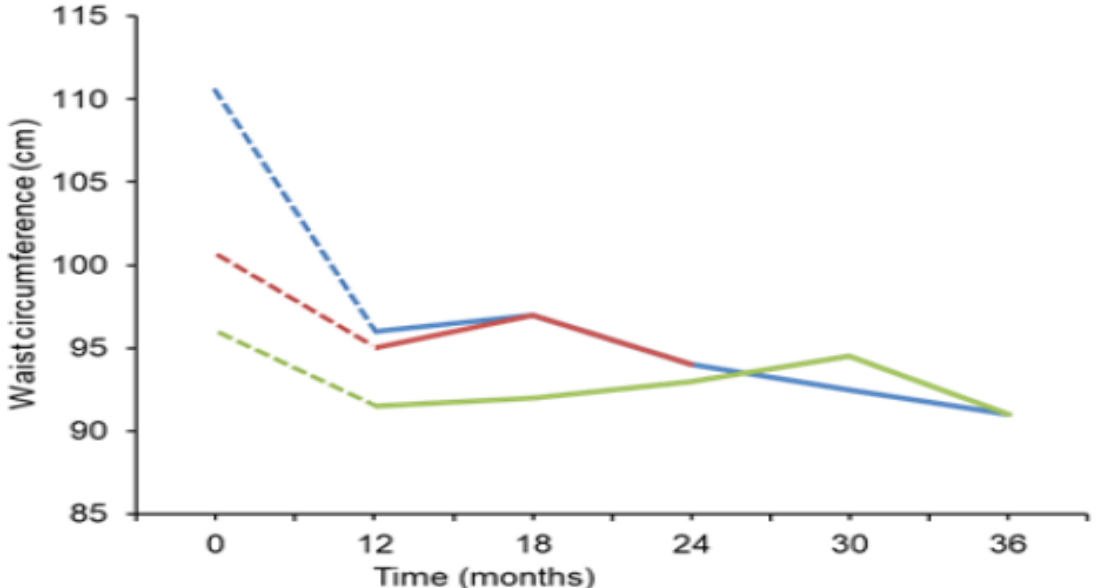
Patients with mUFC ≤ULN													
10 mg	5	22	19	19	23	24	24	29	25	25	23	23	26
30 mg	6	28	28	26	28	23	28	31	25	27	22	26	19

Lacriox, Lancet Endocrinology 2018

Long acting Pasireotide for CD: Phase III extension study

- Open label extension study, 81/150 pts from primary study
- Eligible if nl UFC or clinical benefit
- 53% nl UFC at last assessment
- 51.9% people discontinued; high glucose levels in 39.5%
- Improvements in BMI & WC maintained, QOL improved
- No new safety concerns





Fleseriu, Clinical Endocrinology 2019

Thank you

Cortisol Receptor Blockers

Adriana Ioachimescu, MD, PhD

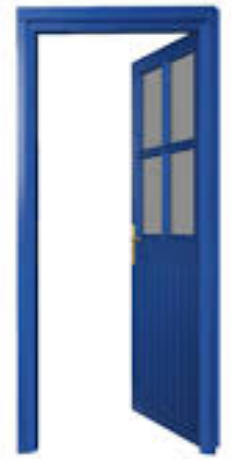
Mifepristone: FDA-approved in 2012

- *"to control hyperglycemia secondary to hypercortisolism in **adult** patients with endogenous **Cushing's syndrome** who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery."*

- Contraindications: pregnancy (abortifacient)
- Oral administration, 300-1,200 mg/day

