Sindrome di Cushing: quando e come la terapia medica. CON QUALI FARMACI TRATTARE

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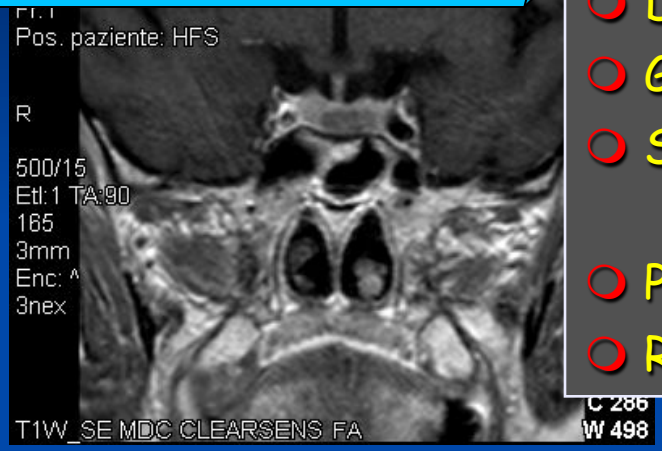
DISCLOSURES

- HRA PHARMA, research grant
- HRA PHARMA, lecture grant
- NOVARTIS, research grant

SO MANY DRUGS….

Pituitary Adenoma



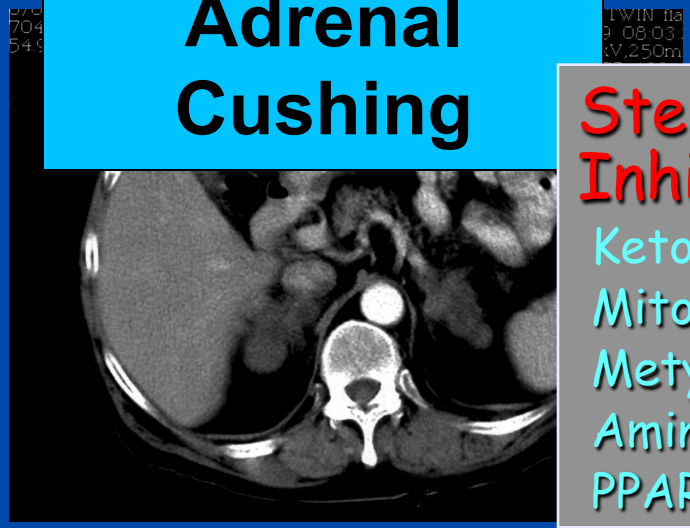
Inhibitors of ACTH Secretion

- Serotonin Antagonists: Cyproheptadine, Ritanserine
- Dopamino-agonists: Bromocriptine, Cabergoline
- GABA-agonists: Valproic Acid
- Somatostatin Analogs: Octreotide, Lanreotide, SOM230
- PPAR-γ Agonists: Rosiglitazone, Pioglitazone
- Retinoic Acid

GR Antagonist

Mifepristone (RU-486)

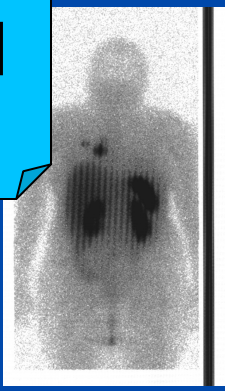
Adrenal Cushing



Steroidogenesis Inhibitors

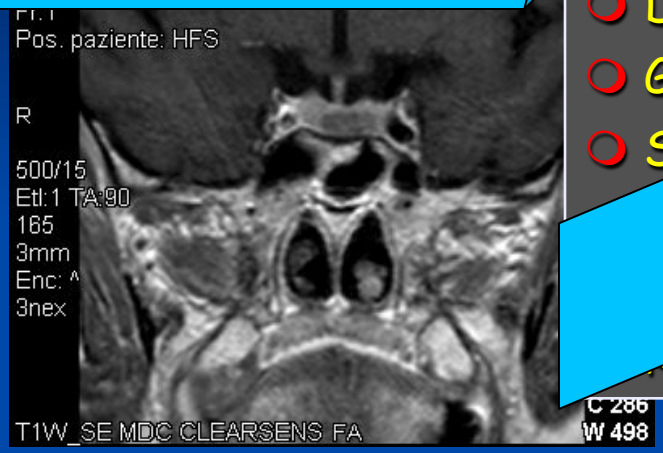
Ketoconazole
Mitotane
Metyrapone
Aminoglutethimide
PPAR-γ Agonists

Ectopic ACTH Secretion



….BUT WHAT CAN WE USE?

Pituitary Adenoma



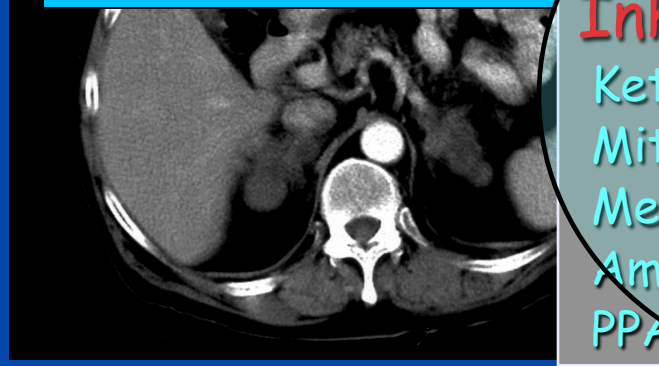
Inhibitors of ACTH S…

- Seroto… …serine
- Dopami… …oline
- GABA-…
- Som… …tide,
- …gonists: Rosiglitazone, Pioglitazone
- …etinoic Acid

SOM 230
Cabergolina

GR Antagonist
Mifepristone (RU-486)

Adrenal Cushing



Steroidogenesis Inhibitors
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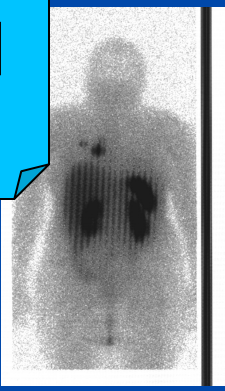
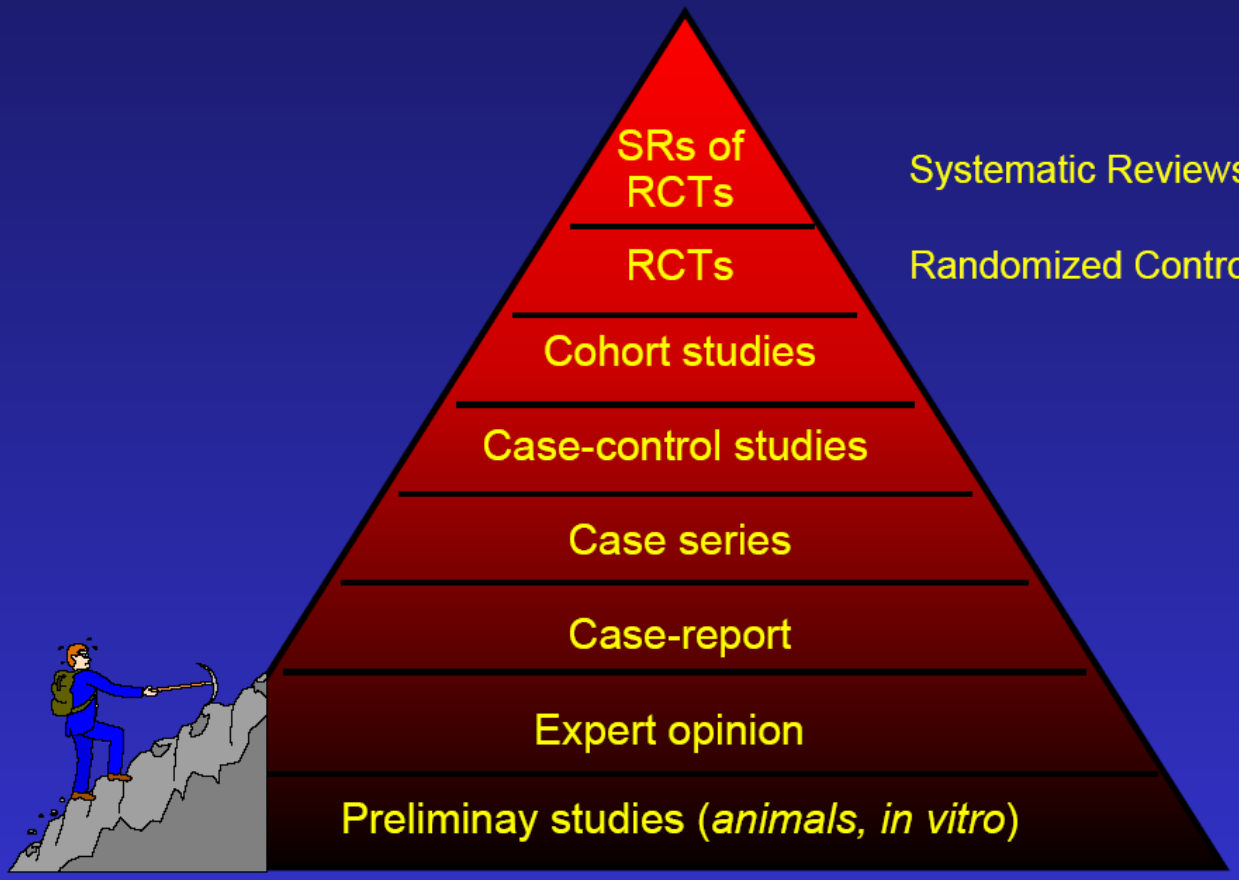
Ectopic ACTH Secretion



