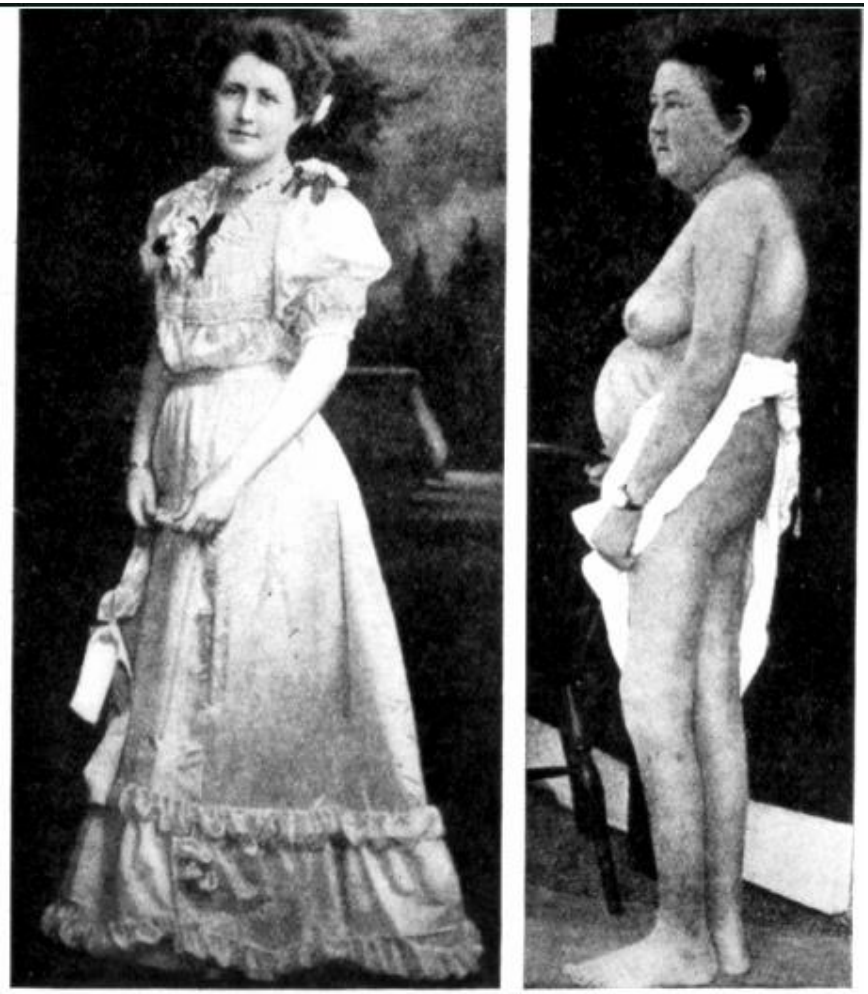
SESSION 3: A PECULIAR ASPECT OF TREATMENT IN CUSHING'S DISEASE: PASIREOTIDE BETWEEN PRESENT AND FUTURE

THE ROLE OF PASIREOTIDE ON CLINICAL PICTURE

Carla Scaroni
Endocrinologia Padova, DIMED
carla.scaroni@unipd.it

Sindrome di Cushing



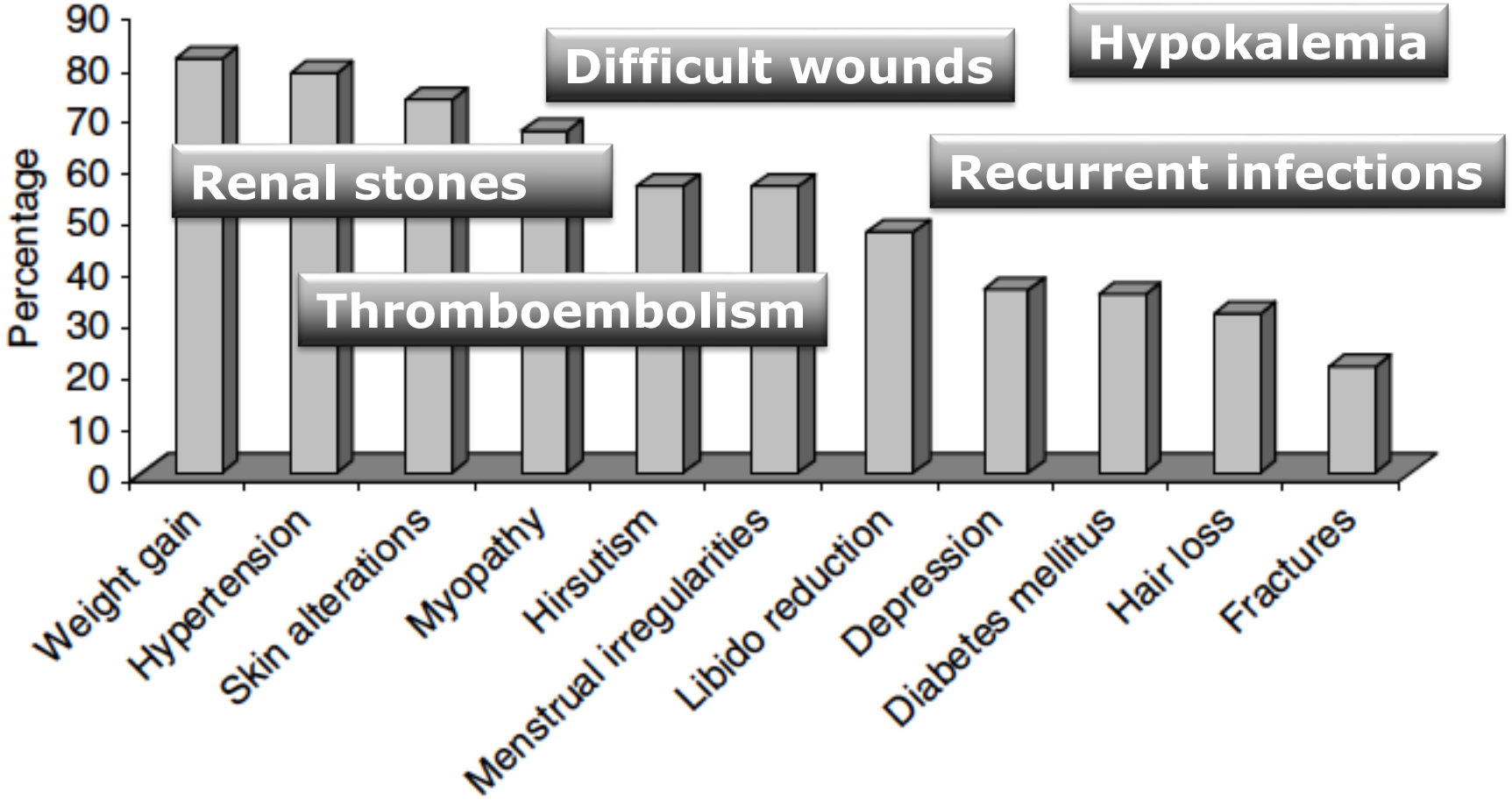
FIGS. 6 AND 7. Dr. Turney's patient at the age of 20 and five years later (1913) at the height of the disorder.

- Multiple eziologie
- Variabile presentazione clinica
- Diagnosi complessa
- Multiple complicanze
- Prognosi sfavorevole
- Difficoltà terapeutiche
- Follow-up a lungo termine

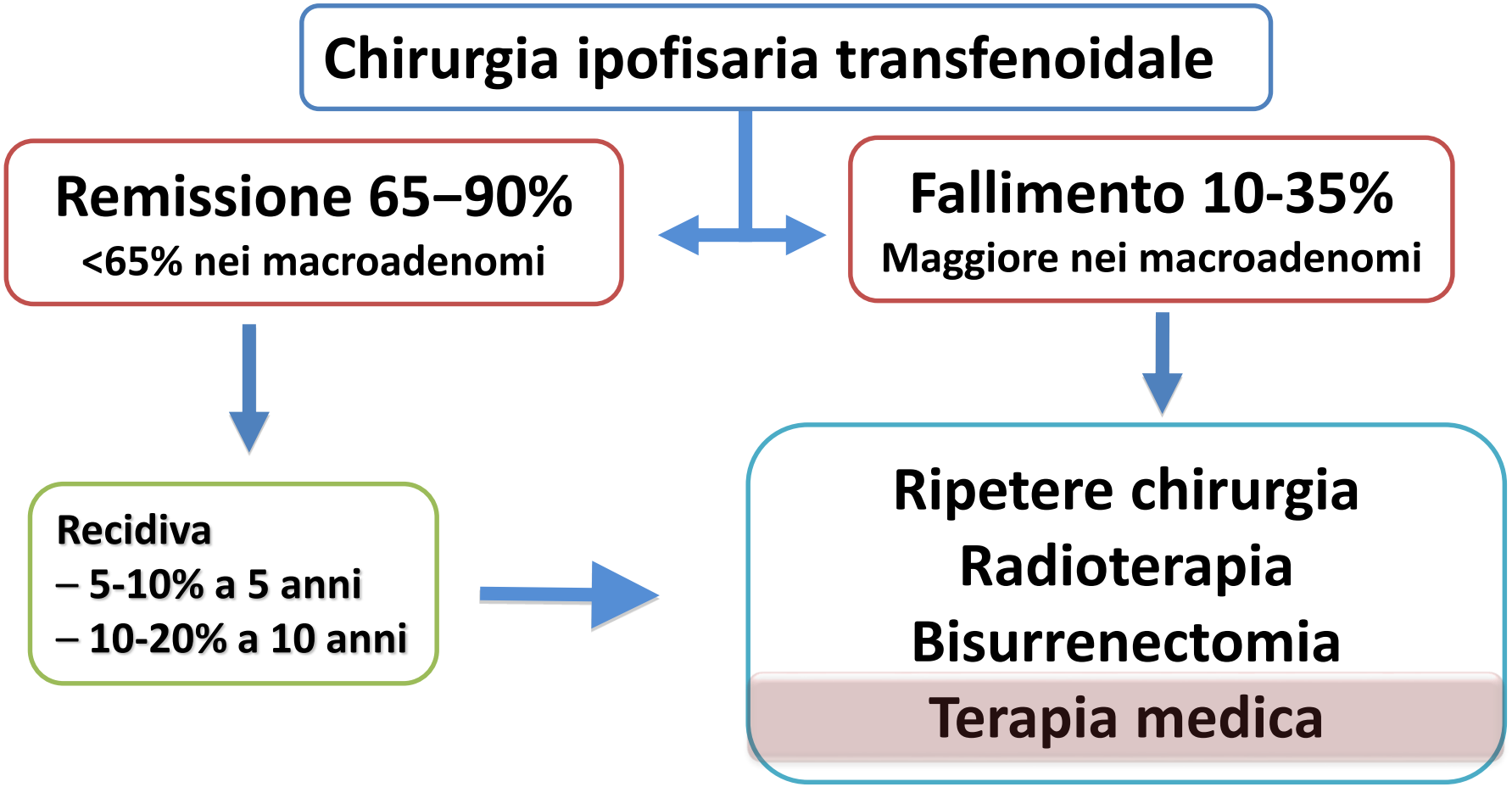
The European Registry on Cushing's syndrome: 2-year experience. Baseline demographic and clinical characteristics

Elena Valassi, Alicia Santos, Maria Yaneva[1], Miklós Tóth[2], Christian J Strasburger[3], Philippe Chanson[4,5,6], John A H Wass[7], Olivier Chabre[8], Marija Pfeifer[9], Richard A Feelders[10], Stylianos Tsagarakis[11], Peter J Trainer[12], Holger Franz[13], Kathrin Zopf[3], Sabina Zacharieva[1], Steven W J Lamberts[10], Antoine Tabarin[14], Susan M Webb and on behalf of The ERCUSYN Study Group

European Journal of Endocrinology 165 383–392



Treatment of Adrenocorticotropin-Dependent Cushing's Syndrome: A Consensus Statement



Biller B.M.K. et al., JCE&M 2008

Terapia medica nella Malattia di Cushing

In pazienti non candidabili alla chirurgia

Quando

Prima

In preparazione alla chirurgia (specialmente in pazienti con diabete, ipertensione e severa coagulopatia)