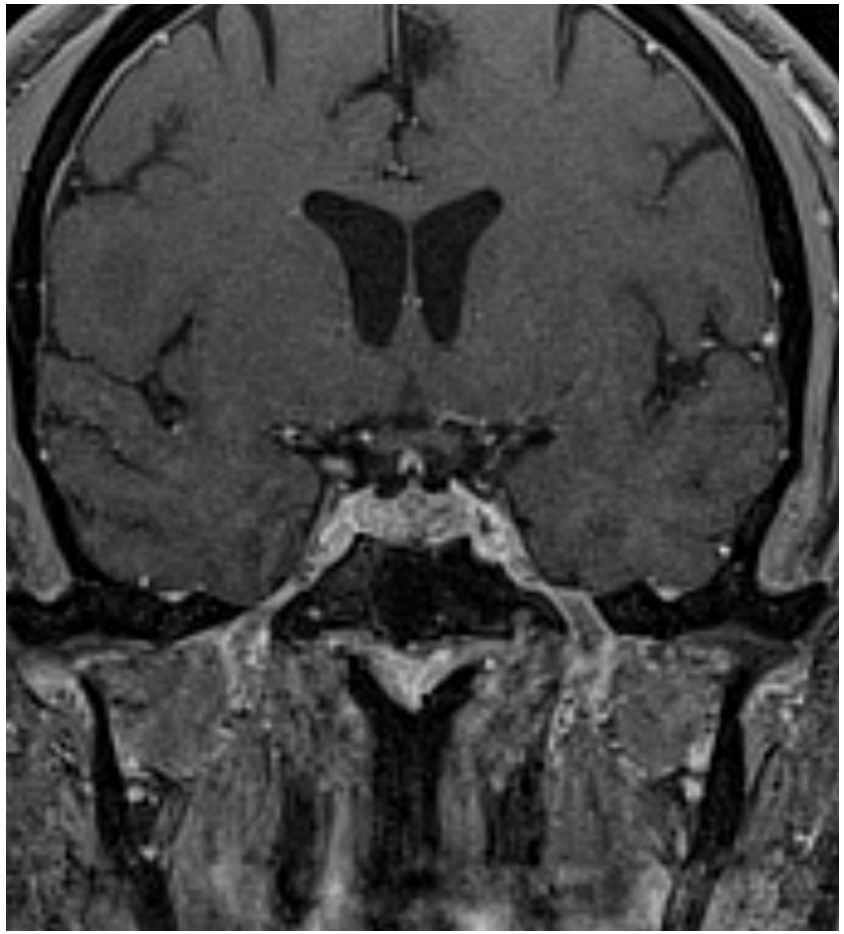
Mechanism: (b)locks the cortisol receptors

Adverse Events



- Excess cortisol activates other receptors
  - Mineralocorticoid effects
    - leg swelling, ↓ potassium, sometimes ↑blood pressure
- Mifepristone blocks other receptors
  - Progesterone
    - Vaginal bleeding, uterine endometrial thickening
- Manifestations of low cortisol
  - Treated with high dose dexamethasone *(rescue medication)*
- Nausea, fatigue, headaches, joint pain, dizziness

Mifepristone does not target the tumor and MRI surveillance is important



Efficacy

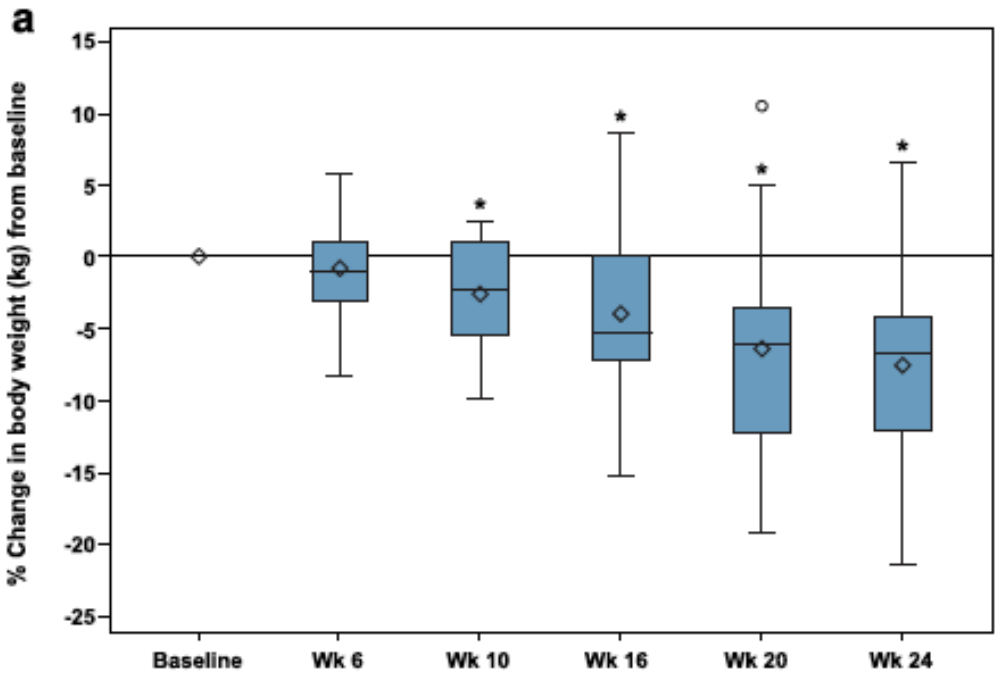
- Improves glucose control
- Improves BP in 38% of hypertensive patients