HIERARCHY OF EVIDENCE



1° RCT nella M. di Cushing

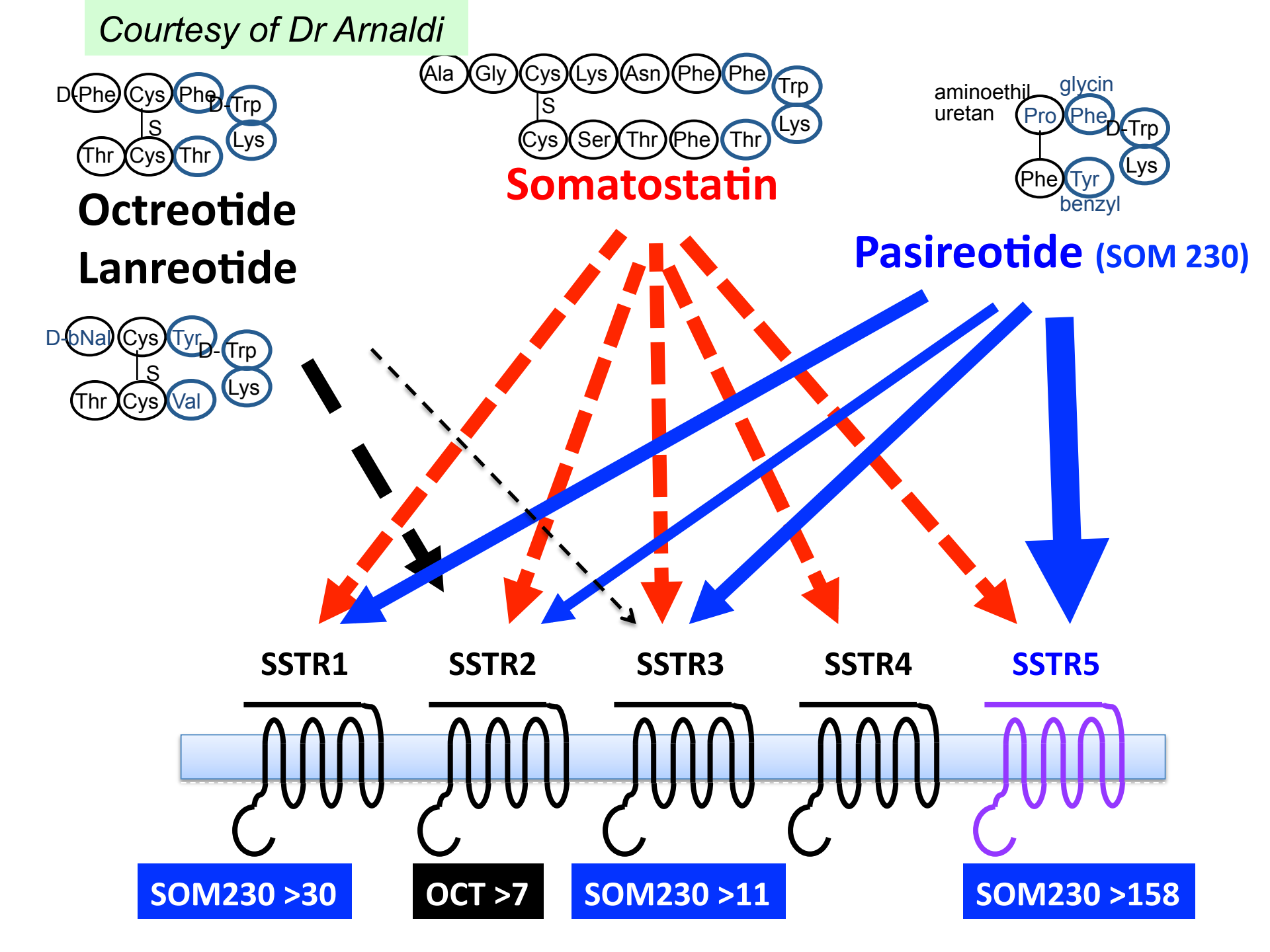
Roma,
9-11 novembre 2012

The NEW ENGLAND JOURNAL of MEDICINE

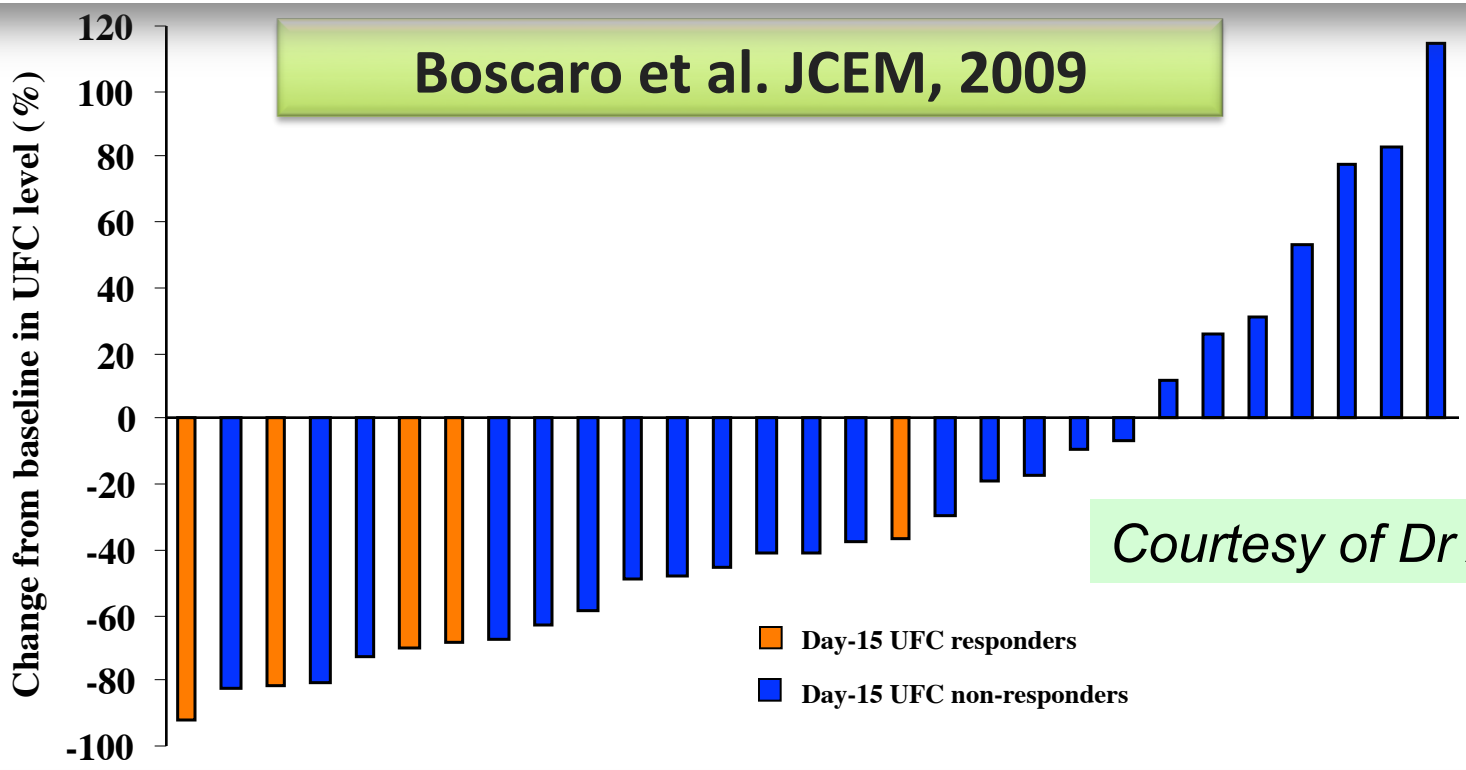
ORIGINAL ARTICLE

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*


Courtesy of Dr Arnaldi
D-Phe Cys Phe D-Trp Lys Thr Cys Thr
S
Octreotide
Lanreotide
D-bNal Cys Tyr D-Trp Lys Thr Cys Val
S
Ala Gly Cys Lys Asn Phe Phe Trp Lys Cys Ser Thr Phe Thr
S
Somatostatin
aminoethil uretan
glycin
Pro Phe D-Trp Lys Phe Tyr
benzyl
Pasireotide (SOM 230)
SSTR1
SSTR2
SSTR3
SSTR4
SSTR5
SOM230 >30
OCT >7
SOM230 >11
SOM230 >158

Treatment of Pituitary-Dependent Cushing's Disease with the Multireceptor Ligand Somatostatin Analog Pasireotide (SOM230): A Multicenter, Phase II Trial