Prima della bisurrenectomia

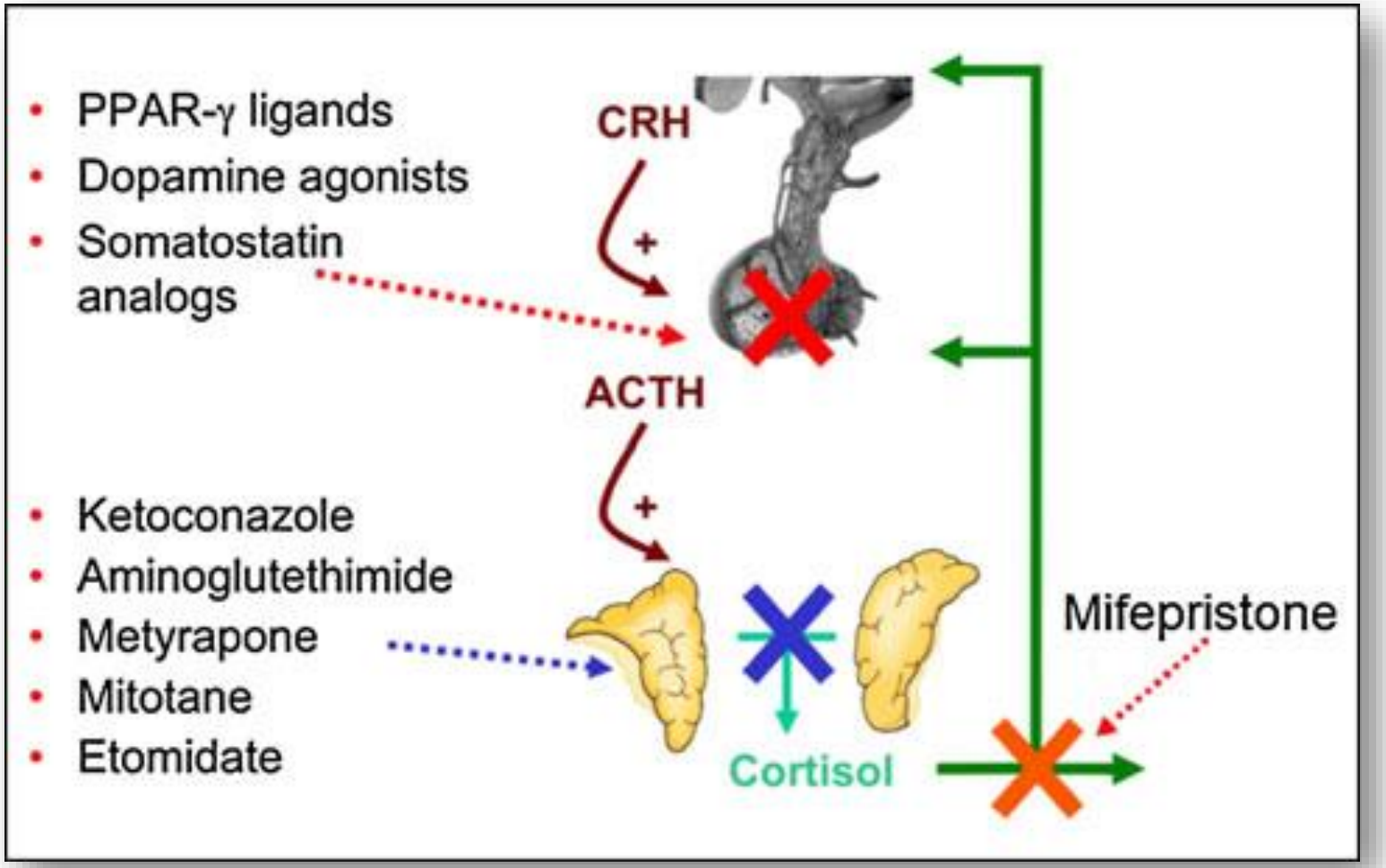
Dopo

Dopo fallimento della chirurgia ipofisaria

Nelle recidive dopo chirurgia ipofisaria

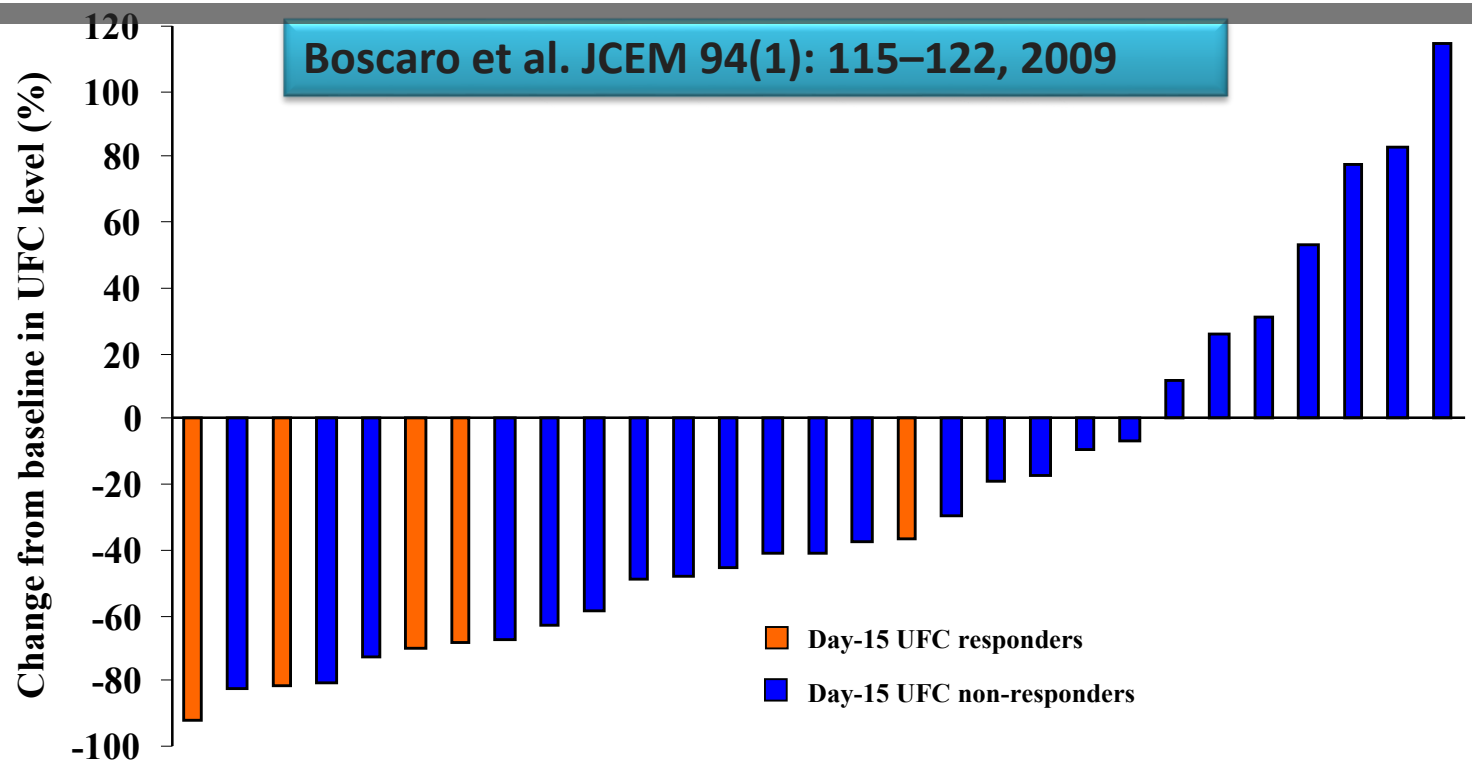
Dopo la radioterapia

Malattia di Cushing: Quale farmaco ?



Fleseriu M. & Petersenn S., Pituitary 2012

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



Dopo 15 giorni di trattamento con pasireotide 600 mcg bid sc (n=29)

- 76% (22/29) dei pazienti ha ridotto i livelli di cortisoluria
- 17% (5/29) dei pazienti ha normalizzato i livelli di cortisoluria
- La media dei livelli di CLU si è ridotta del 44.5% rispetto al baseline (p = 0.021)

Extended treatment of Cushing's disease with pasireotide: results from a 2-year, Phase II study

M. Boscaro · J. Bertherat · J. Findling · M. Fleseriu · A. B. Atkinson · S. Petersenn · J. Schopohl · P. Snyder · G. Hughes · A. Trovato · K. Hu · M. Maldonado · B. M. K. Biller

I patienti con malattia di Cushing che hanno **completato la fase core dello studio** sono stati considerati idonei ad **entrare nella fase di estensione** se:

- presentavano normali livelii di CLU alla fine della fase core, oppure
- avevano ottenuto un significativo beneficio clinico col pasireotide

Dei 38 pazienti che hanno completato la fase core, 19 sono entrati nell'estensione e 18 sono stati inclusi nell'analisi di efficacia

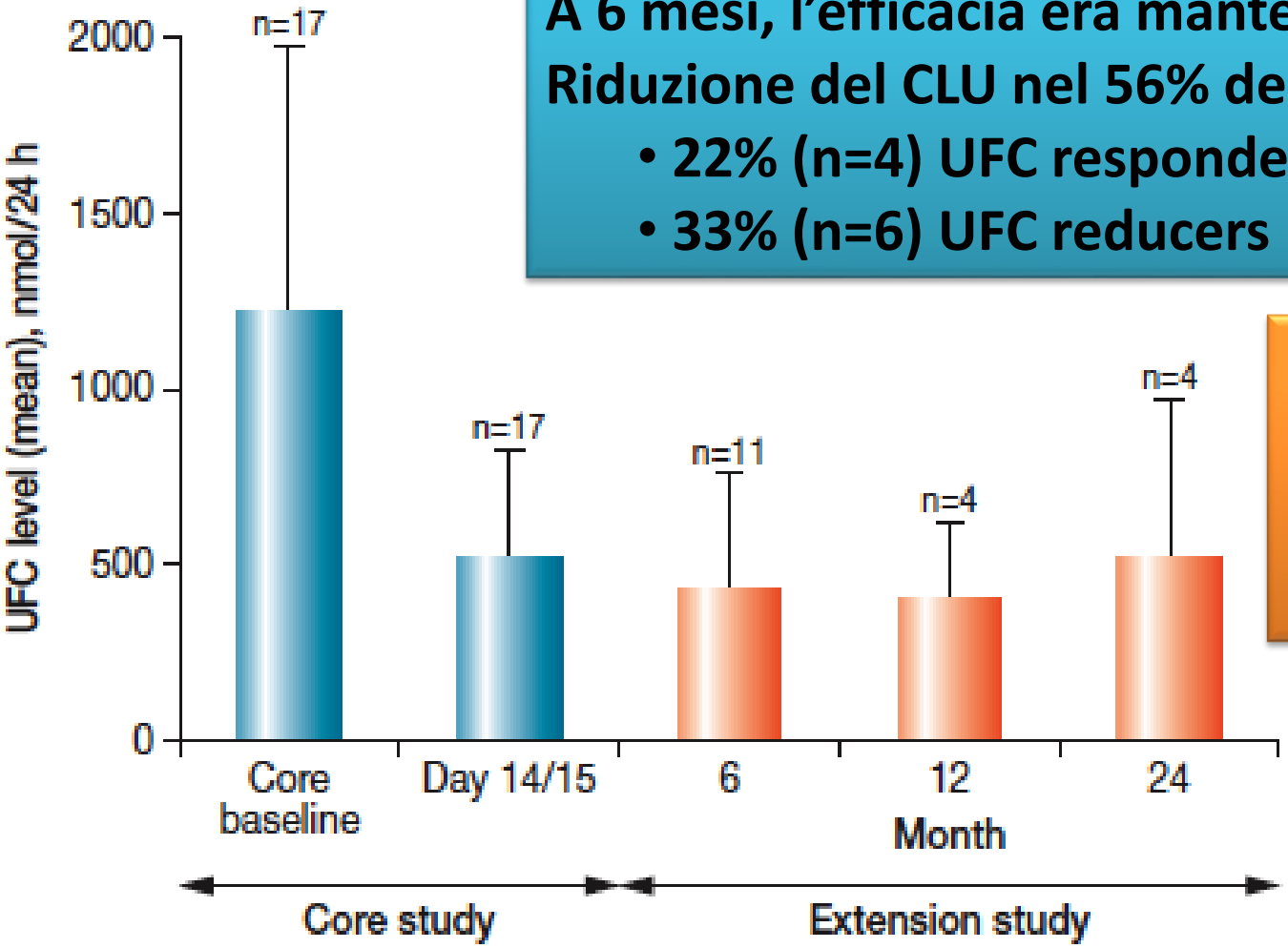
Tutti i pazienti hanno iniziato la fase di estensione con **pasireotide 600 µg sc bid**. Durata di trattamento: da 2 mesi a 4.8 anni (mediana 16 mesi).

Boscaro et al., Pituitary 2014

Extended treatment of Cushing's disease with pasireotide: results from a 2-year, Phase II study

A 6 mesi, l'efficacia era mantenuta:
Riduzione del CLU nel 56% dei pazienti (10/18)

- **22% (n=4) UFC responders**
- **33% (n=6) UFC reducers**



Miglioramento clinico:
- Peso corporeo – 7%
- Pressione arteriosa diastolica – 7.4% al 6° mese

Boscaro et al., Pituitary 2014

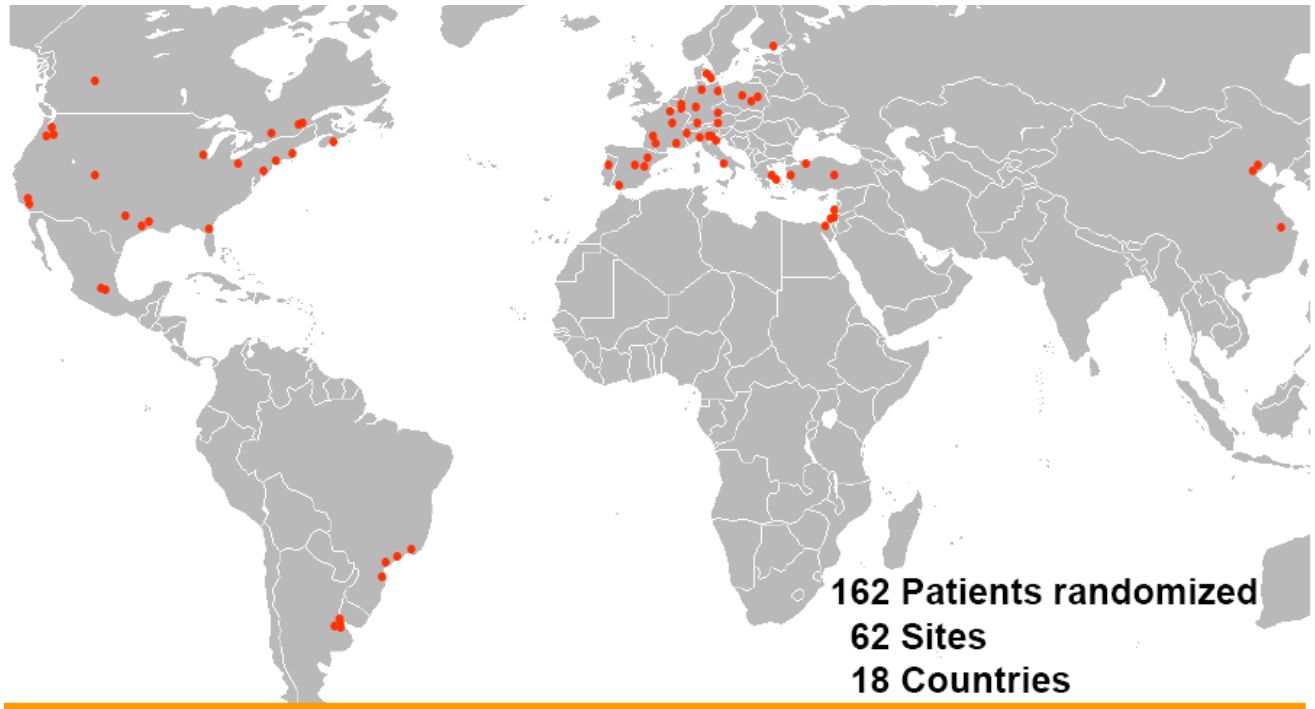
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

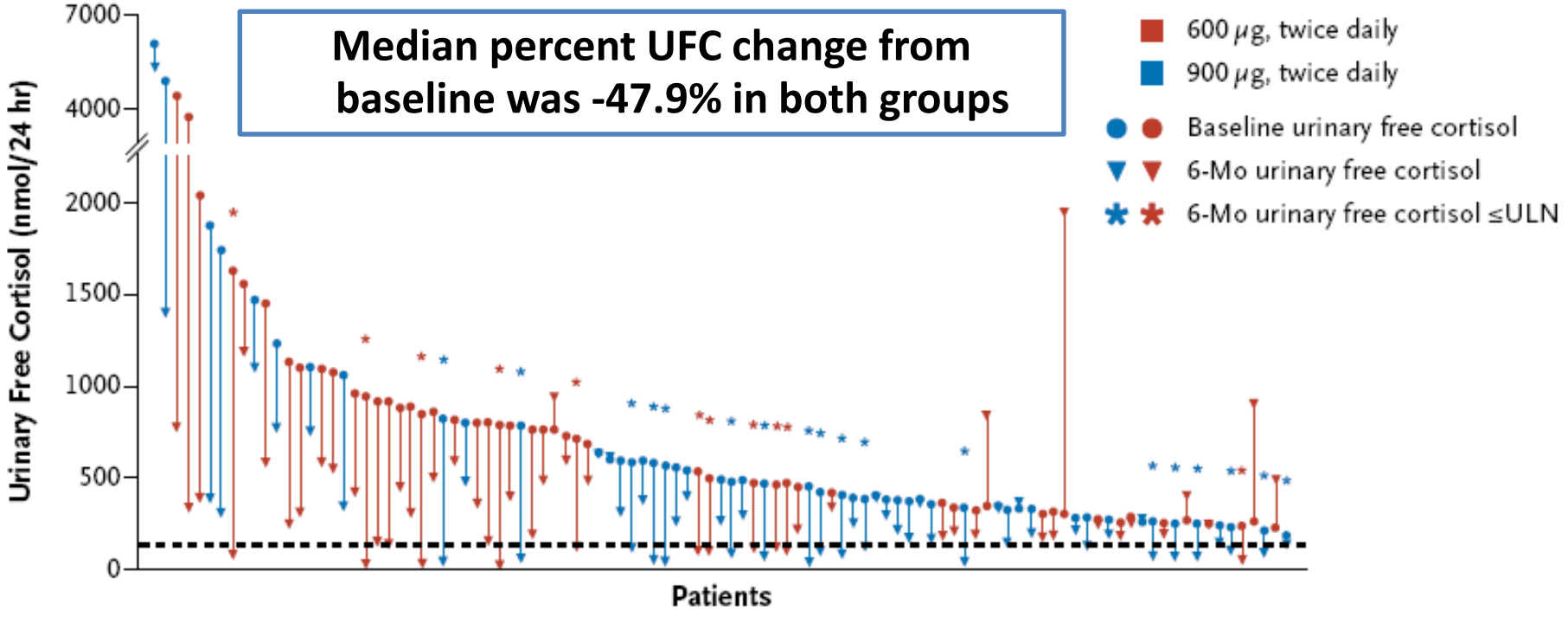
Annamaria Colao, M.D., Ph.D., Stephan Petersenn, M.D., John Newell-Price, M.D., Ph.D., James W. Findling, M.D., Feng Gu, M.D., Mario Maldonado, M.D., Ulrike Schoenherr, Dipl.-Biol., David Mills, M.Sc., Luiz Roberto Salgado, M.D., and Beverly M.K. Biller, M.D. for the Pasireotide B2305 Study Group

N Engl J Med 2012; 366:914-924 | March 8, 2012



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

Colao et al. N Engl J Med 366: 914–24, 2012



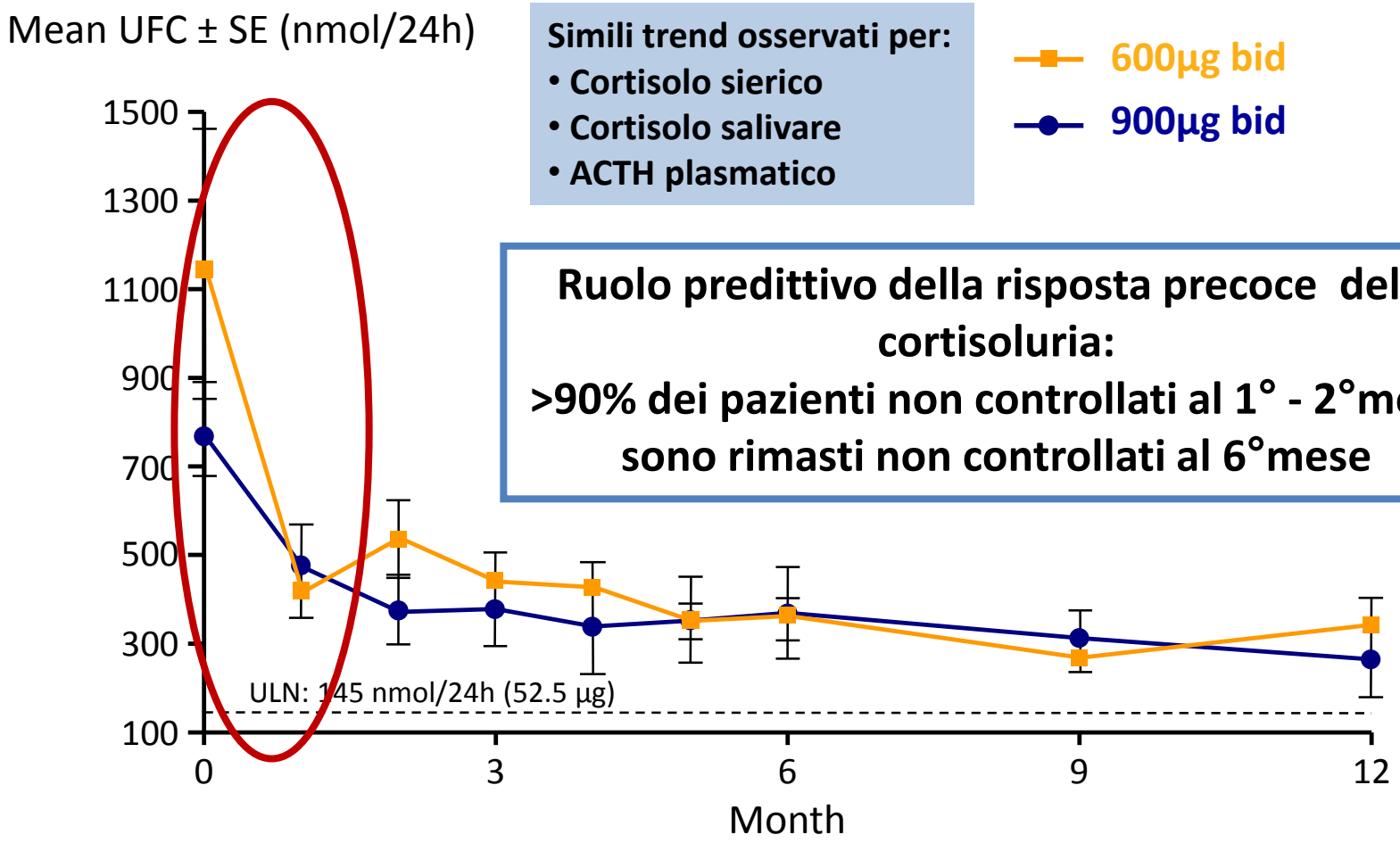
END POINT PRIMARIO (normalizzazione UFC a 6 mesi senza incremento di dose):