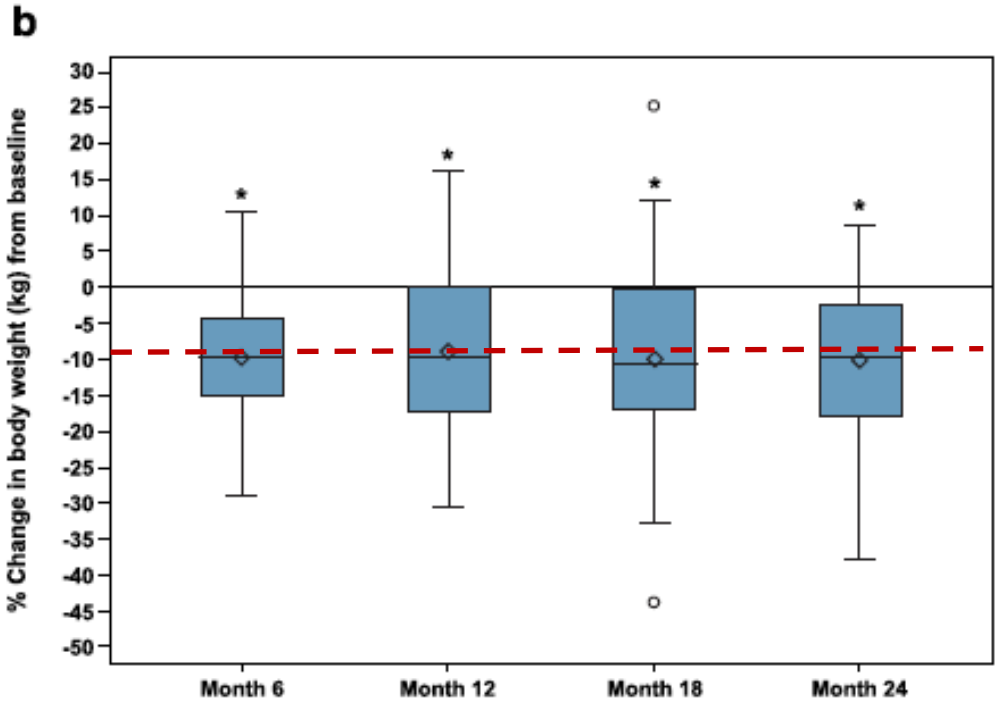
- Improves other manifestations of high cortisol
  - Body weight and composition
  - Waist circumference
  - Appearance
  - Strength
  - Moods
  - Quality of life

% Changes in body weight

SEISMIC study
- 34% patients lost ≥ 10%
- 62% patients lost ≥ 5%

Long-term Extension Study
- 80% maintained the weight loss





Fein et al. BMC Endocrine Disorders (2015) 15:63

Dose titration

- Clinical evaluation
  - Feeling better? Tolerating the new medication?
  - Weight
  - Blood pressure
  - Home glucose records
- Are cortisol and ACTH levels helpful?
- What tests should be done?
  - Chemistry panel: potassium, creatinine, glucose
  - HbA1c
  - Thyroid tests
  - Lipids
  - EKG

Changes in concomitant medications

- Potassium supplements (especially with increasing mifepristone dose)
  - Both low and high potassium levels can be dangerous
- Blood pressure medications
  - Diuretics that decrease aldosterone effects are helpful
  - The usual diuretics that work for high blood pressure (HCTZ) may be stopped
  - Blood pressure medications that can cause edema may be decreased or stopped
- Insulin and oral antidiabetic medications are usually reduced

Proactive attitude – seek immediate advice

- Acute illness
- Procedures under general anesthesia
- New medications started by other physicians
- Vaginal bleeding
- Significant weight loss
- Low potassium

Clinical trials with cortisol-receptor blockers

- **A Study of the Efficacy and Safety of Relacorilant in Patients With Endogenous Cushing Syndrome (GRACE)**

- This is a Phase 3, double-blind, placebo-controlled, randomized-withdrawal study to assess the safety and efficacy of relacorilant in patients with endogenous Cushing syndrome and concurrent 1) Type 2 diabetes mellitus/impaired glucose tolerance and/or 2) uncontrolled hypertension

- Recorilant does not block the progesterone receptor
- https://clinicaltrials.gov

- *Thank you!*