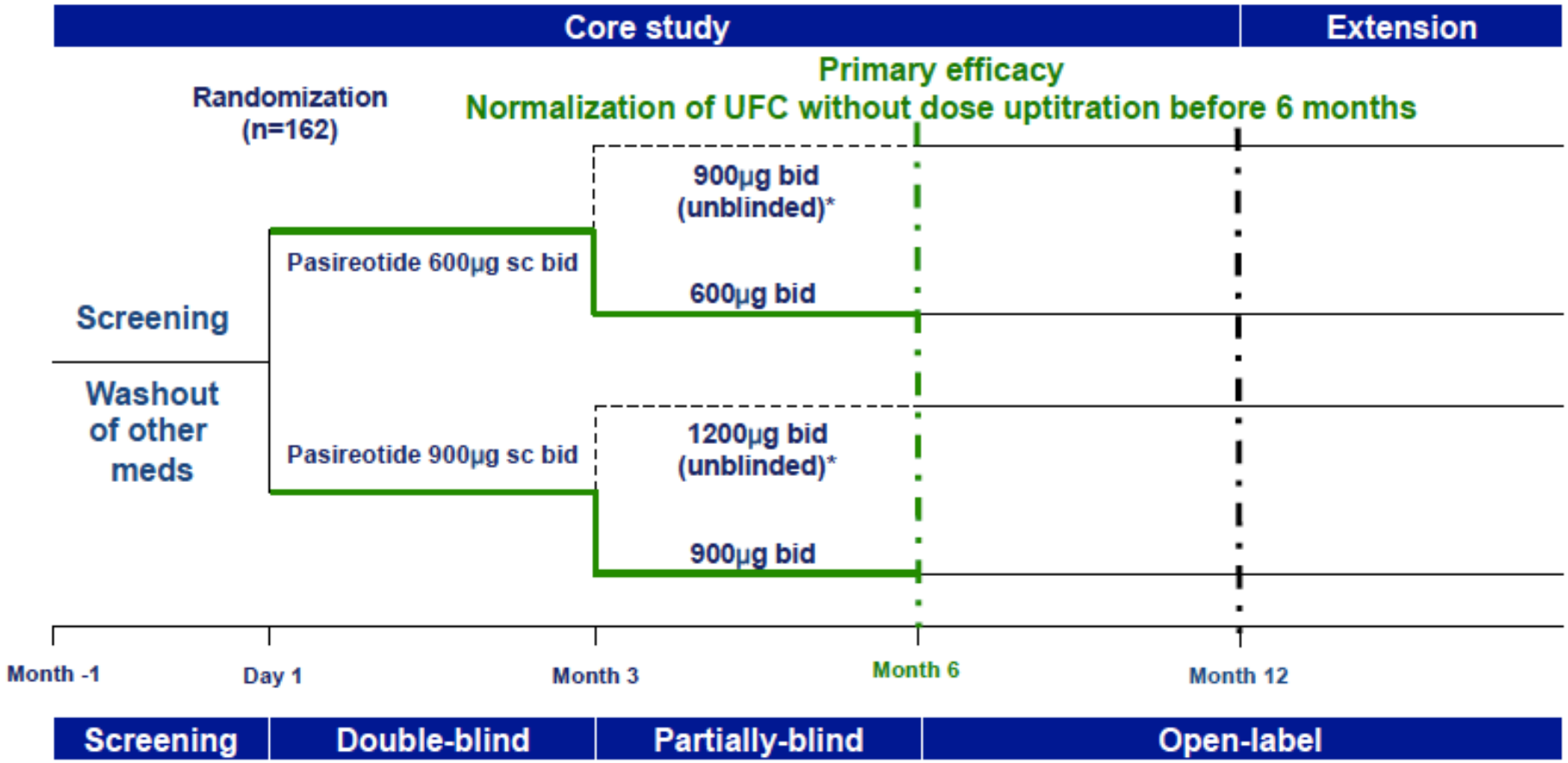


Courtesy of Dr Arnaldi

After 15 days of treatment with pasireotide 600 mcg bid sc (n=29)

- 17% of patients with Cushing's disease normalized UFC levels
- 76% of patients exhibited reduced UFC levels
- The mean UFC level decreased from baseline by 44.5% (p = 0.021)

DESIGN OF THE STUDY



*For patients who had a mean baseline UFC ≥2xULN with a 3-month UFC >2xULN *OR*
For patients who had a mean baseline UFC 1.5-2xULN with a 3-month UFC above their baseline UFC

Pasireotide nella M. di Cushing

Table 1. Baseline Demographic and Clinical Characteristics of the Overall Study Population and Each Dose Group.*

Characteristic	Pasireotide 600 μg Twice Daily (N=82)	Pasireotide 900 μg Twice Daily (N=80)	Overall (N=162)
Previous treatment — no. (%)			
Surgery	64 (78)	64 (80)	128 (79)
Medication	36 (44)	42 (52)	78 (48)
Pituitary irradiation	3 (4)	4 (5)	7 (4)
Urinary free cortisol			
Baseline measurement — no. of patients (%)	77 (94)	76 (95)	153 (94)
≥3 samples collected — no. of patients (%)	77 (94)	76 (95)	153 (94)
Level — nmol/24 hr			
Mean	1156	782	970
Median	730	487	565
Range	220–22,944	195–6123	195–22,944

Pasireotide nella M. di Cushing

Table 1. (Continued.)

Characteristic	Pasireotide 600 μg Twice Daily (N=82)	Pasireotide 900 μg Twice Daily (N=80)	Overall (N=162)
Severity of hypercortisolism — no. (%)‡			
Mild	12 (15)	14 (18)	26 (16)
Moderate	26 (32)	40 (50)	66 (41)
Severe	28 (34)	13 (16)	41 (25)
Very severe	11 (13)	9 (11)	20 (12)
Missing data	5 (6)	4 (5)	9 (6)
Months of study completed — no. of patients (%)§			
3	68 (83)	65 (81)	133 (82)
6	54 (66)	53 (66)	107 (66)
12	39 (48)	39 (49)	78 (48)

* The study was not powered to detect significant differences between dose groups.

Pasireotide nella M. di Cushing

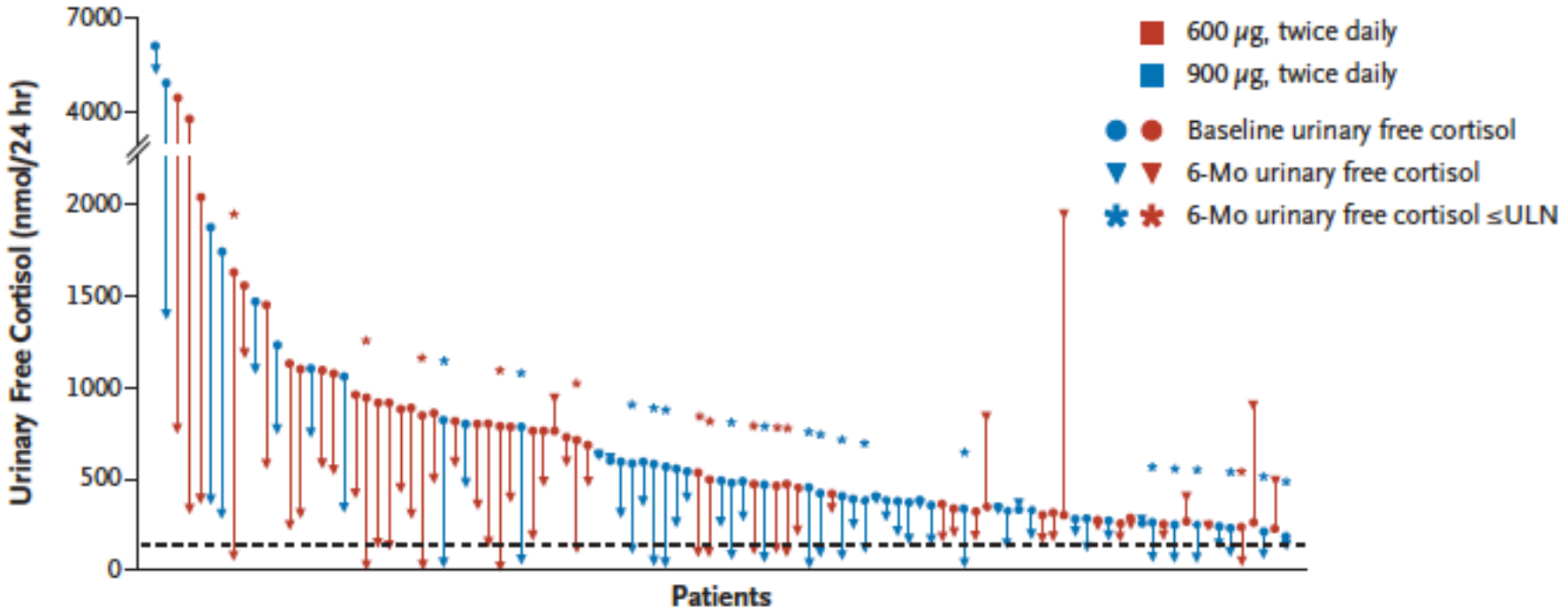
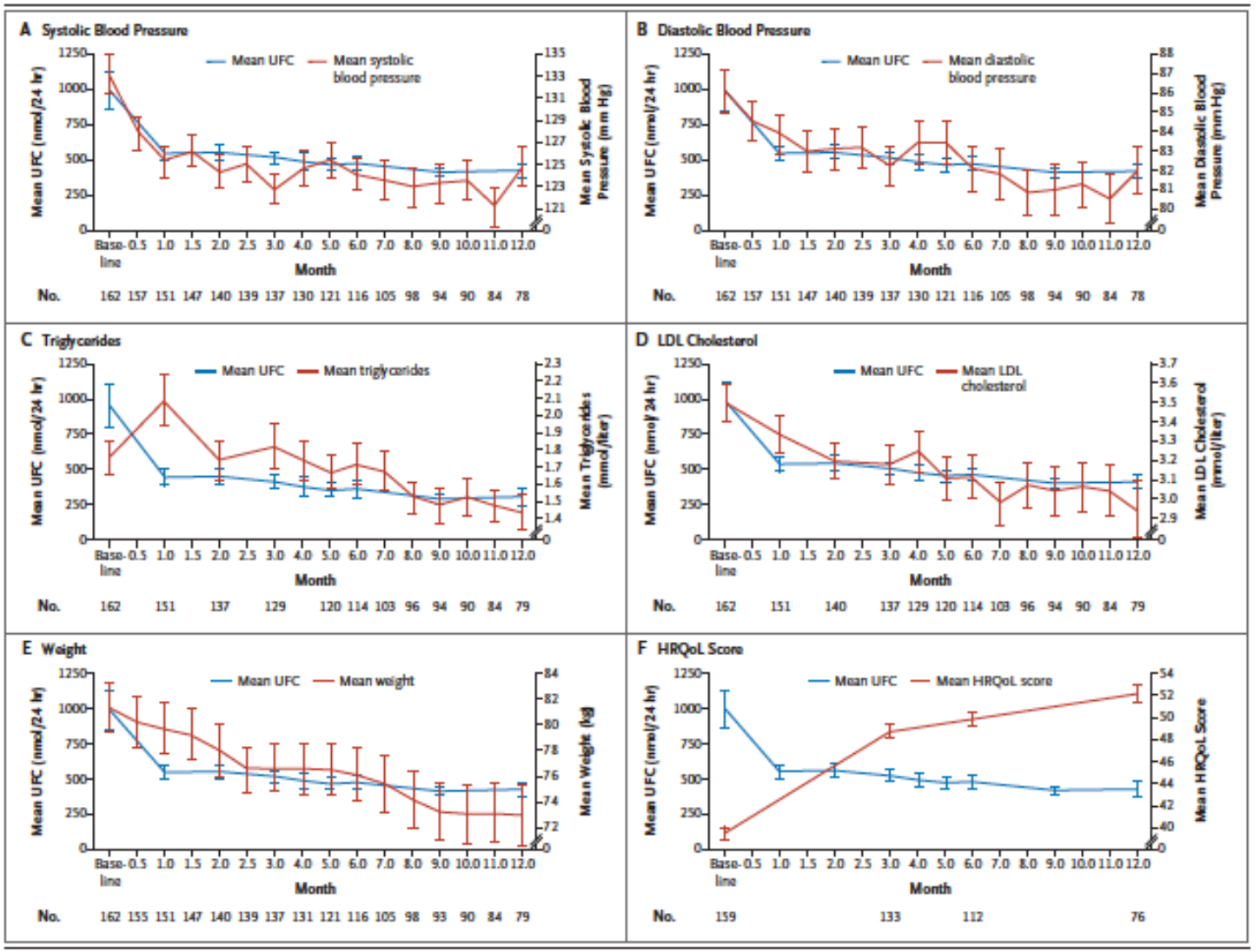