- **15% dei pz nel gruppo a 600 mcg bid**
- **26% dei pz nel gruppo a 900 mcg bid**

50/103 : significativa risposta di UFC a 6 mesi (normalizzazione o riduzione ≥ 50% vs baseline)

Valore medio di UFC

Rapida e marcata riduzione mantenuta nel tempo



Simili trend osservati per:
- **Cortisolo sierico**
- **Cortisolo salivare**
- **ACTH plasmatico**

600µg bid

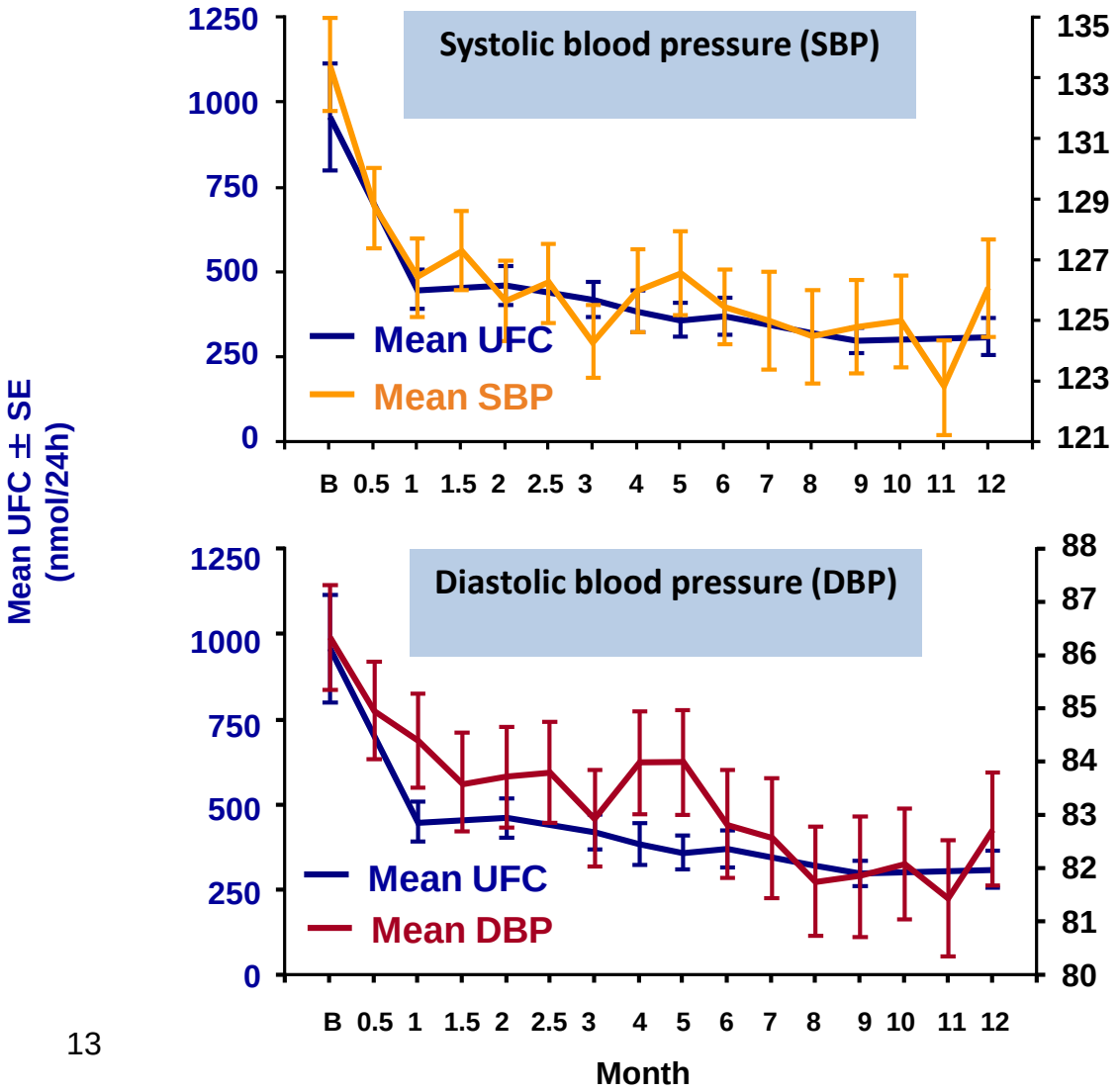
900µg bid

Ruolo predittivo della risposta precoce della cortisoluria:
>90% dei pazienti non controllati al 1° - 2°mese sono rimasti non controllati al 6°mese

Riduzione statisticamente significativa (p<0.001) rispetto al baseline al 6 °e al 12°mese per entrambi i dosaggi

Colao et al. N Engl J Med 2012

Miglioramento biochimico e clinico - Andamento di UFC e valori pressori nel tempo



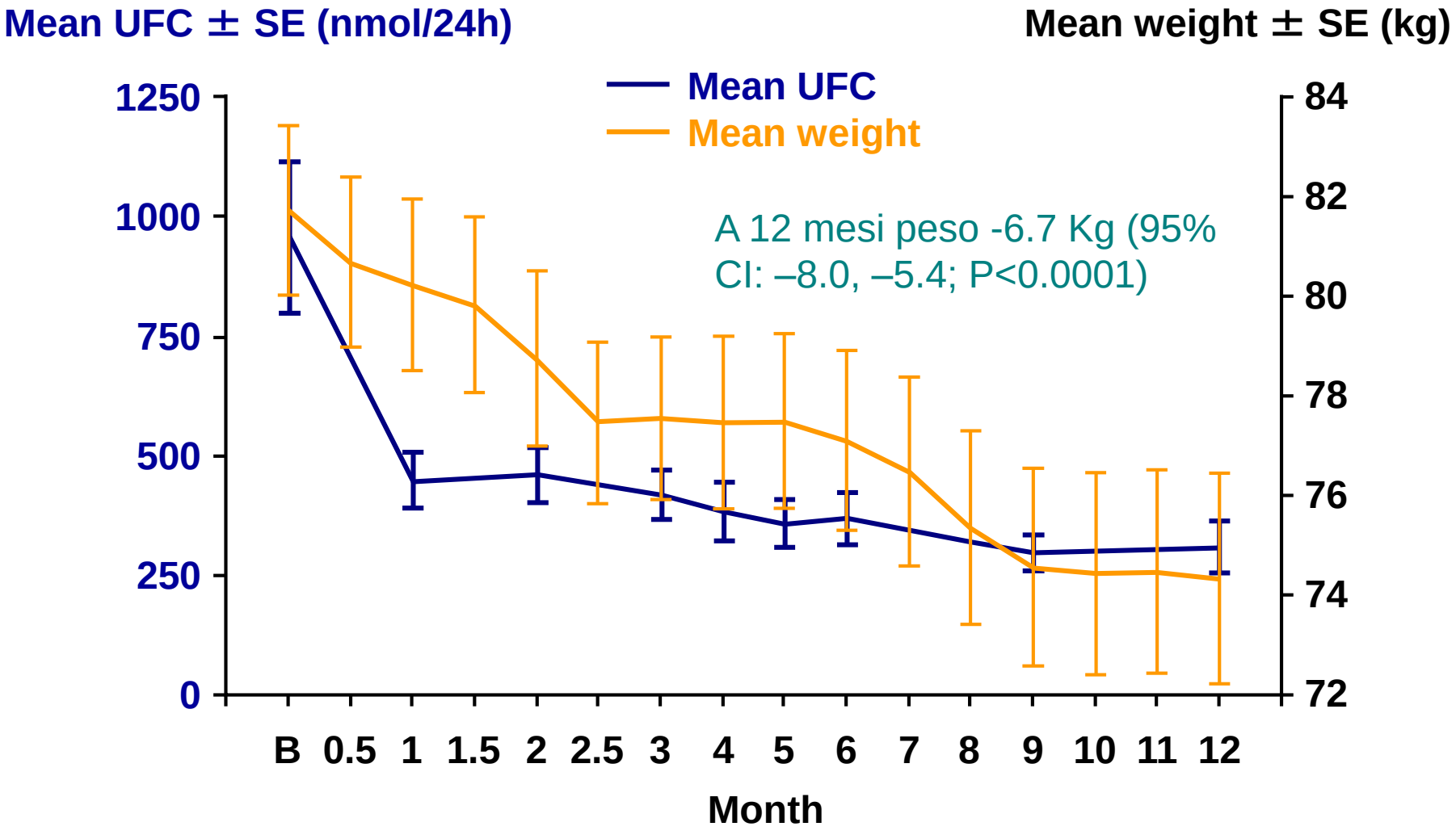
Un cambiamento significativo dal baseline al mese 12 è stato osservato per:

PA sistolica -6.1 mmHg (95% CI: -9.8, -2.4)

PA diastolica -3.7 mmHg (95% CI: -6.2, -1.2)

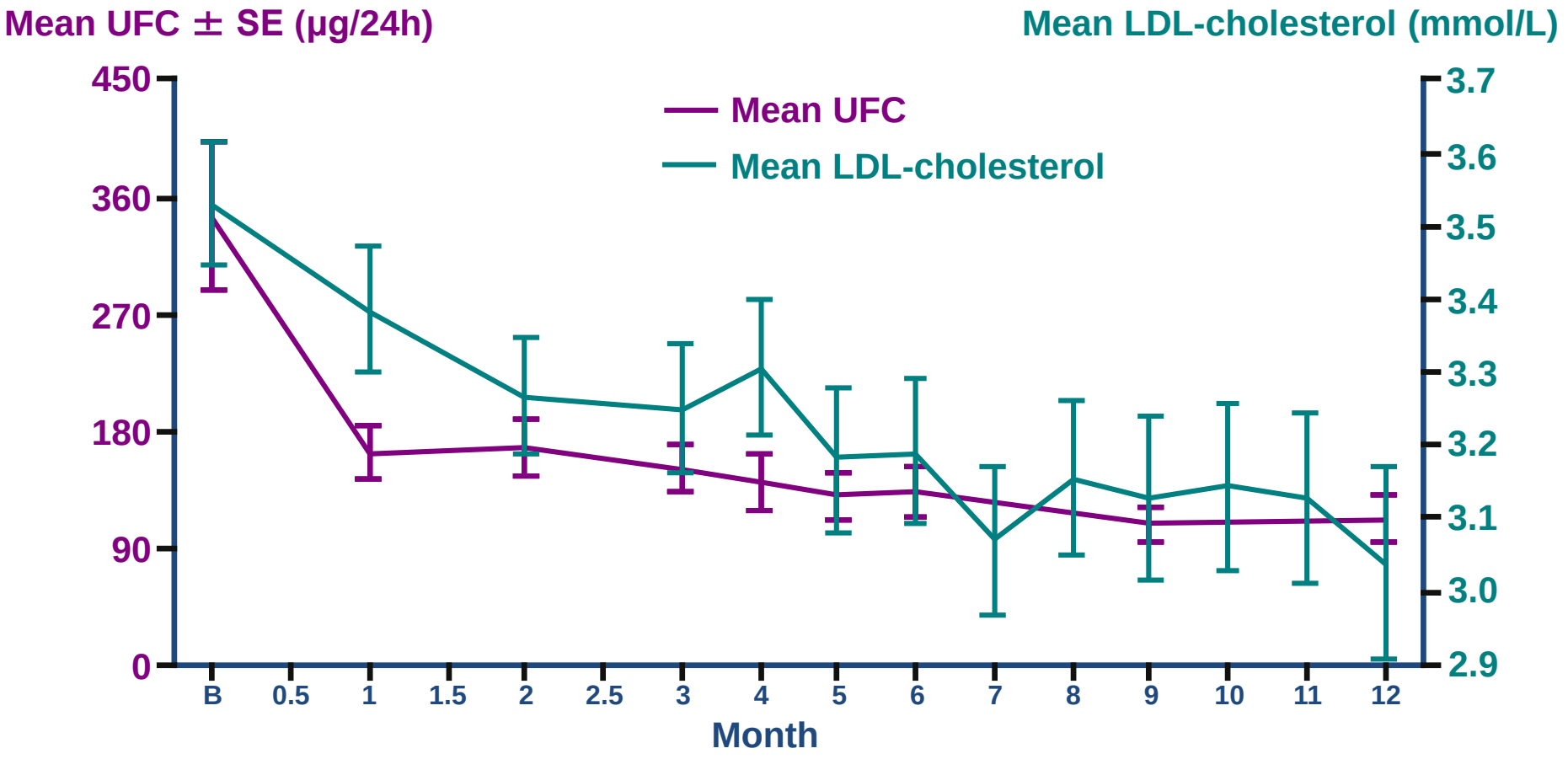
Colao et al., N Engl J Med 2012

Miglioramento biochimico e clinico - Andamento di UFC e peso corporeo nel tempo



Miglioramento biochimico e clinico - Andamento di UFC e colesterolo LDL nel tempo

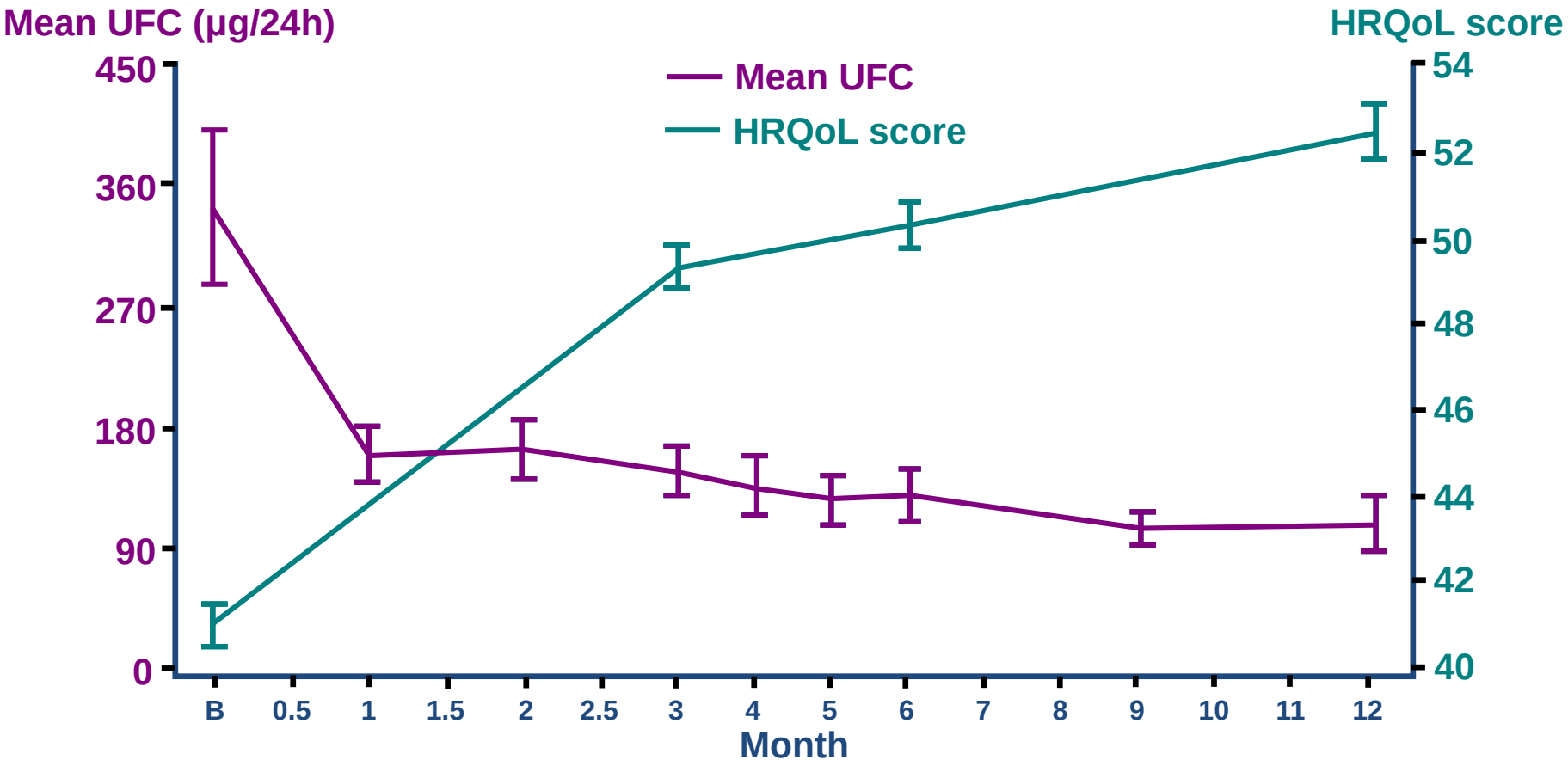
Significativa riduzione del colesterolo LDL di 0.4 mmol/L dal baseline al mese 12 (95% CI:-0.6, -0.2)