Figure 1. Absolute Change in Urinary Free Cortisol Levels from Baseline to Month 6.

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]).

Pasireotide nella M. di Cushing

Roma,
9-11 novembre 2012



Primary Endpoint Analysis

	600µg bid N=82	900µg bid N=80	Overall N=162
6-month response, n (%)	12 (14.6)	21 (**26.3**)	33 (20.4)
95% Confidence Interval	(7.0, 22.3)	(**16.6, 35.9**)	(14.2, 26.6)
12-month response, n (%)	11 (13.4)	20 (**25.0**)	31 (19.1)

6-month response: normal UFC without uptitration at 3 months

Median percent UFC change from baseline was -47.9% for both groups

900 µg bid met the statistical criterion for efficacy:
the lower bound of the 95% CI for a dose group had to be >15%

Early prediction of response

	Early non-responders	Month-6 response			Month-12 response		
	Uncontrolled (UC)	FC	PC	UC	FC	PC	UC
Month 1 + 2	72 (100.0%)	4 (5.6%)	2 (2.8%)	66 (91.7%)	6 (8.3%)	2 (2.8%)	64 (88.9%)
Month 1 + 2 + 3	63 (100.0%)	2 (3.2%)	1 (1.6%)	60 (95.2%)	5 (7.9%)	1 (1.6%)	57 (90.5%)

Controlled: UFC ≤ULN;

Partially Controlled: UFC >ULN, but ≥ 50% reduction from baseline

Uncontrolled: UFC >ULN and <50% reduction from baseline

Safety analysis

Table 2. Most Frequently Reported Adverse Events (Occurring in ≥10% of Patients in Either Dose Group).*

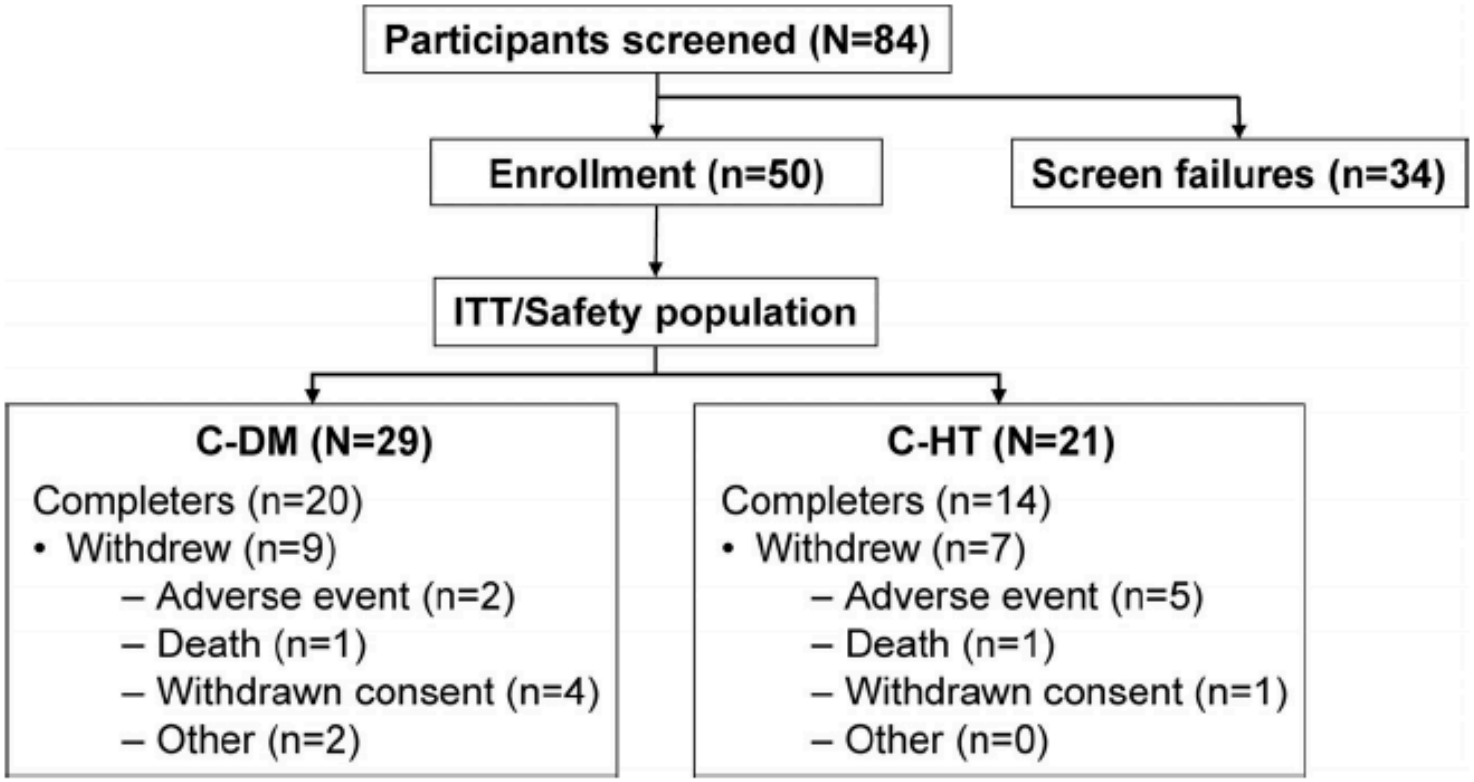
Adverse Event	Pasireotide 600 μg Twice Daily (N=82)		Pasireotide 900 μg Twice Daily (N=80)		Overall (N=162)	
	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades
	number of patients (percent)					
Diarrhea	3 (4)	48 (59)	2 (2)	46 (58)	5 (3)	94 (58)
Nausea	1 (1)	38 (46)	3 (4)	46 (58)	4 (2)	84 (52)
Hyperglycemia	8 (10)	31 (38)	13 (16)	34 (42)	21 (13)	65 (40)
Diabetes mellitus	6 (7)	13 (16)	6 (8)	16 (20)	12 (7)	29 (18)

73% of patients had hyperglycemia and 6% discontinued treatment because of it.
A new antidiabetic drug was initiated in 74/162 (46%) patients.
HbA1c increased from 5.8% to 7.4% in the 900 μg group.
At study end, 51 (48%) of the 107 patients without diabetes at baseline had a HbA1c ≥ 6.5%.

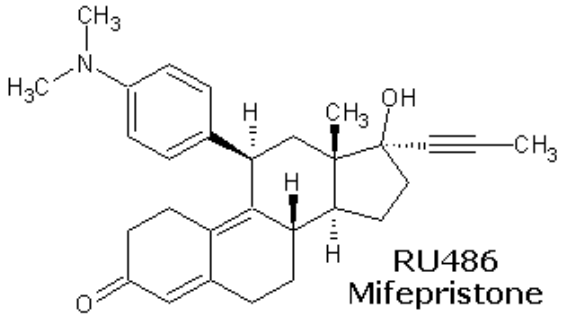
Open-label prospective study

Mifepristone, a Glucocorticoid Receptor Antagonist, Produces Clinical and Metabolic Benefits in Patients with Cushing's Syndrome

Maria Fleseriu, Beverly M. K. Biller, James W. Findling, Mark E. Molitch, David E. Schteingart, and Coleman Gross, on behalf of the SEISMIC Study Investigators



MIFEPRISTONE



RU486 binds to the human GR with an affinity 3 to 4 times higher than of dexamethasone and about 18 times higher that of cortisol

RU486 blocks the GR in a competitive manner and the effects can be reversed by glucocorticoid administration

Receptor	Daily dose	Potential side effects
PR	>5 mg	Amenorrhoea
	>10 mg	Endometrial hyperplasia
GR	>50 mg	Increase in cortisol, ACTH, adrenal androgens
	>100–200 mg	Mild to moderate fatigue/nausea
	>200–400 mg	Adrenal insufficiency (severe nausea, severe fatigue and other symptoms)
	>200 mg	Gynecomastia (due to elevated oestradiol levels derived from adrenal androgens)
	>200 mg (isolated cases)	Hypokalaemia (due to MR activation by cortisol?)
	>400 mg (isolated cases)	Hypothyroidism
AR	>200 mg	Gynecomastia, decrease *in libido*

Dose designations are estimated based on the results from long-term trials, exact doses at which the listed side effects occur may vary between individuals.
PR, progesterone receptor; GR, glucocorticoid receptor; AR, androgen receptor; MR, mineralocorticoid receptor.

Open-label prospective study

CS with T2DM, IGT or HTN.
CS diagnosed by increased UFC (2 times) and increased NSC and/or altered DST, with at least 2 of the followings: Cushingoid appearance (moon facies, dorsocervical fat pad, and plethora), increased BW or central obesity, proximal muscle weakness, low bone mineral density, psychiatric symptoms, and skin changes (hirsutism, violaceous striae, or acne).

TABLE 2. Biochemistry at baseline (ITT/safety population)

	CD	Ectopic ACTH	Adrenal cancer	Overall
Biochemistry	(n=43)	(n=4)	(n=3)	
ACTH (pg/ml)	63 (51)	153 (140.3)		66 (66)
24 h UFC (μg/24 h)	139 (137)	2471 (3266)	812 (559)	366 (1049)
Serum cortisol (μg/dl)	21.2 (6.0)	42.6 (14.3)	37.4 (15.4)	23.9 (10.0)
Late-night salivary cortisol (μg/dl)	0.29 (0.29)	1.90 (2.26)	1.02 (0.58)	0.47 (0.83)

Open-label prospective study

Treatment began at 300 mg/d; doses could be progressively increased to 1200 mg/d.
72% of patients with CD had a 2-fold increase in ACTH/cortisol.
MRI were stable in all cases but one.
AEs occurred in 88% of patients; 7 interrupted treatment for AE.

TABLE 3. Summary of responder analyses (mITT population)

Statistics (mITT population)	Responder [n (%)]	Nonresponder [n (%)]	Lower bound one-sided 95% exact binomial CI (%)	*P* value
C-DM (n = 25)				
Participants with or without a 25% reduction from baseline in $AUC_{glucose}$ at wk 24/ET	15 (60)	10 (40)	41.7	<0.0001
C-HT (n = 21)				
Participants who had ≥5 mm Hg reduction from baseline in DBP at wk 24/ET	8 (38.1)	13 (61.9)	20.6	<0.05
Median clinical improvement score of +1 at any reviewed visit[b]				
Combined cohorts (n = 46)	40 (87.0)	6 (13.0)	75.9	<0.0001
C-DM (n = 25)	23 (92.0)	2 (8.0)	76.9	
C-HT (n = 21)	17 (81.0)	4 (19.0)	61.6	

Prospective cohort study

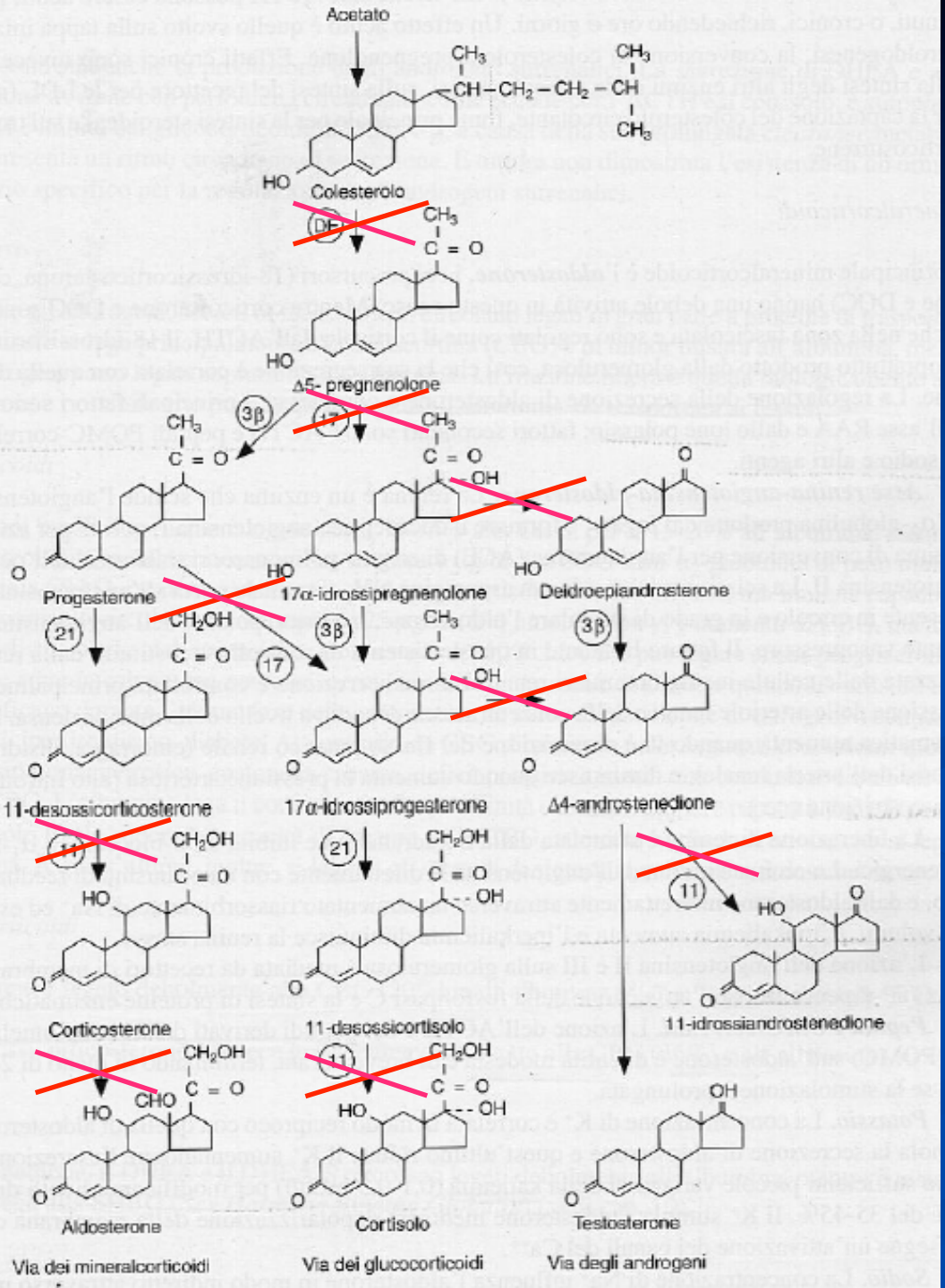
Roma,
9-11 novembre 2012

Mitotane, Metyrapone, and Ketoconazole Combination Therapy as an Alternative to Rescue Adrenalectomy for Severe ACTH-Dependent Cushing's Syndrome