Miglioramento biochimico e clinico - Andamento di HRQoL e UFC nel tempo

Misurato tramite CushingQoL (Webb *et al. Eur J Endocrinol* 2008;158(5):623–30)

Significativo miglioramento (11.1 punti) dal baseline al mese 12 (95% CI: 6.8, 15.5)



Miglioramento dei segni clinici di ipercorticismo

Dopo 12 mesi di trattamento, un'elevata proporzione di pazienti presentava anche miglioramenti nei segni cinici della malattia di Cushing

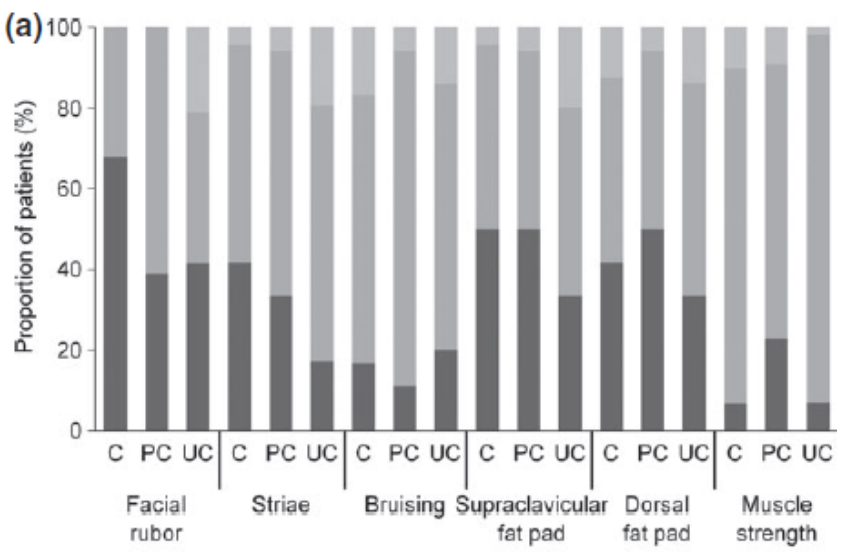
	Percentuale di pazienti con miglioramento (%)	
	600 µg BID	900 µg BID
Rubeosi facciale	40.0	61.8
Strie	25.7	33.3
Ecchimosi	29.4	28.1
Cuscinetti adiposi sopraclaviculari	51.4	57.6
Gibbo nucale	52.9	57.6
Forza muscolare	8.1	10.5

Colao A et al. N Engl J Med 2012;366:914–924

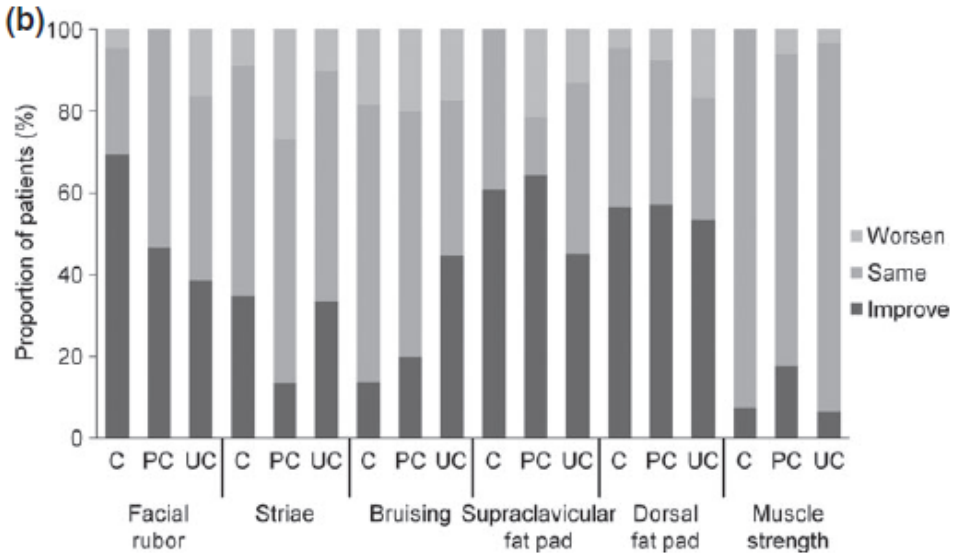
Pasireotide treatment significantly improves clinical signs and symptoms in patients with Cushing's disease: results from a Phase III study

Rosario Pivonello*, Stephan Petersenn†, John Newell-Price‡, James W. Findling§, Feng Gu¶, Mario Maldonado**, Andrew Trovato**, Gareth Hughes††, Luiz R. Salgado‡‡, André Lacroix§§, Jochen Schopohl¶¶ and Beverly M.K. Biller*** on behalf of the Pasireotide B2305 Study Group[1]

6 mesi

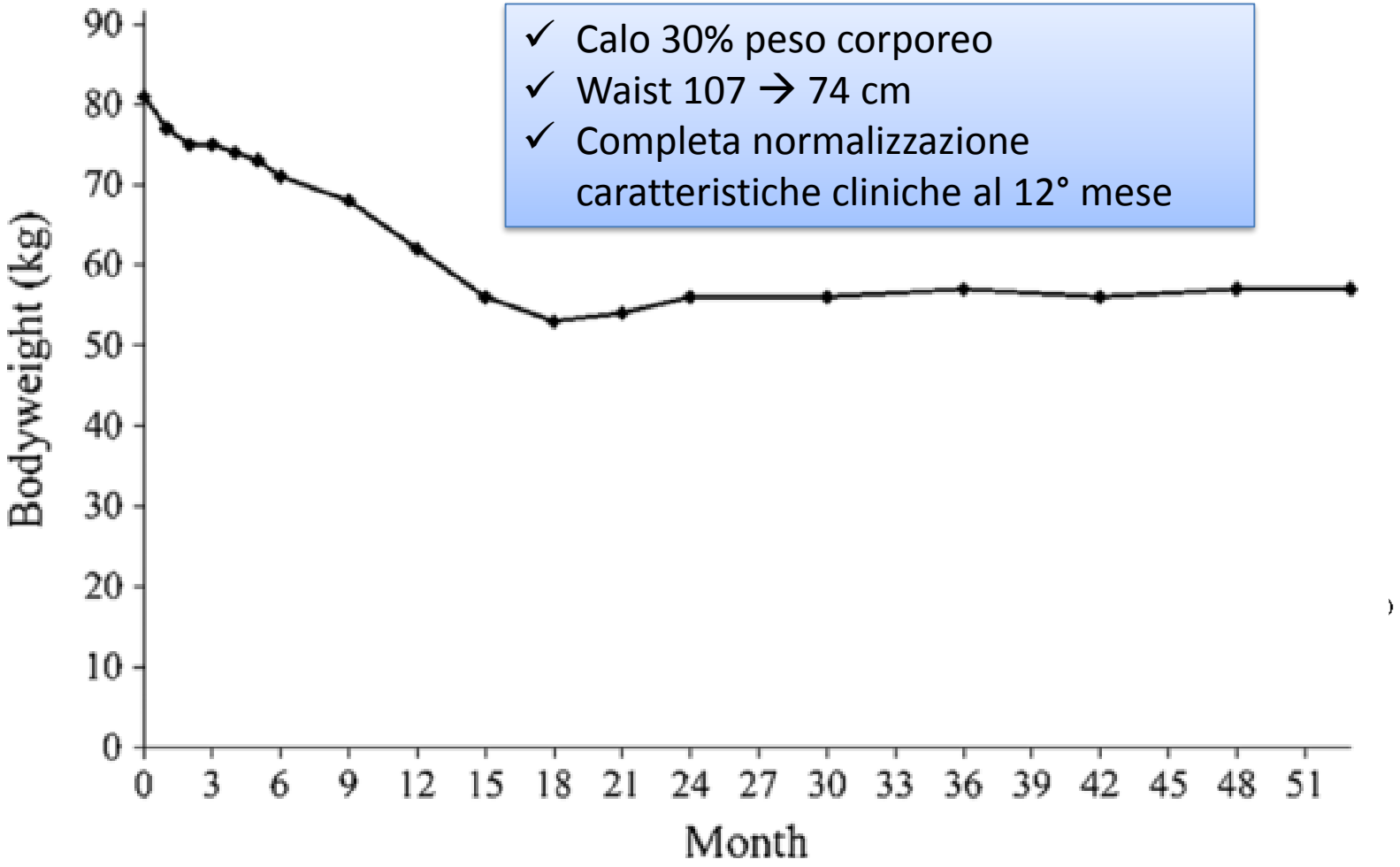


12 mesi



Clinical Endocrinology 2014

Changes in UFC levels and therapy for diabetes mellitus during long-term pasireotide treatment



- ✓ Calo 30% peso corporeo
- ✓ Waist 107 → 74 cm
- ✓ Completa normalizzazione caratteristiche cliniche al 12° mese

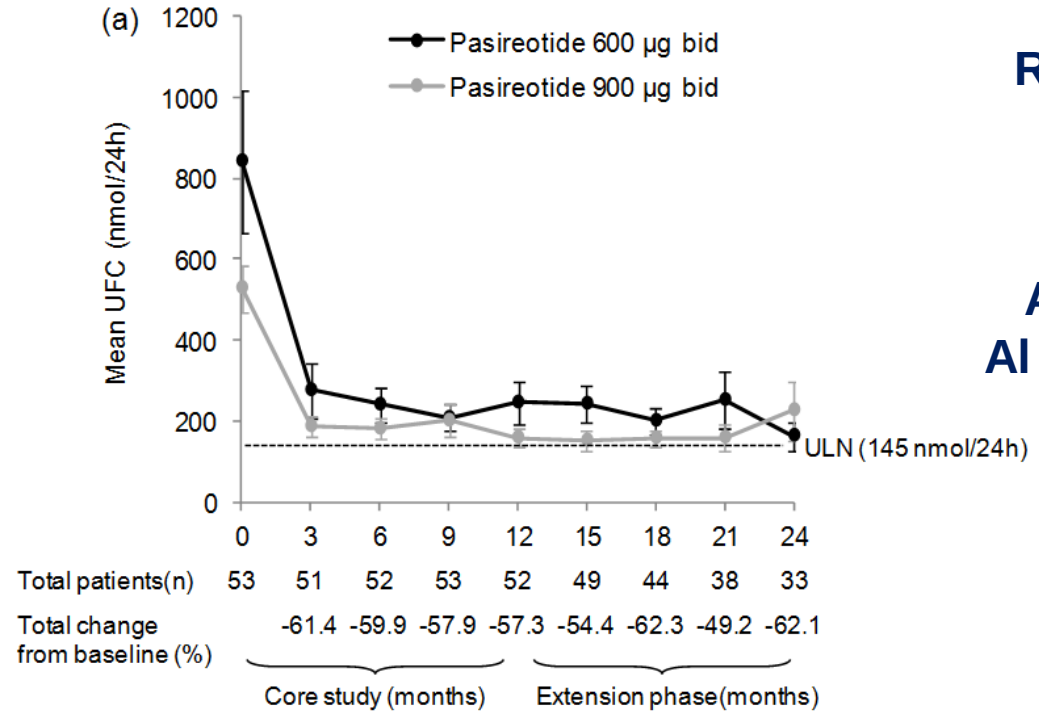
Trementino et al., Pituitary 2014

Pasireotide can induce sustained decreases in urinary cortisol and provide clinical benefit in patients with Cushing's disease: results from an open-ended, open-label extension trial

Jochen Schopohl · Feng Gu · Robert Rubens · Luc Van Gaal · Jérôme Bertherat · Monica Ligueros-Saylan · Andrew Trovato · Gareth Hughes · Luiz R. Salgado · Marco Boscaro · Rosario Pivonello

ESTENSIONE STUDIO di FASE III

58 pz che al termine dello studio core di 12 mesi avevano UCF normalizzato o significativo beneficio clinico sono stati inclusi nella fase di estensione
→ ulteriori 12 mesi per valutare l'efficacia fino a 24 mesi di trattamento
40/58 pz hanno completato i 24 mesi di terapia



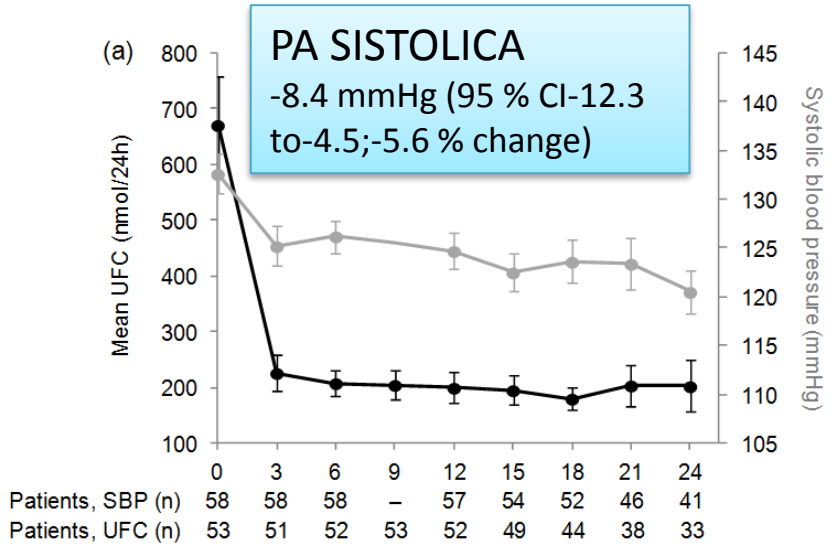
Riduzione media UFC rispetto al core baseline:
- 57.3% a 12 mesi, - 62,1% a 24 mesi

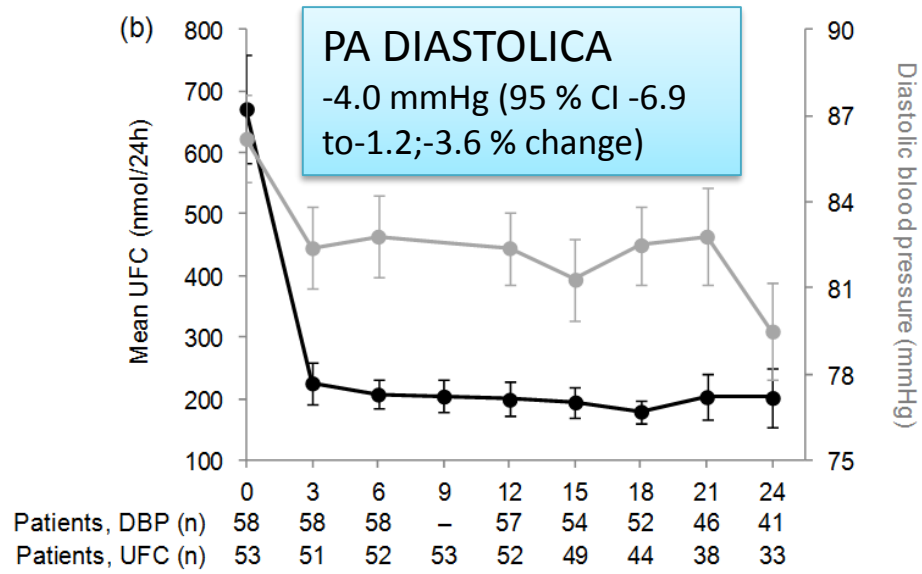
Al mese 12: 29/58 pz (50%) controllati
Al mese 24: 20/58 pz (34.5%) controllati (UFC ≤ULN)