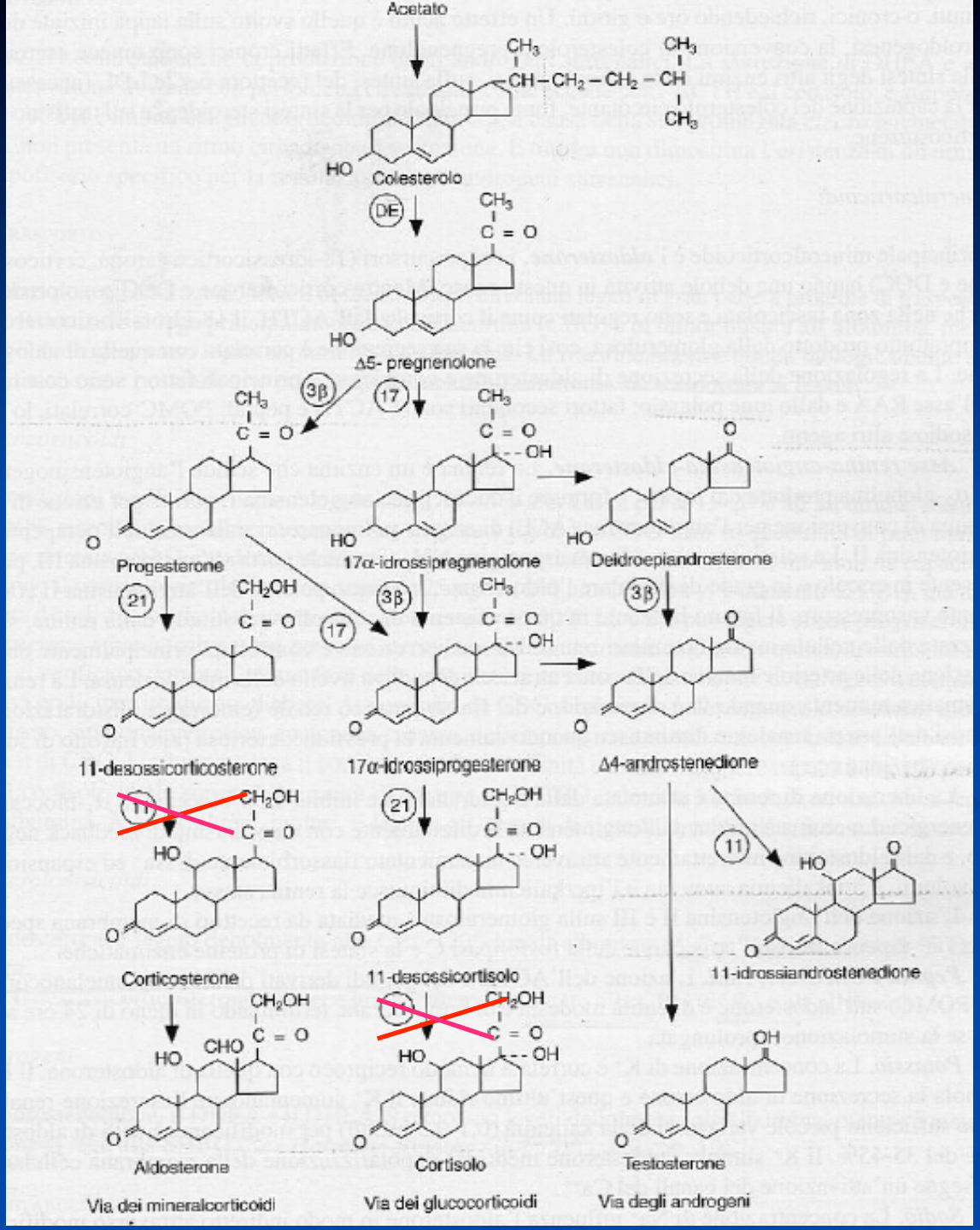
Peter Kamenický, Céline Droumaguet, Sylvie Salenave, Anne Blanchard, Christel Jublanc, Jean-François Gautier, Sylvie Brailly-Tabard, Sophie Leboulleux, Martin Schlumberger, Eric Baudin, Philippe Chanson, and Jacques Young

TABLE 1. Baseline clinical and hormonal parameters

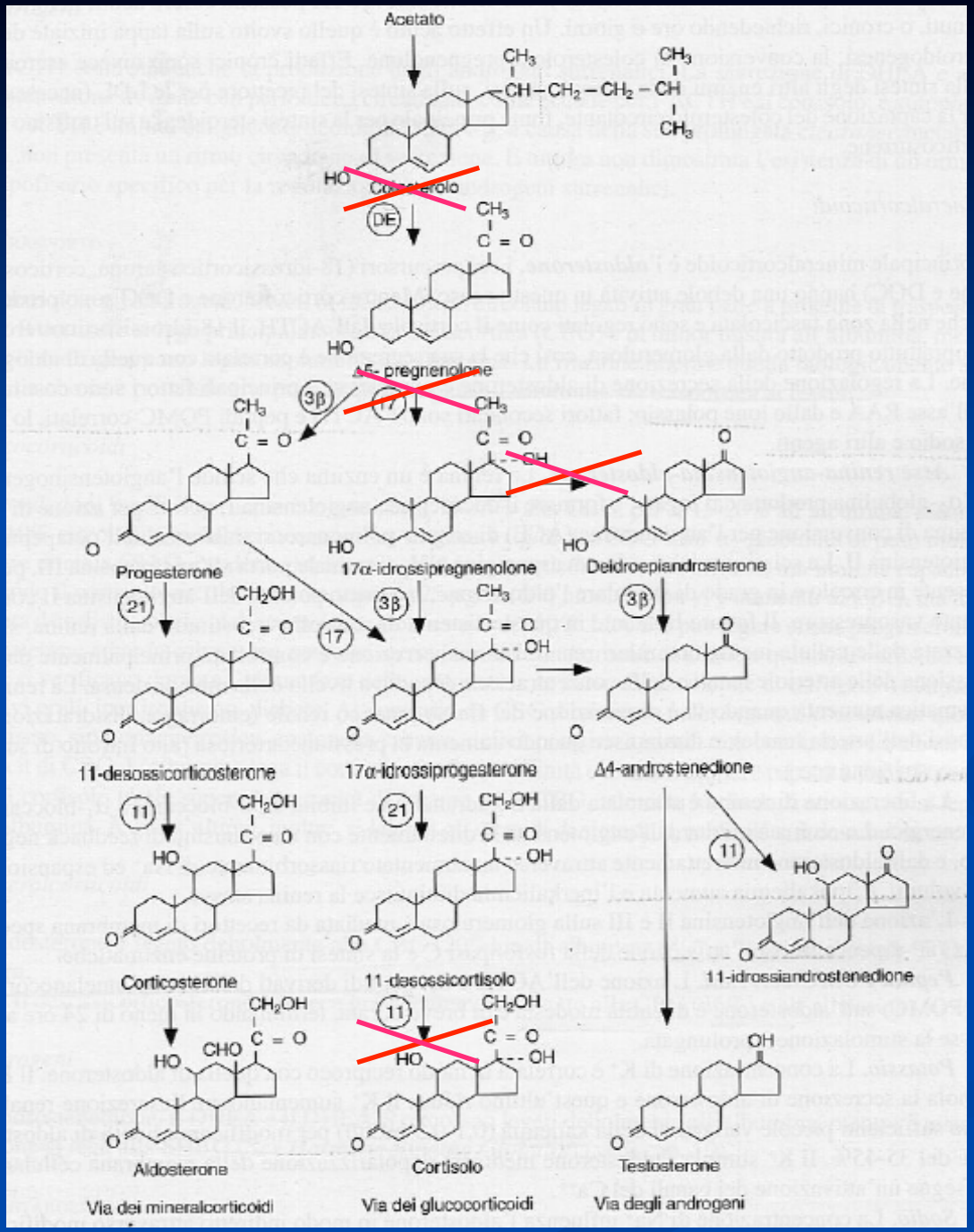
Patient	Age/sex	UFC (μg/24 h)	ACTH (pg/ml)	K (mmol/liter)	Complications
1	17/M	2737	206	2.9	Pulmonary embolism, heart failure
2	46/M	853	102	3.5	Heart failure
3	38/F	3764	250	3.3	Femoral osteonecrosis
4	23/F	1227	59	3.4	Preterm induction of delivery
5	65/F	3190	154	2.8	Pelvic abscesses
6	75/F	1190	140	3.3	Acute respiratory distress
7	29/F	1457	76	3.0	Pulmonary embolism
8	66/F	1150	156	2.8	Pulmonary embolism
9	73/M	5687	1023	3.4	Pulmonary embolism, sepsis
10	46/M	4391	24	2.7	Pneumocystosis, sepsis
11	39/F	22605	653	2.4	Ketoacidosis, pneumonia, herpes zoster