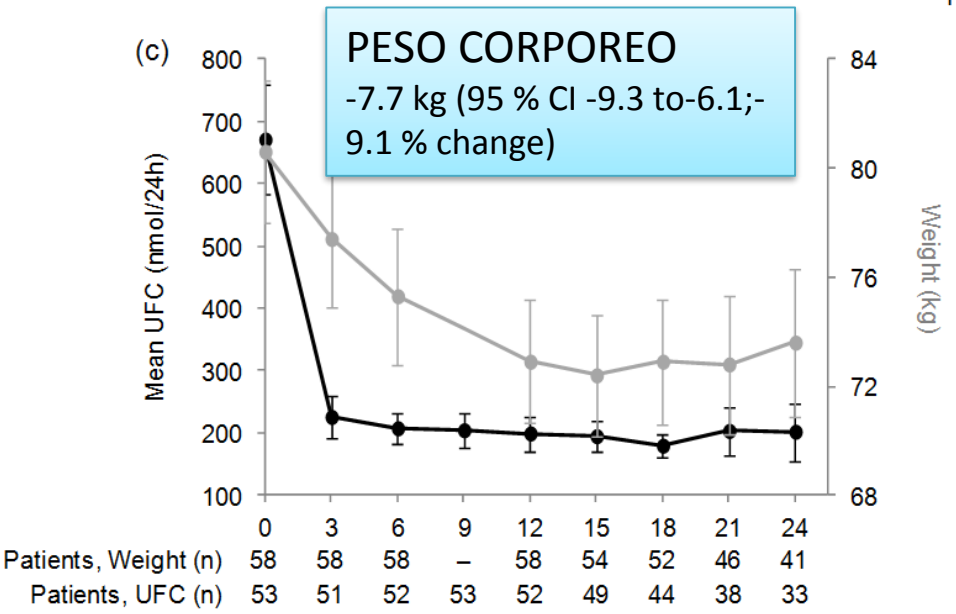
(NB: i pz usciti dallo studio o non valutati a 24° m considerati non controllati)

Pituitary 2014

Sustained decreases in urinary cortisol and clinical benefit may be obtained with pasireotide: results from an open-ended, open-label extension trial







EFFICACIA CLINICA MANTENUTA A 24 MESI

Pituitary 2014

Clinical management of critically ill patients with Cushing's disease due to ACTH-secreting pituitary macroadenomas: effectiveness of presurgical treatment with pasireotide

S. Cannavo[1] · E. Messina[1] · A. Albani[1] · F. Ferrau[1] · V. Barresi[2] · S. Priola[3] · F. Esposito[3] · F. Angileri[3]

	Patient no. 1				Patient no. 2			
		Pasireotide treatment				Pasireotide treatment		
	Baseline	3rd day	7th day	21st day	Baseline	3rd day	7th day	21st day
Plasma ACTH h. 8 (pg/ml)	416	87	26.9	35.2	218	119	125	88
Serum cortisol h. 8 (ng/ml)	553	486	422	375	409	286	242	267
UFC (x ULN)	15.4	–	6.5	7.9	17.1	–	6.4	3.5
Na^+ (mEq/L)	147	140	139	141	148	146	141	143
K^+ (mEq/L)	2.1*,#	3.4#	4.2	3.9	2.4*,#	3.8#	4.4	3.8
Ca^{2+} (mmol/L)	0.6	0.9	1.1	1.1	1.1	1.1	1.2	1.2
P^+ (mg/dL)	2.4	4.5	4.3	4.3	3.1	3.0	3.8	3.5
pH	7.64	7.40	7.42	–	7.48	7.43	7.40	–
pO_2 (mmHg)	53.0	84.2	98.0	–	78.2	84.5	93.4	–
SO_2 (%)	90	94	95	–	94	97	97	–
pCO_2 (mmHg)	46.5	41.2	38.2	–	48.0	35.2	38.0	–
HCO_3^-(mEq/L)	48.7	28.0	27.4	–	36.0	20.4	24.8	–
SBP/DBP (mmHg)	200/110[a]	160/90[a]	140/80[a]	140/90[b]	180/120[c]	150/90[d]	130/80[d]	120/65[d]
FGL (mg/dL)	96[e]	416[e]	219[f]	109[f]	103	164[f]	169[f]	127[f]

* Parenteral potassium supplementation (KCl 80–120 mEq/day) # Oral potassium supplementation (KCl 0.6–1.8 g/day)

[a] On treatment with valsartan (320 mg/day), hydrochlorothiazide (25 mg/day), and doxazosin (4 mg/day)

[b] On treatment with valsartan (320 mg/day), hydrochlorothiazide (25 mg/day), and doxazosin (2 mg/day)

[c] On treatment with canrenone (100 mg/day) and hydrochlorothiazide (25 mg/bid)

[d] On treatment with canrenone (100 mg/day) and nebivolol (5 mg/day)

[e] On treatment with metformin 1000 mg/bid [f] On treatment with basal bolus insulin regimen

Endocrine 2015

La nostra esperienza

9 pz trattati con pasireotide s.c. nell'ambito della legge 648/96

- 6 microadenomi
- 3 macroadenomi

9 PAZIENTI

- 6 pz con persistenza dopo NCH/RT
- 2 pz con recidiva
- 1 pz con macro-adenoma ACTH- silente poi secernente

3 DROP OUT

-1 decesso dopo 1 m per rottura aneurisma aortico
-1 pz STOP dopo 3 m per DM scompensato
- 1 pz STOP dopo 9 m per inefficacia

6 pz in terapia

1 pz follow-up 3 m 600 mcg bid

4 pz follow-up di 12 m

1 pz follow-up-up 24 m 900 mcg bid dal 12^ mese

2 pz 600 mcg bid

2 pz 900 mcg bid dal 9^ m

The role of an acute pasireotide suppression test in predicting response to treatment in patients with Cushing's disease: findings from a pilot study

L. Trementino · M. Zilio · G. Marcelli · G. Michetti · M. Barbot · F. Ceccato · M. Boscaro · C. Scaroni · G. Arnaldi

TEST ACUTO al PASIREOTIDE:
Somministrazione di una singola dose s.c. di 600 mcg di pasireotide alle ore 9:00. Determinazione di cortisolo sierico, ACTH e cortisolo salivare basali e ogni 2 ore per le 8 ore successive alla somministrazione. Determinazione del cortisolo salivare alle ore 23 (LNSC) dello stesso giorno del test.

Pts normalizing LNSC

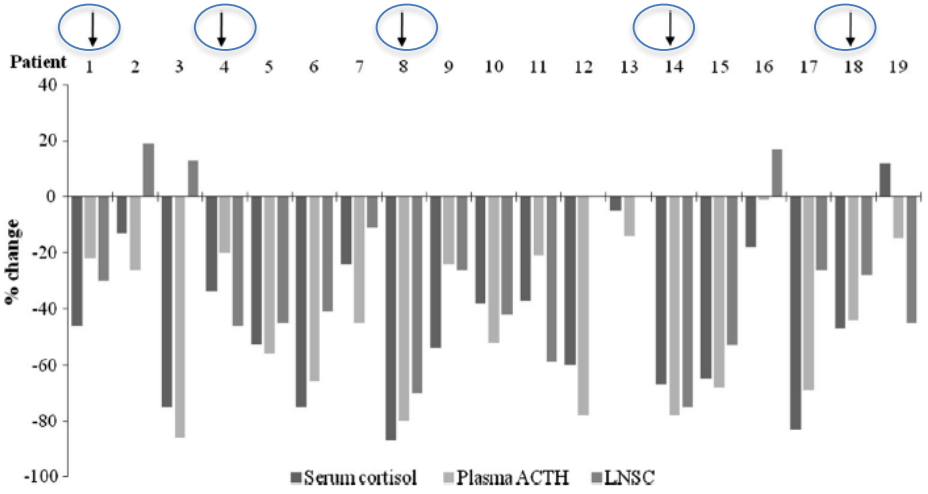


Table 2 Prognostic profiles (%) of various suppression values during acute PST in predicting medium/long-term response to treatment with pasireotide in patients with CD ($n = 16$)

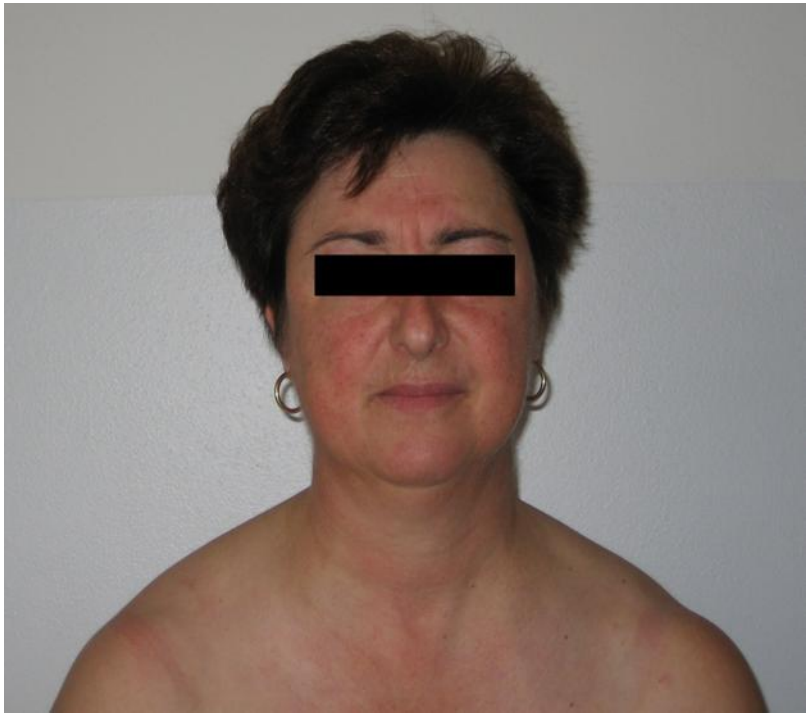
	Serum cortisol fall >28 %	Serum cortisol fall >57 %	Plasma ACTH fall >35 %	Plasma ACTH fall >48 %	LNSC fall >27 %
SE	92	46	69	61	91
SP	75	100	75	100	100
PPV	92	100	100	100	100
NPV	66	30	42	37	75

Endocrine 2014

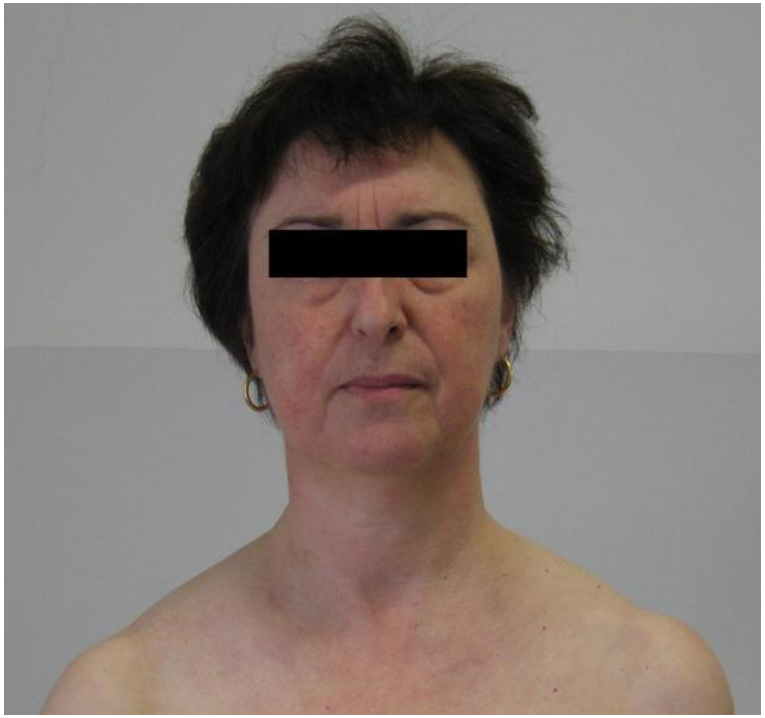
La nostra esperienza

	2 MESI	3 MESI	6 MESI	9 MESI	12 MESI	24 MESI
N° PZ	8	8	6	6	5	1
NORMALIZZAZIONE UFC	5 (62%)	8 (100%)	4 (67%)	3 (50%)	4 (80%)	1 (100%)
RISPOSTA PARZIALE UFC	2 (25%)	0	2 (33%)	2 (33%)	1 (20%)	0
RISPOSTA ASSENTE UFC	1	0	0	1	0	0
NORMALIZZAZIONE LNSC	2 (25%)	2 (25%)	3 (50%)	2 (33%)	4 (80%)	1 (100%)
AUMENTO DOSE	1	0	0	2	1	0
DROP OUT	1 (decesso)	-	1 (iperglicemia)	-	1 (inefficacia)	-
Follow-up non ancora raggiunto	0	0	1	1	1	5

MARINA, 51 anni

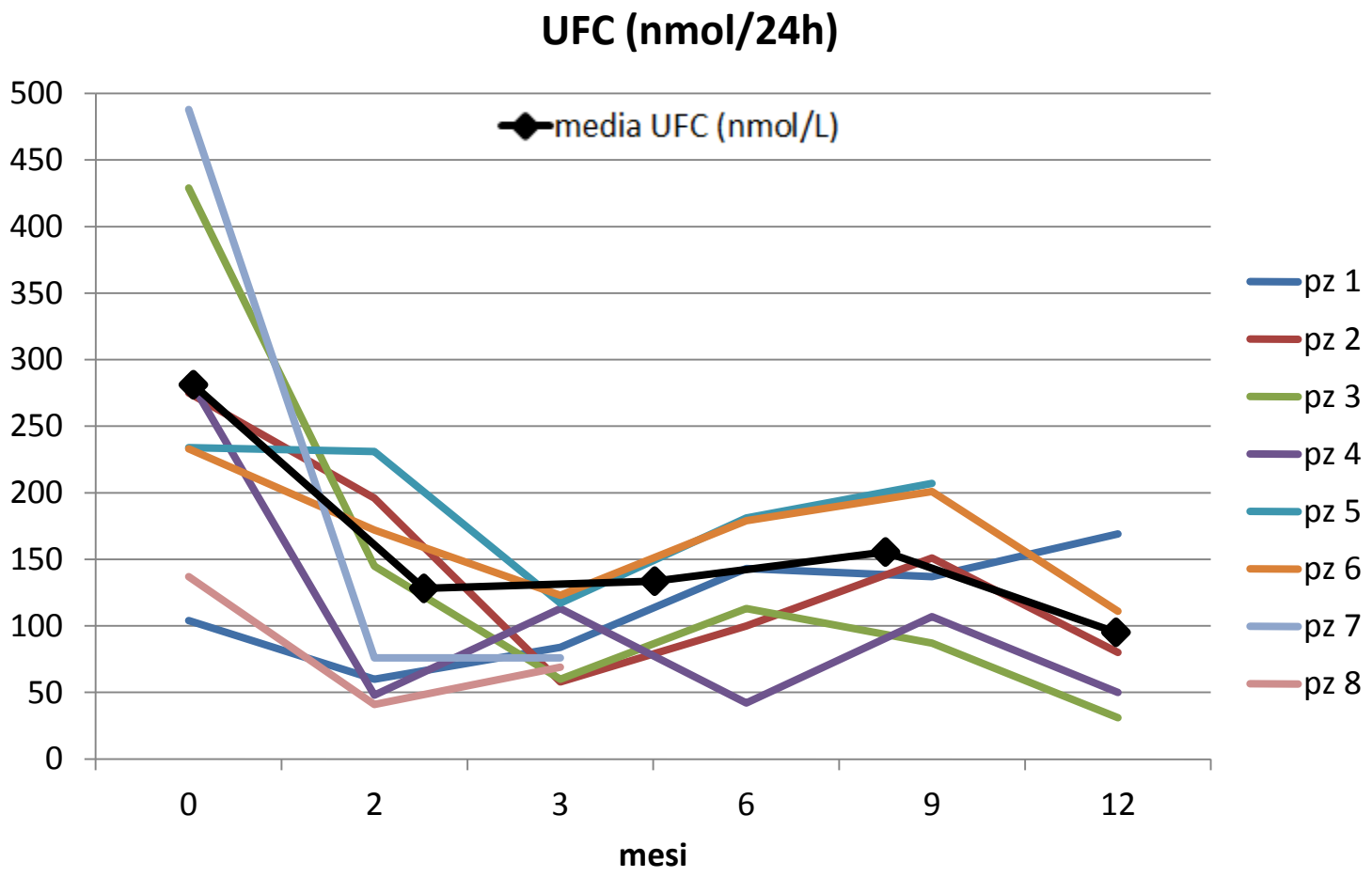


prima

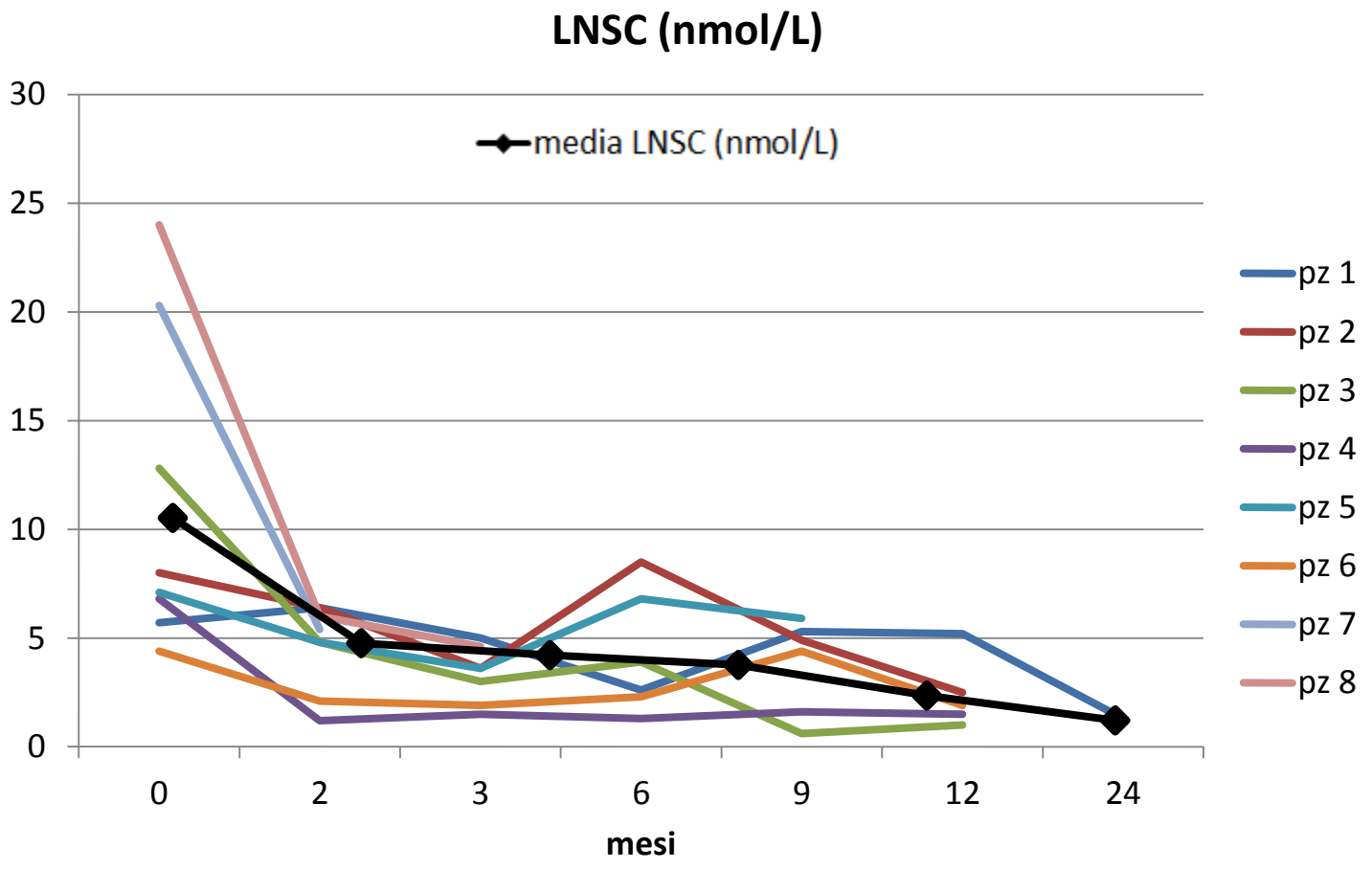


dopo

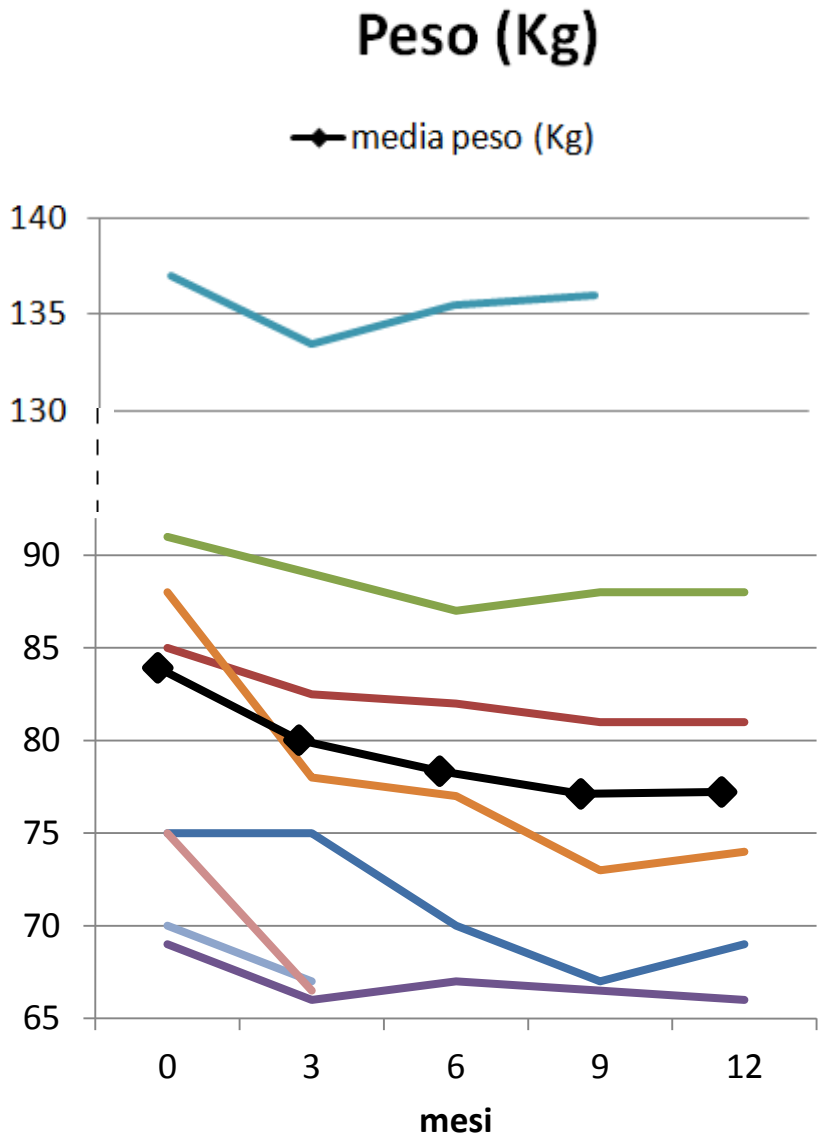
La nostra esperienza

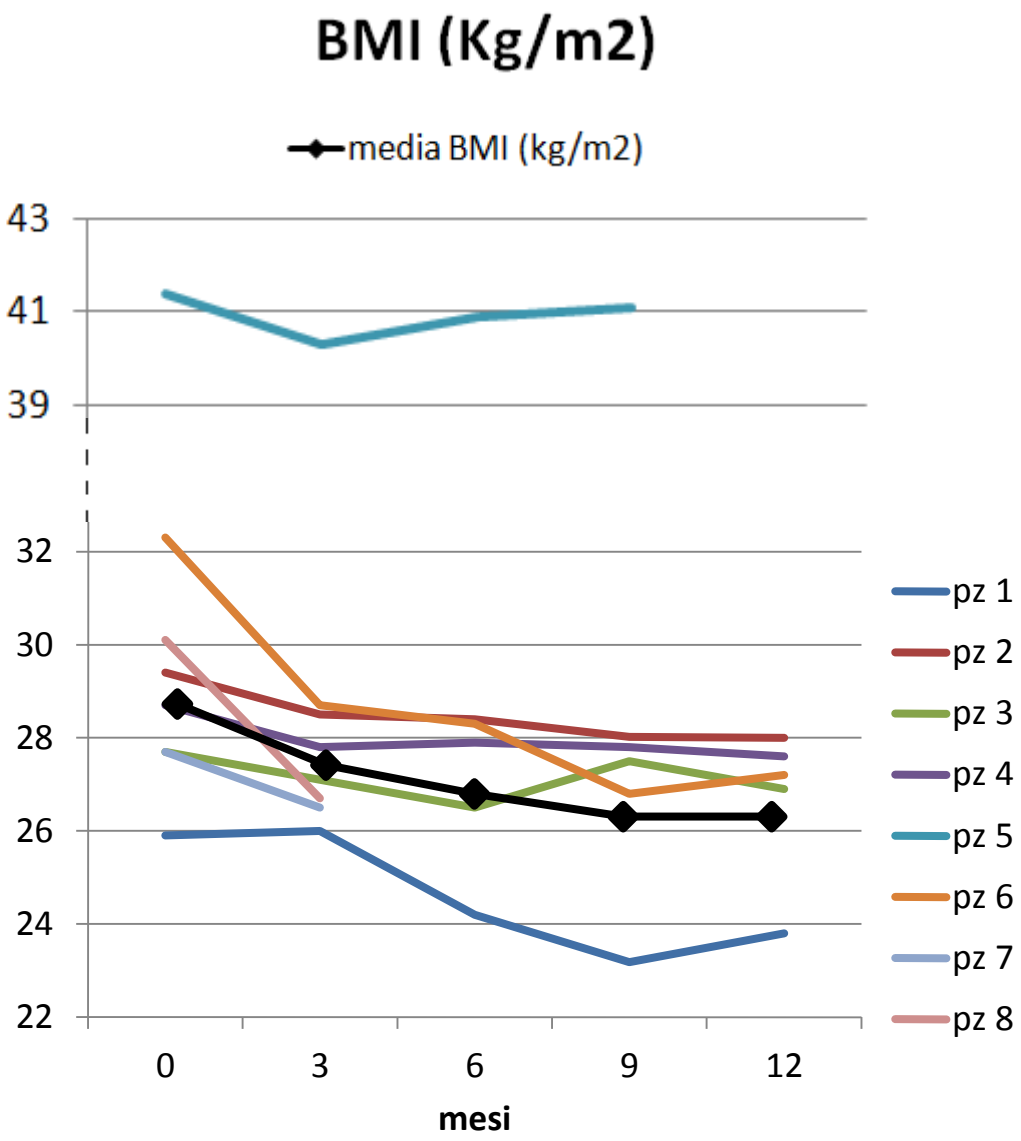


La nostra esperienza

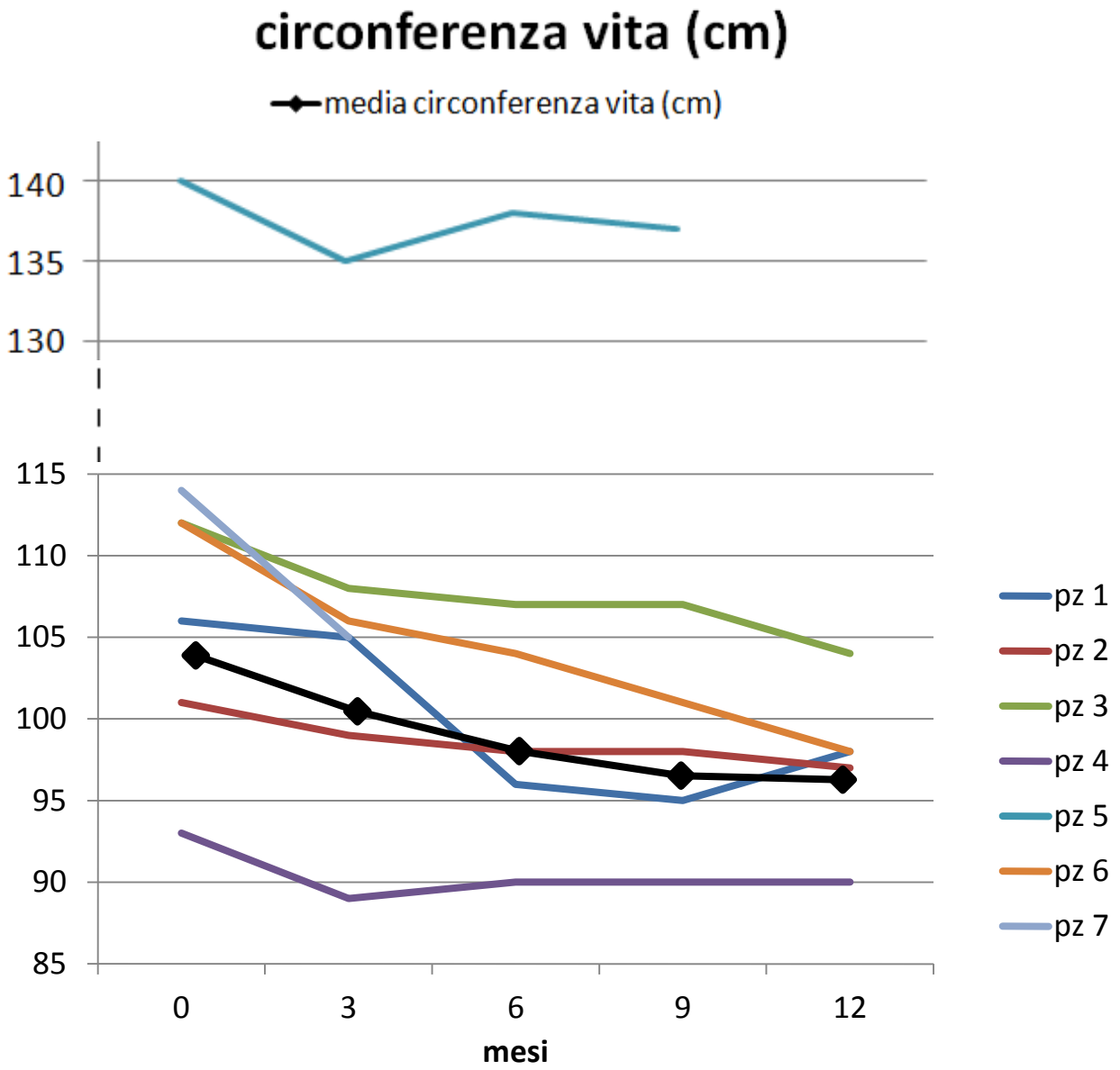


La nostra esperienza

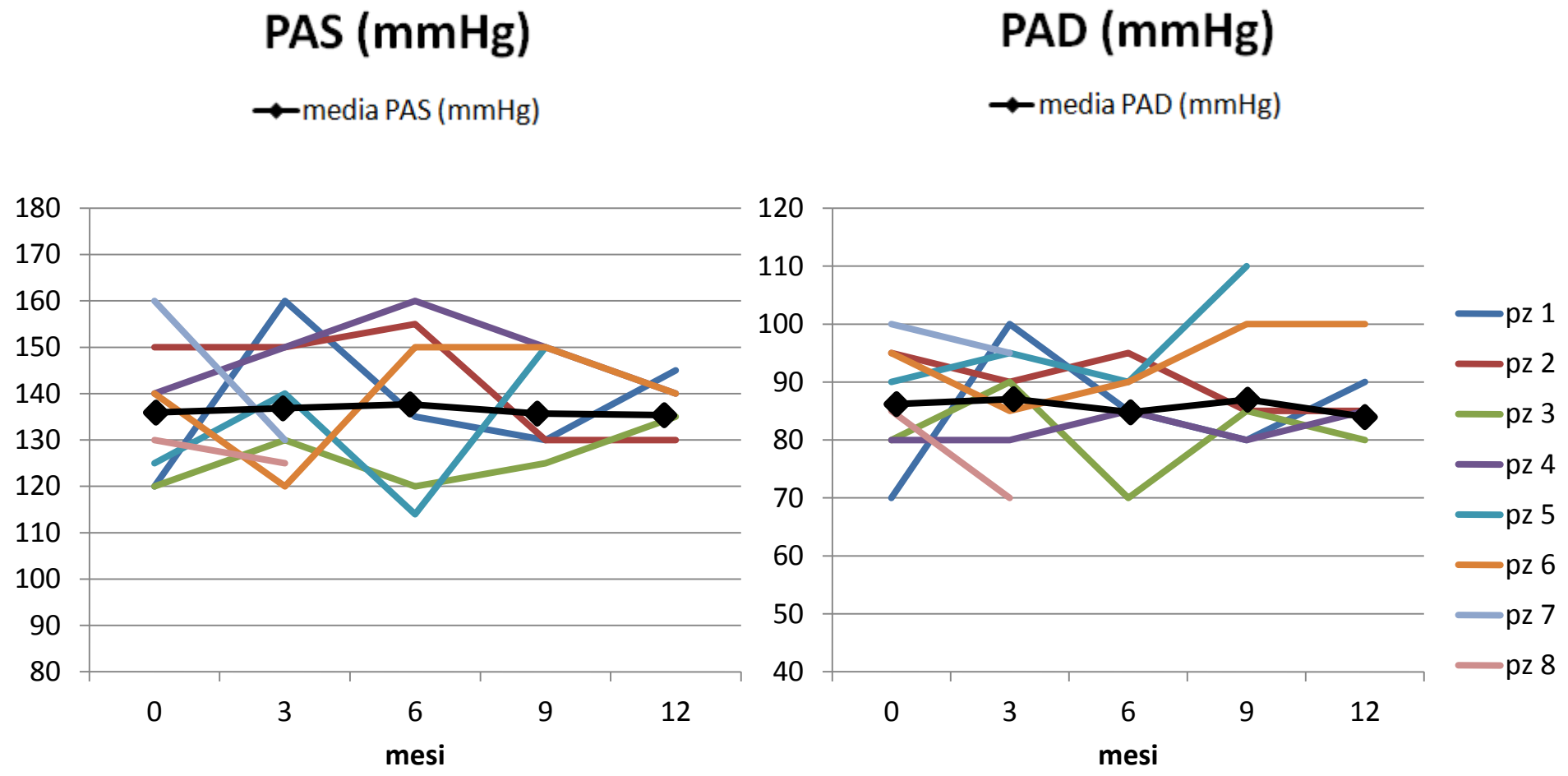




La nostra esperienza



La nostra esperienza



Riduzione numero farmaci antipertensivi in 3/8 pazienti (37.5%)