Effects of ketoconazole on steroidogenesis



Effects of metyrapone on steroidogenesis



Effects of mitotane on steroidogenesis

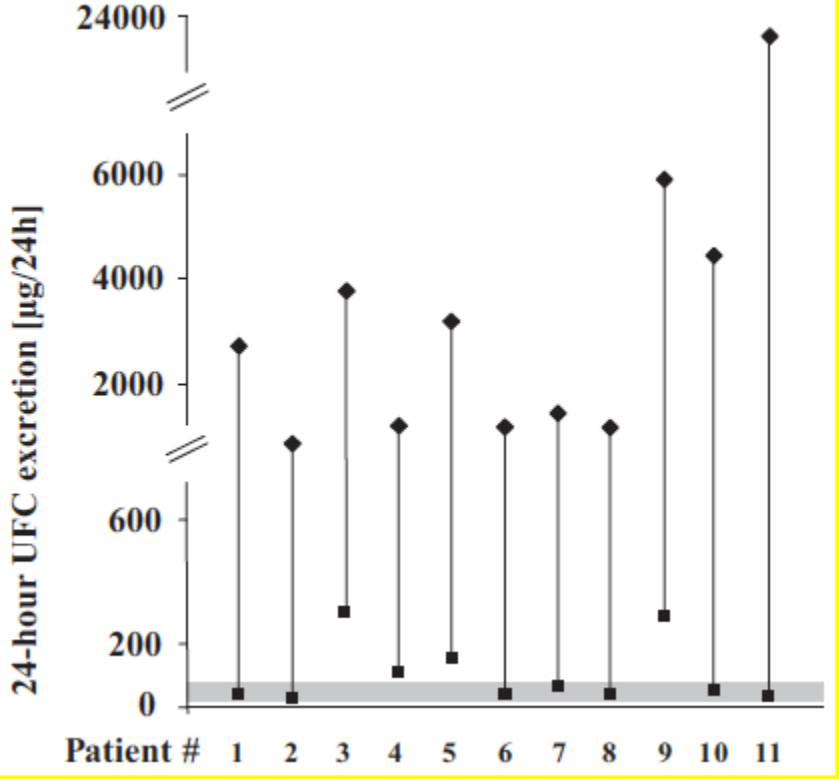
Prospective cohort study

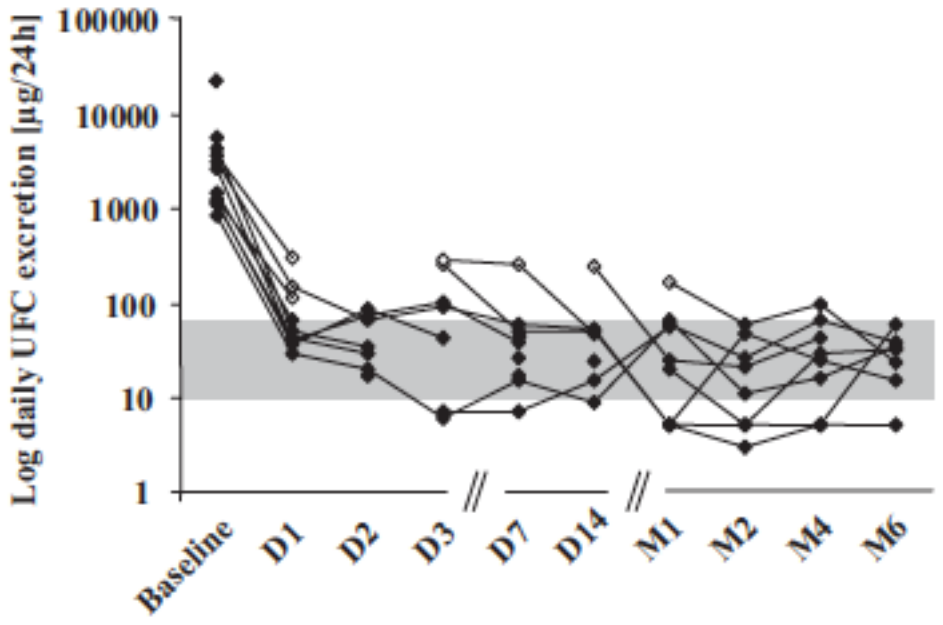
TABLE 2. Etiology of hypercortisolism, duration of treatment, and treatment outcomes

Patient	Etiology	Tumor	Duration of combination therapy (months)	Duration of mitotane monotherapy (months)	Follow-up (months)	Outcome
1	CD	Micro	3.5	27	42	Surgery, remission
2	CD	Micro	3.5	3	14	Surgery, mitotane
3	CD	Micro	3	3	14	Surgery, remission
4	CD	Micro	3	3	25	Surgery, remission
5	EAS?	Occult	6	13	19	Mitotane
6	EAS?	Occult	9		9	Death (respiratory distress)
7	EAS	Occult	4	2	35	Surgery, remission
8	EAS	Metastatic	4	10	14	Death (tumor progression)
9	EAS	Metastatic	1		1	Death (myocardial infarction)
10	EAS	Metastatic	4		4	Death (tumor progression)
11	EAS	Metastatic	1		6	Surgery, remission

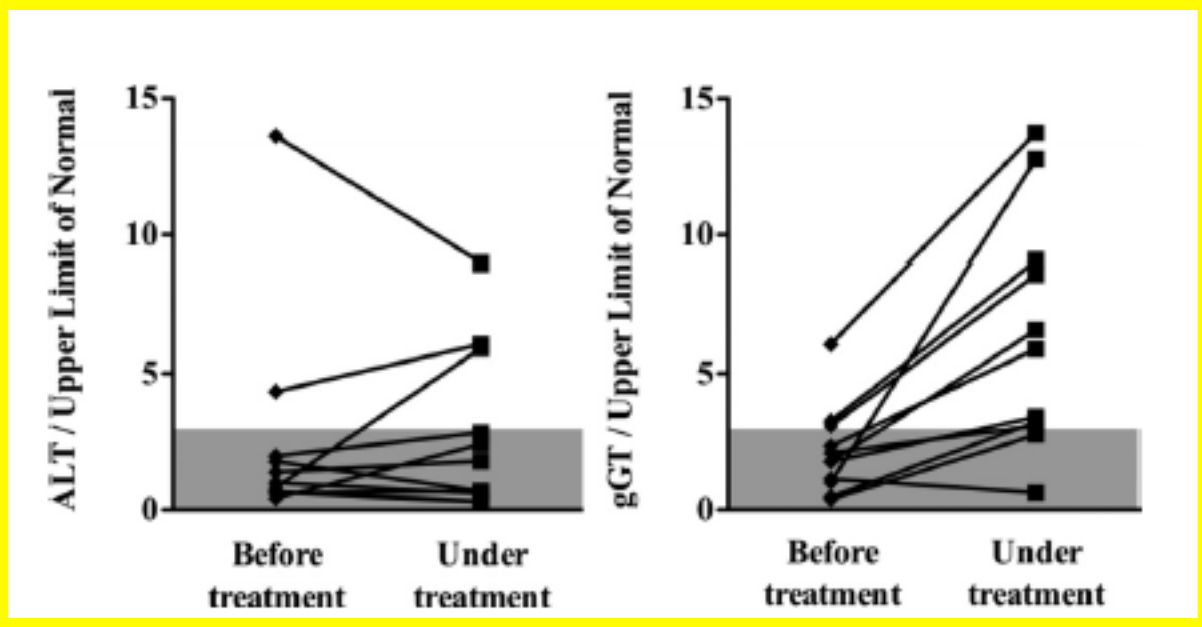
Combination therapy (median doses): metyrapone 3.0 g/d (range 3.0–4.5), ketoconazole 800 mg/d (range 400-1200), and mitotane 3.0 g/d (range 3.0 –5.0). Oral hydrocortisone was also given to prevent iatrogenic adrenal insufficiency.

Prospective cohort study





Prospective cohort study



BW fell significantly from 66 to 63 kg.
SBP fell from 170 to 120 mmHg; DBP fell from 100 to 70 mmHg.
FPG fell from 9.2 to 4.7 mmol/l. HbA1c fell from 6.9% to 5.8%.
Transient GI AEs in 7 patients, dizziness in 1, acute AI in 4.
Initial hypokalemia that improved with treatment.
Median mitotane concentration was 10.1 mg/l.

Retrospective cohort study

Baudry et al., EJE 2012

Table 1. Main characteristics of the 76 patients treated with mitotane, either as a first-line treatment or as a second-line therapy after pituitary surgery.

	First line treatment n=49	Second line treatment n=27
	Baseline Characteristics	
Gender: women/ men	36 (73) / 13 (27)	23 (85) / 4 (15)
Age at diagnostic (years)	39 (14-71)	34 ± 12 (14-61) *
Baseline hormonology		
• Urinary cortisol (µg/24h)	383 (84-3750)	240 (122-1094)*
• Plasma ACTH (pg/ml)	65 (16-2100)	51 (20-216)*
Negative baseline MR imaging	39 (80)	15 (56) *
Indication		
• No pituitary adenoma	39 (80)	-
• Invasive pituitary adenoma	3 (6)	-
• Pituitary surgery failure	-	16 (59)
• Relapse after pituitary surgery	-	9 (33)
• Preparation before surgery	7 (14)	2 (8)
	Treatment characteritics	
Initial daily dose (g/d)	2.7 (0.3-4.5)	2.0 (1.0-8.0)
Treatment duration (months)	6.9 (0.3-114.9)	16.4 (0.8-68.9)
Cumulative dose (g)	543 (43-4435)	1076 (46-5676)*
Mean daily dose (g/d)	2.5 (1.1-4.3)	2.4 (0.9-6.1)

Retrospective cohort study

Table 2. Comparison of hormonal parameters and metabolic outcomes in the 45 patients in whom remission had been obtained,with available data, before and 6 months after mitotane initiation.

Parameter	Before mitotane	Under mitotane	*p value*
Urinary cortisol (µg/24h)	285.5 (104-2457)	44 (7-182)	<0.0001
Post prandial serum glucose (mmol/l)	7.3 (4.6-15.2)	6.3 (5-10.5)	<0.01
Total cholesterol (mmol/l)	5.8 (3.5-8.2)	7.7 (5.1-14)	<0.0001
LDL cholesterol (mmol/l)	3.7 (1.4-5.7)	4.2 (1.9-10.9)	<0.05
HDL cholesterol (mmol/l)	1.6 (0.8-3.1)	1.8 (1.0-3.6)	<0.05
Triglycerides (mmol/l)	1.2 (0.4-11.8)	1.6 (0.6-5.5)	<0.01

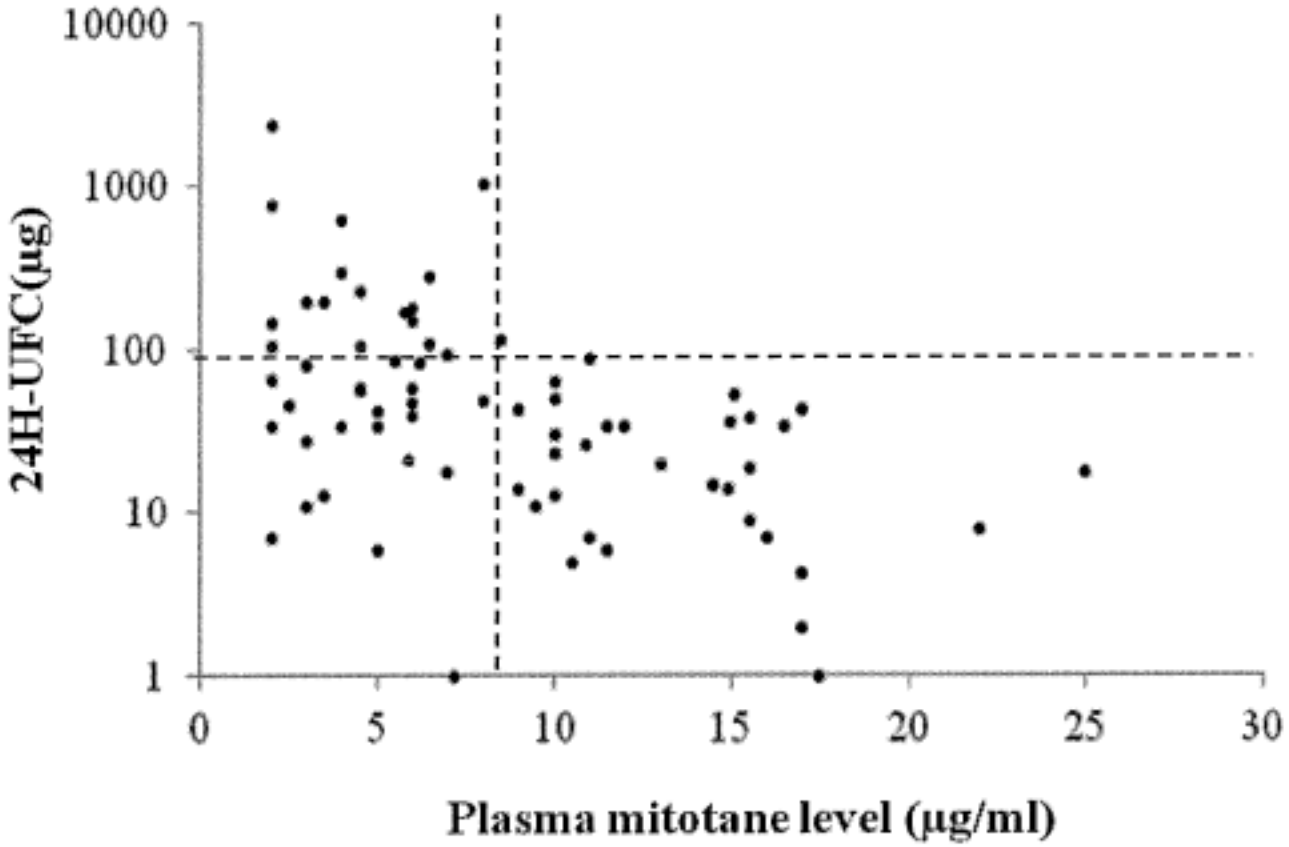
Remission was achieved in 48 (72%) of the 67 after a median time of 6.7 months.
Mean plasma mitotane at the time of remission was 10.5 mg/l with a mean daily dose of 2.6 g.
Intolerance leading to treatment discontinuation occurred in 19 patients (29%).

Retrospective cohort study

Table 3. Main adverse effects observed during mitotane therapy in the 76 patients who received the treatment.

	Mild intolerance	Serious intolerance
Gastro-intestinal signs	36 (47.4%)	5 (6.6%)
Increased transaminases	13 (17.1%)	1 (1.3%)
>ULN	11	
>3x ULN	2	
Increased GGT	36 (47.4%)	
>3xULN	24	
>5xULN	12	
Neurologic signs	23 (30.3%)	6 (9%)
Lipid disorders	54 (71.1%)	
LDL cholesterol > 3.35 mmol/l	15 (19.7%)	
LDL cholesterol > 5.16 mmol/l	19 (25%)	
Triglycerides > 2.28 mmol/l	25 (32.9%)	
Mild neutropenia	5 (6.6%)	
Skin rash	3 (3.9%)	5 (6.6%)
Gynecomastia (men)	3 (17.6%)	

Retrospective cohort study



Retrospective cohort study

Valassi et al., EJE 2012

Table 2. Number of patients taking each therapy (KTZ, MTP or KTZ + MTP) in the overall series and in each group

	KTZ (%)	MTP (%)	KTZ + MTP (%)
CO (n = 20)	9 (45)*	6 (30)	5 (25)
PC (n = 12)	0	7 (58)†	5 (42)
NC (n = 30)	8 (27)	10 (33)	12 (40)
Overall (n = 62)	17 (27)	23 (37)	22 (35)

Controlled: Patients achieving either biochemical (normal UFC) or clinical control

Partially controlled: Patients achieving biochemical (normal UFC) control without clinical control

Not controlled: neither biochemical nor clinical control

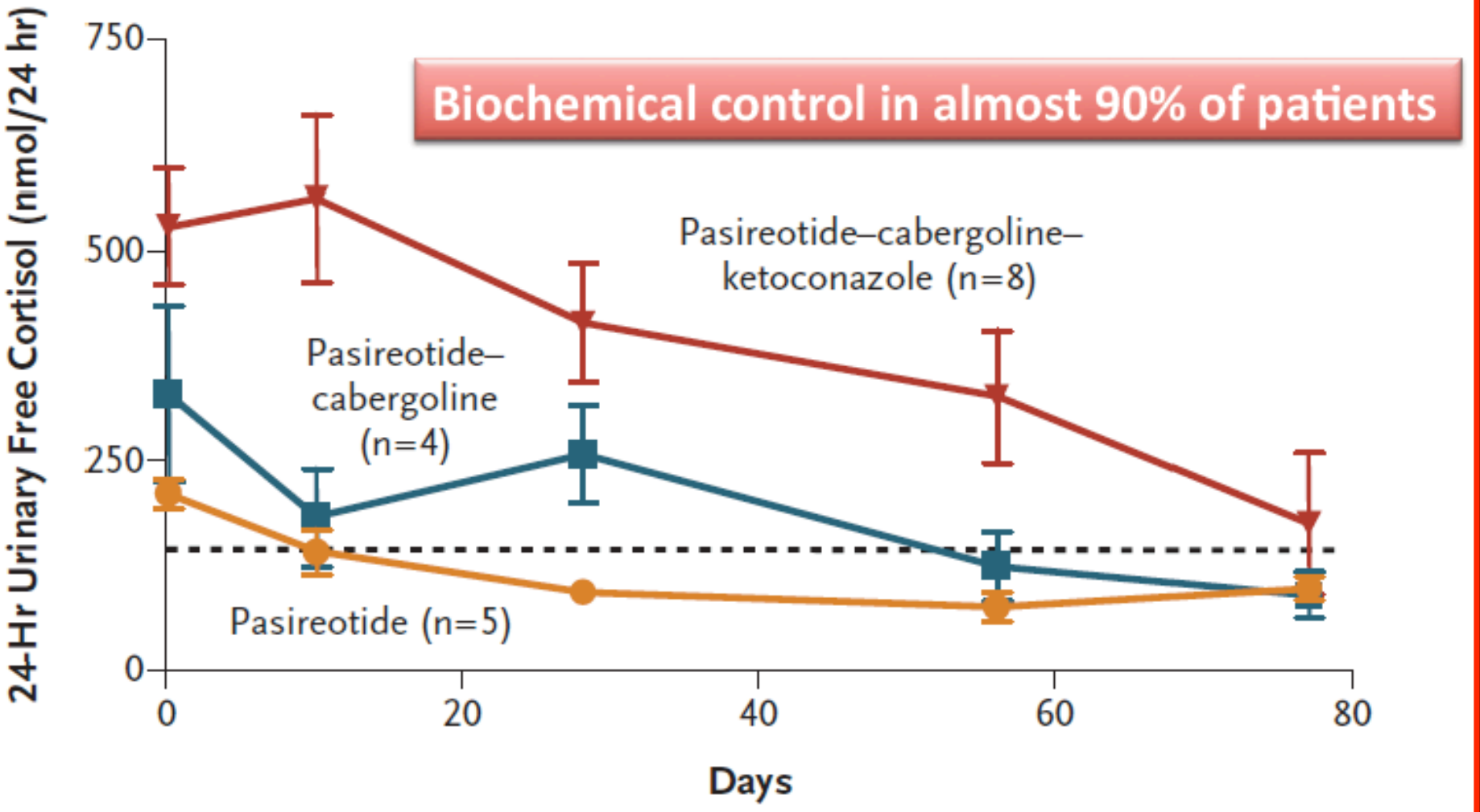
Retrospective cohort study

Table 3. Events occurring in patients with CS during medical treatment with steroidogenesis inhibitors

Event	Mean time of onset (range of days)	Medication	Number of cases
Headache + hypertensive crisis	5	KTZ	1
Skin rash	14	KTZ	1
Exacerbation of previous erythema nodosum	60	KTZ	1
Autoimmune hypothyroidism	60	KTZ	1
Amenorrhoea	73	MTP	1
Obstructive sleep apnoea	270	MTP	1

Preoperative administration of KTZ, MTP or both normalized UFC levels in 52% of 62 patients after a median of 4 months, of whom 20 (63%) also improved clinical features.

Pasireotide alone, or with cabergoline and ketoconazole in Cushing's disease



PASIREOTIDE
-Conclusions-

- Pasireotide is the first drug ever evaluated in a RCT
- Pasireotide is effective (normalization of UFC in about 25%)
- Disease control is usually attained within 3 months
- Pasireotide is associated with significant toxicity (hyperglycemia)
- Pasireotide has an unpleasant way of administration

KETOCONAZOLE & METYRAPONE
-Conclusions-

- These drugs are most known and used even if not approved in Italy for CS
- These drugs are effective (normalization of UFC in about 60%)
- Disease control is usually attained rapidly (within days with MTP)
- These drugs are associated with significant toxicity (liver, HTN)
- These drugs are given orally
- These drugs are not easily available

MITOTANE
-Conclusions-

- Mitotane is approved only for some types of CS
- Mitotane is effective (normalization of UFC in about 70%)
- Disease control is slow but long-lasting
- Mitotane is associated with significant toxicity (GI, liver, CNS)
- Mitotane is given orally
- Mitotane is commercially available

GRAZIE PER L'ATTENZIONE !