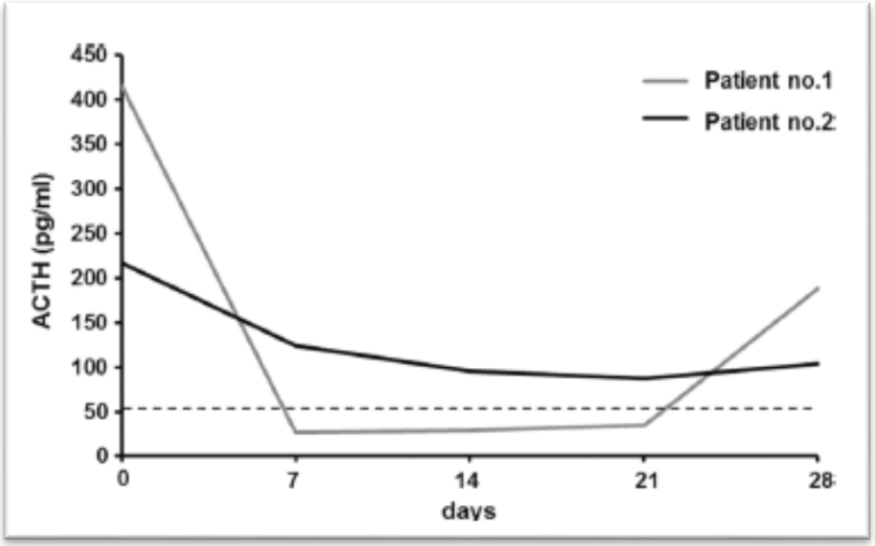
Take Home messages

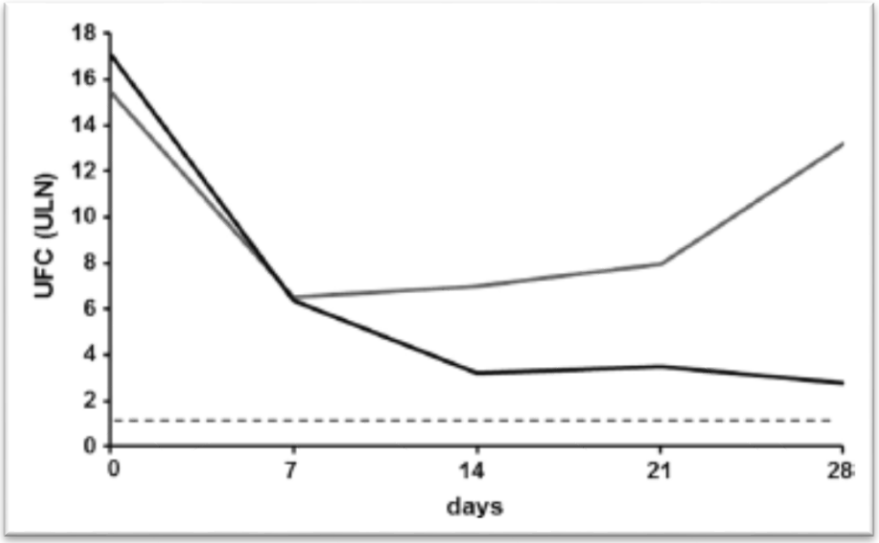
- Reduction in UFC levels during pasireotide therapy was accompanied by improvements in signs / symptoms of hypercortisolism that in some cases occurred in pts who did not achieve normal UFC levels
- Normalization of UFC should be a clear goal of treatment, however a partial response may be beneficial to some pts(awaiting surgery, effects of radiotherapy)

Clinical management of critically ill patients with Cushing's disease due to ACTH-secreting pituitary macroadenomas: effectiveness of presurgical treatment with pasireotide

S. Cannavo[1] · E. Messina[1] · A. Albani[1] · F. Ferrau[1] · V. Barresi[2] · S. Priola[3] · F. Esposito[3] · F. Angileri[3]

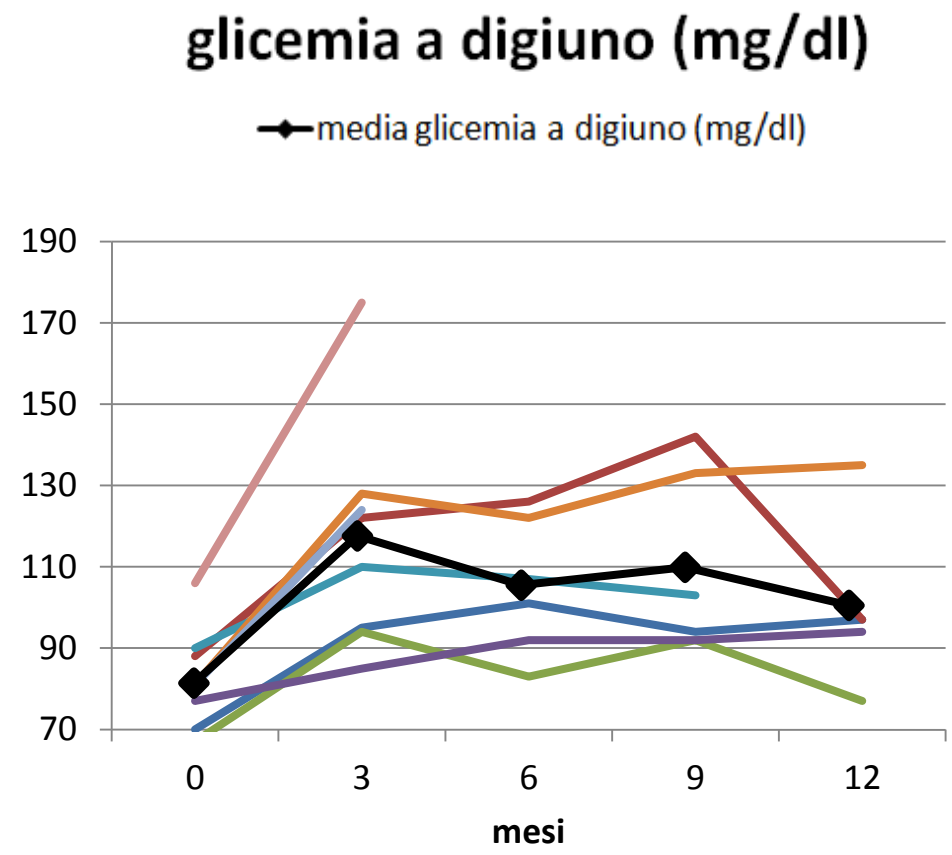
2 pz con ipercorticismo da macroadenoma ACTH secernente associato a disionia e complicanze cardiorespiratorie tali da precludere l'intervento chirurgico, trattati preoperatoriamente con pasireotide

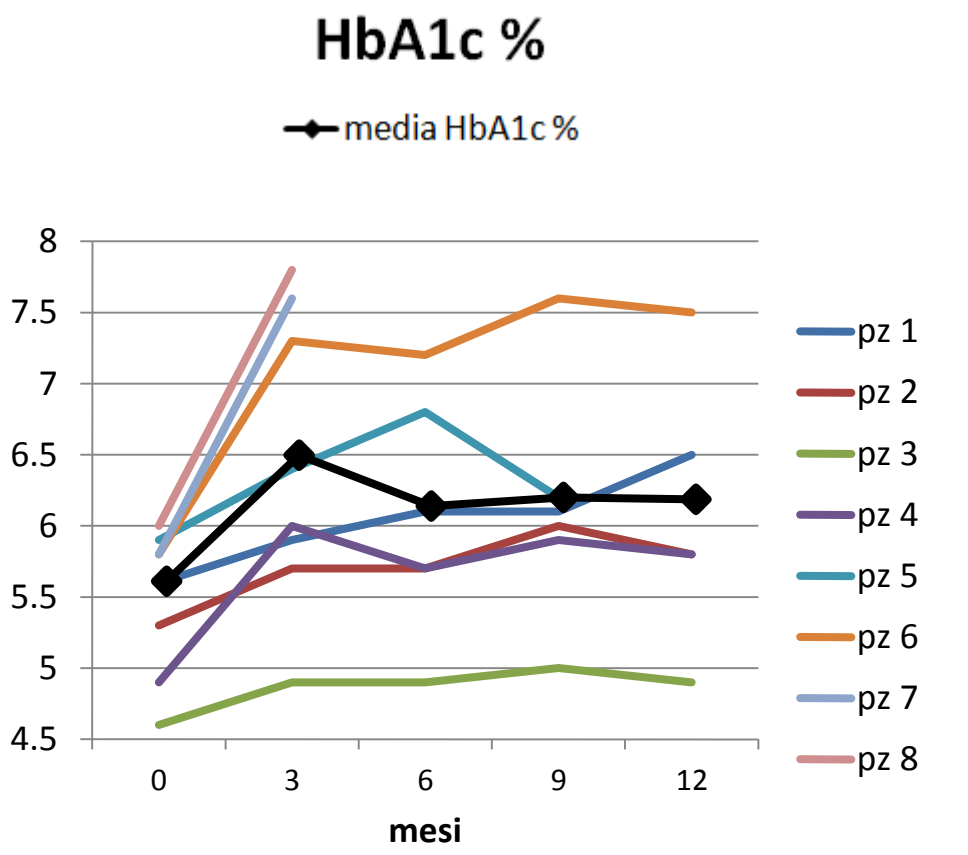




Endocrine 2015

La nostra esperienza





Studio multicentrico italiano sul ruolo del pasireotide nella terapia della malattia di Cushing: una esperienza di reale pratica clinica*

Padova:
Carla Scaroni

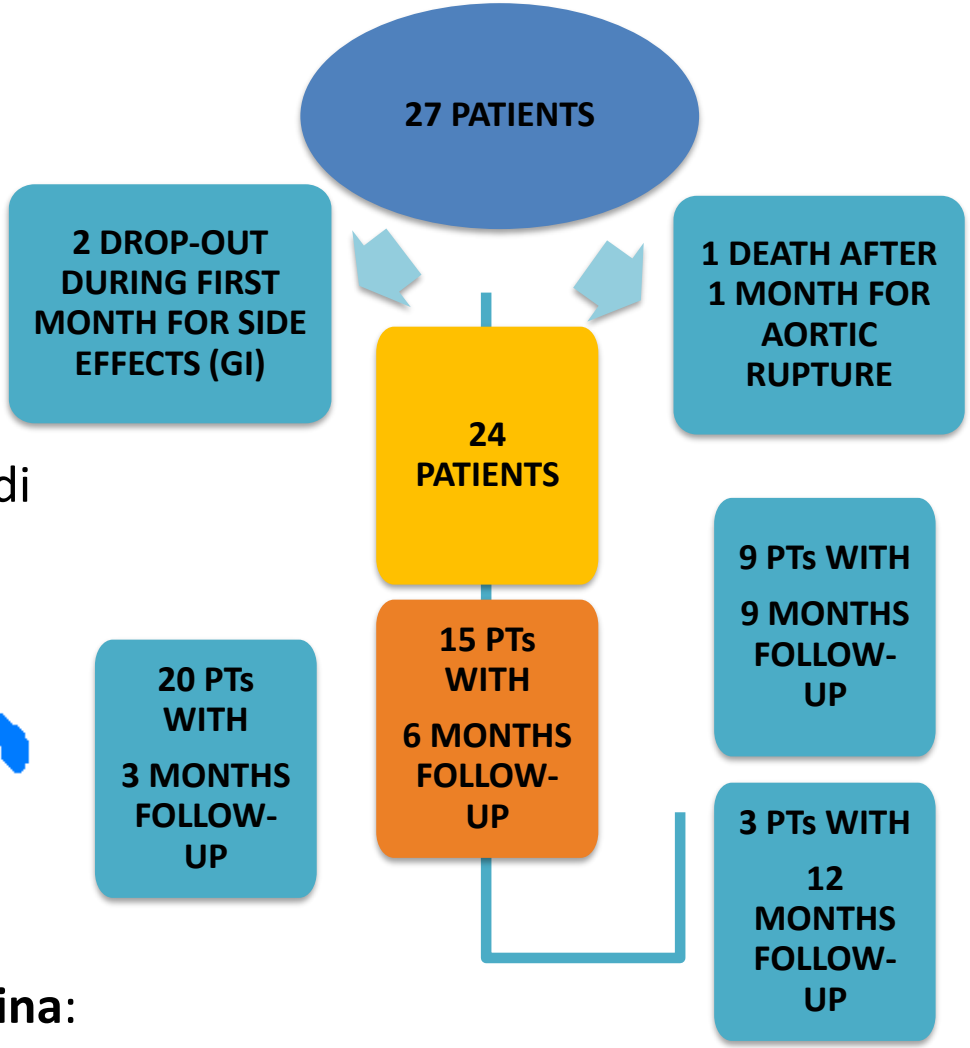
Ancona:
Giorgio Arnaldi

Annamaria Colao
Marco Boscaro

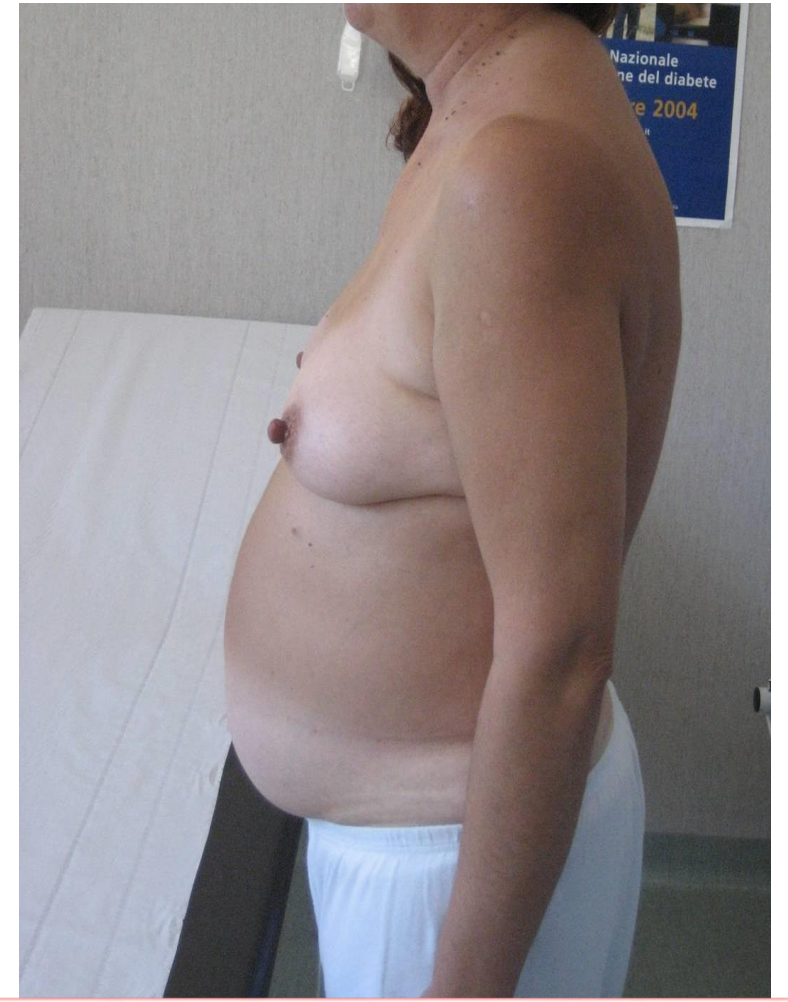
Napoli:
Rosario Pivonello

Palermo:
Carla Giordano

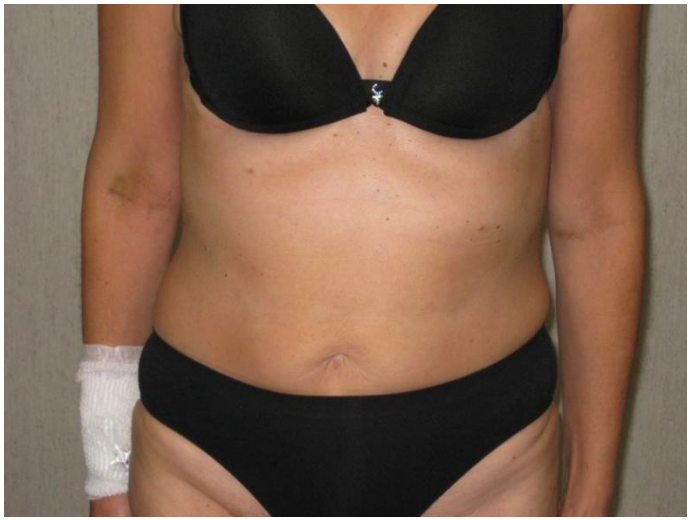
Messina:
Salvo Cannavò

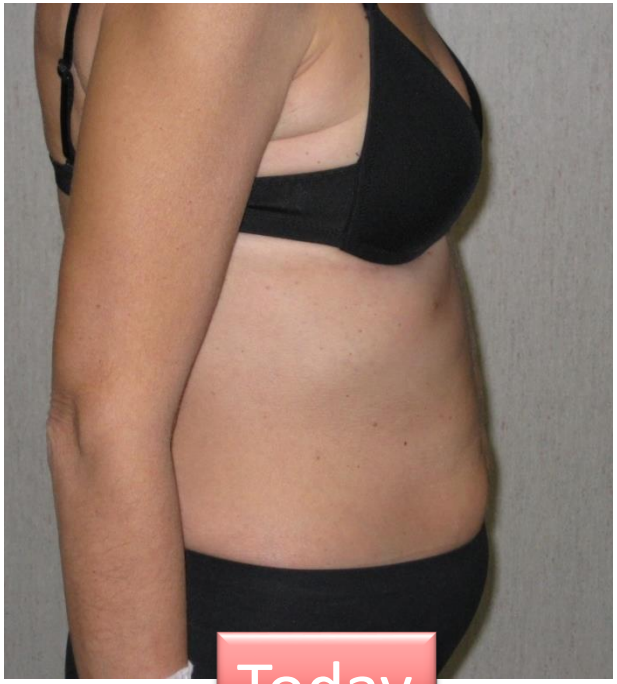


** Pazienti in trattamento in base alla legge 648/94*



Before Pasireotide treatment



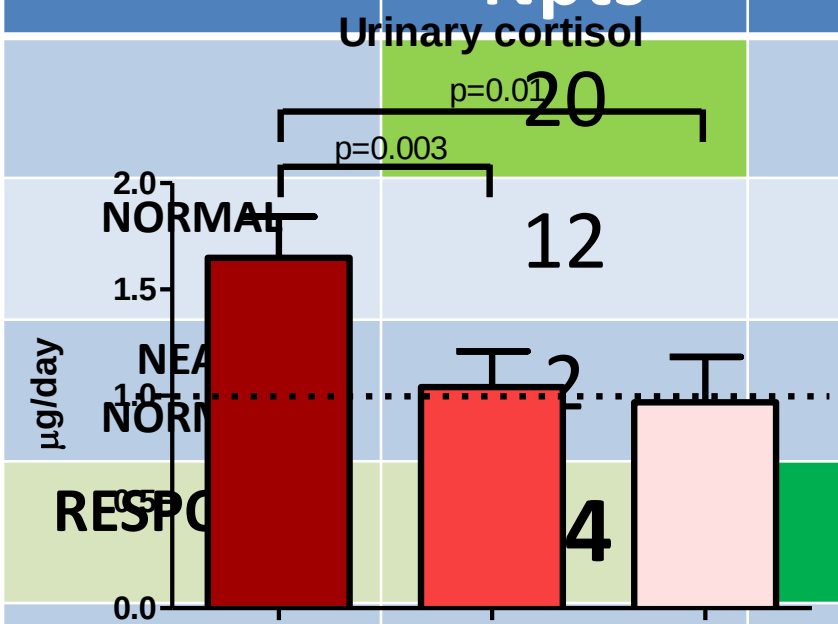


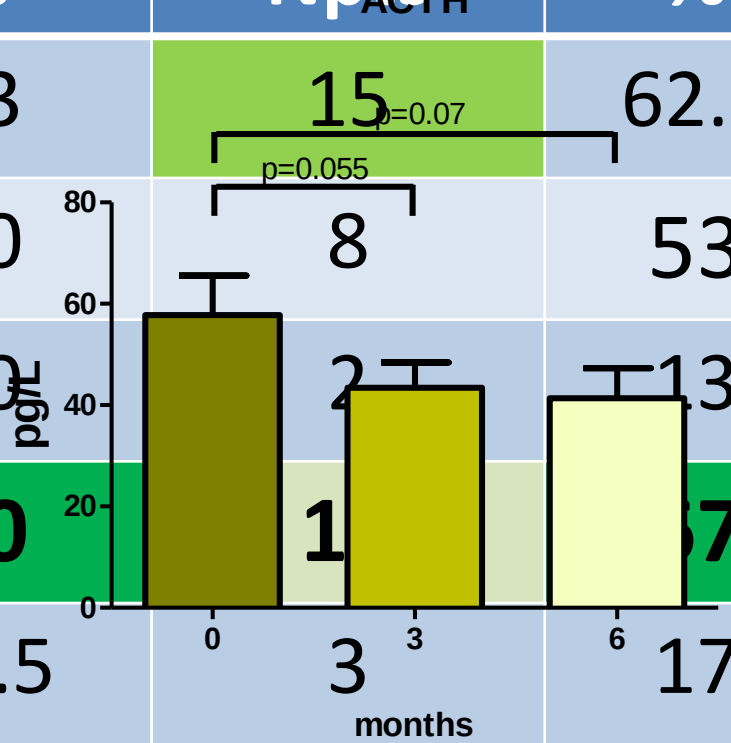
Today

RESPONSE to pasireotide 600 mcg bid

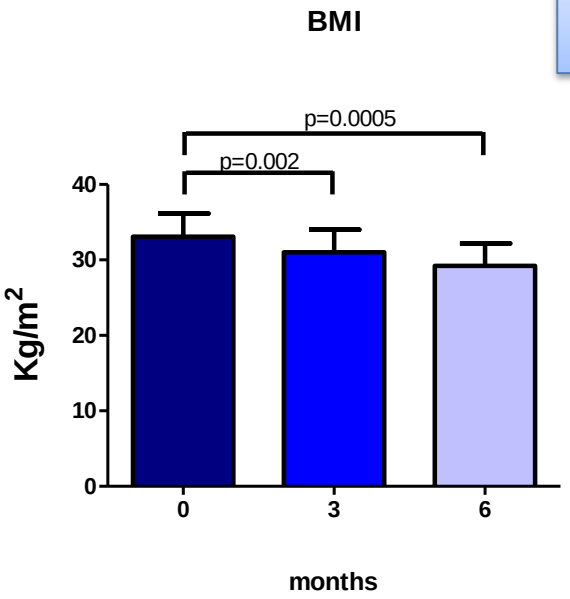
FOLLOW-UP **3 MONTHS** **6 MONTHS**

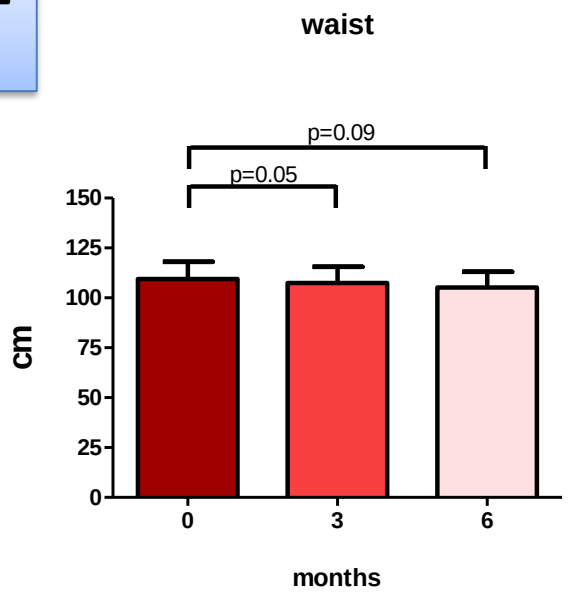
UFC	Npts	%	Npts	%
	20	83	15	62.5
	12	60	8	53
	2	10	2	13
RESPO	4	70	1	7
DROP-OUT	3	12.5	3	17
MISSING	1	5	2	13.3
WAITING	4	20	6	30

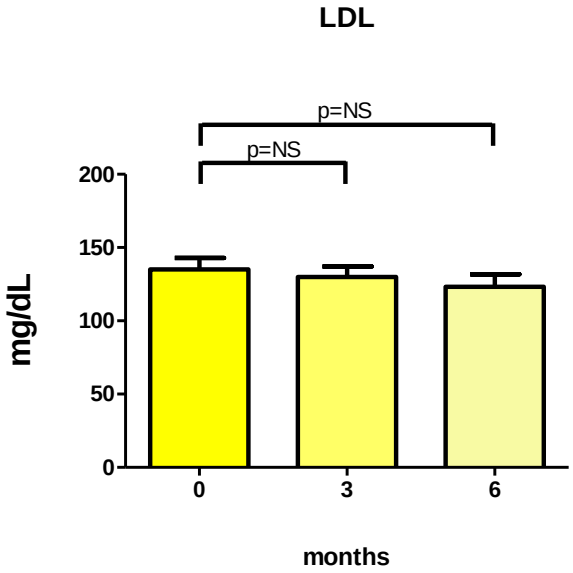


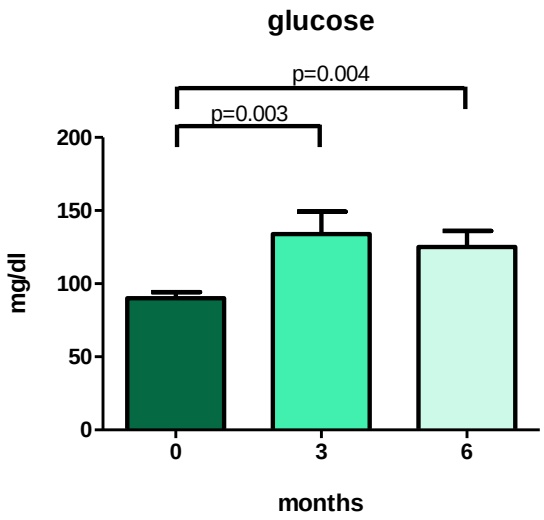


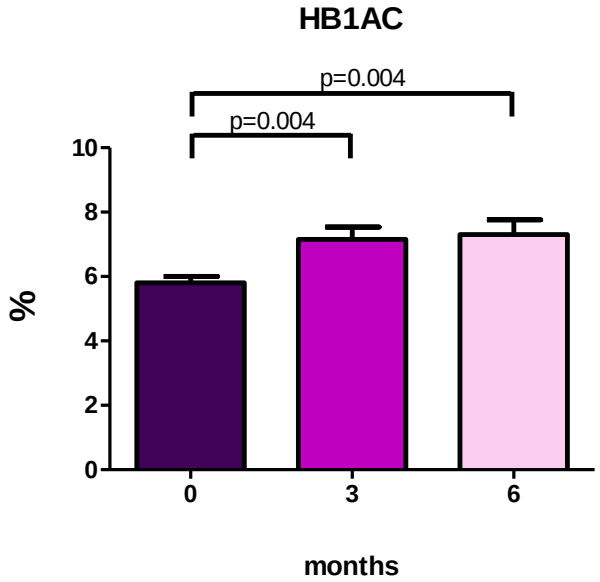
CLINICAL EFFECT











Sicurezza: eventi avversi correlati al farmaco più frequenti (≥ 5%)

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)
Cholelithiasis	1 (1)	25 (30)	1 (1)	24 (30)	2 (1)	49 (30)
Headache	1 (1)	23 (28)	2 (2)	23 (29)	3 (2)	46 (28)
Abdominal pain	1 (1)	19 (23)	2 (2)	20 (25)	3 (2)	39 (24)
Fatigue	1 (1)	12 (15)	2 (2)	19 (24)	3 (2)	31 (19)
Diabetes mellitus	6 (7)	13 (16)	6 (8)	16 (20)	12 (7)	29 (18)
Nasopharyngitis	0	10 (12)	0	11 (14)	0	21 (13)
Alopecia	0	10 (12)	0	10 (12)	0	20 (12)
Asthenia	2 (2)	13 (16)	2 (2)	5 (6)	4 (2)	18 (11)
Glycated hemoglobin elevation	1 (1)	10 (12)	0	8 (10)	1 (1)	18 (11)
ALT elevation	1 (1)	11 (13)	3 (4)	6 (8)	4 (2)	17 (10)
[illegible]						(10)
[illegible]						(10)
[illegible]						(10)
[illegible]						(10)
[illegible]						(10)
Hypoglycemia	3 (4)	12 (15)	0	3 (4)	3 (2)	15 (9)
Type 2 diabetes mellitus	4 (5)	10 (12)	3 (4)	5 (6)	7 (4)	15 (9)
Anxiety	0	5 (6)	0	9 (11)	0	14 (9)
Influenza	0	9 (11)	0	5 (6)	0	14 (9)
Insomnia	0	3 (4)	0	11 (14)	0	14 (9)
Myalgia	1 (1)	10 (12)	0	4 (5)	1 (1)	14 (9)

Il profilo di sicurezza del pasireotide è simile a quello degli altri analoghi della somatostatina eccetto per l'iperglicemia

13 pazienti (8%) hanno sperimentato **sintomi da ipocortisolismo**, risolti con riduzione della dose e/o temporanea sostituzione corticosteroidea.

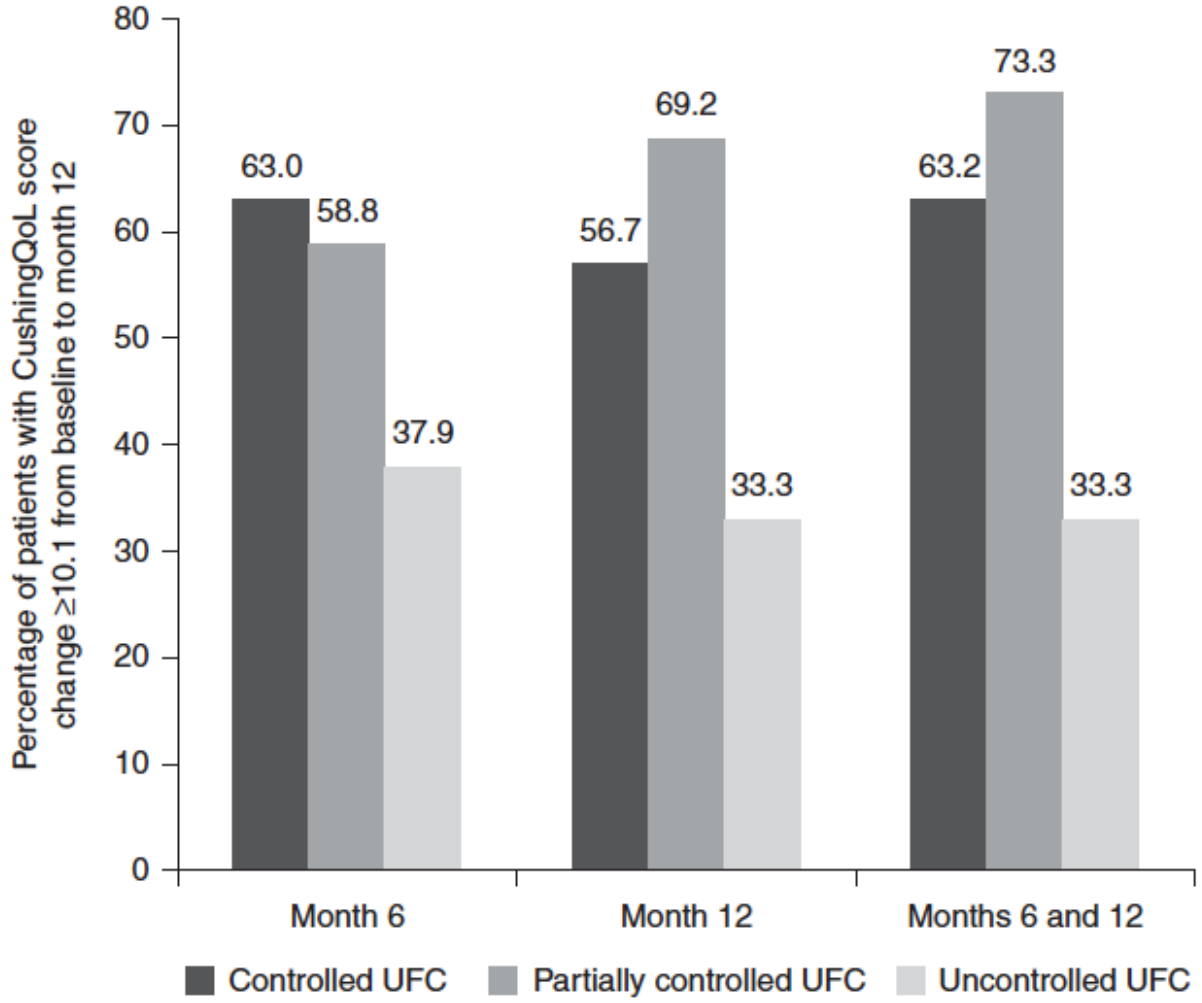
I più frequenti eventi avversi riportati sono quelli gastrointestinali: diarrea (54.9%), nausea (46.9%), colelitiasi (29.6%), dolore addominale (20.4%).

Il 73% dei pazienti ha avuto almeno un evento avverso correlato ad iperglicemia (Il 6% ha interrotto la terapia sperimentale).

Colao et al., N Engl J Med 2012

Treatment effectiveness of pasireotide on health-related quality of life in patients with Cushing's disease

S M Webb and others



European Journal of Endocrinology (2014) **171**, 89–98

Supplemental Table 1. Proportion of patients with an improvement from baseline in signs of Cushing's disease by randomized dose group at month 6 and 12

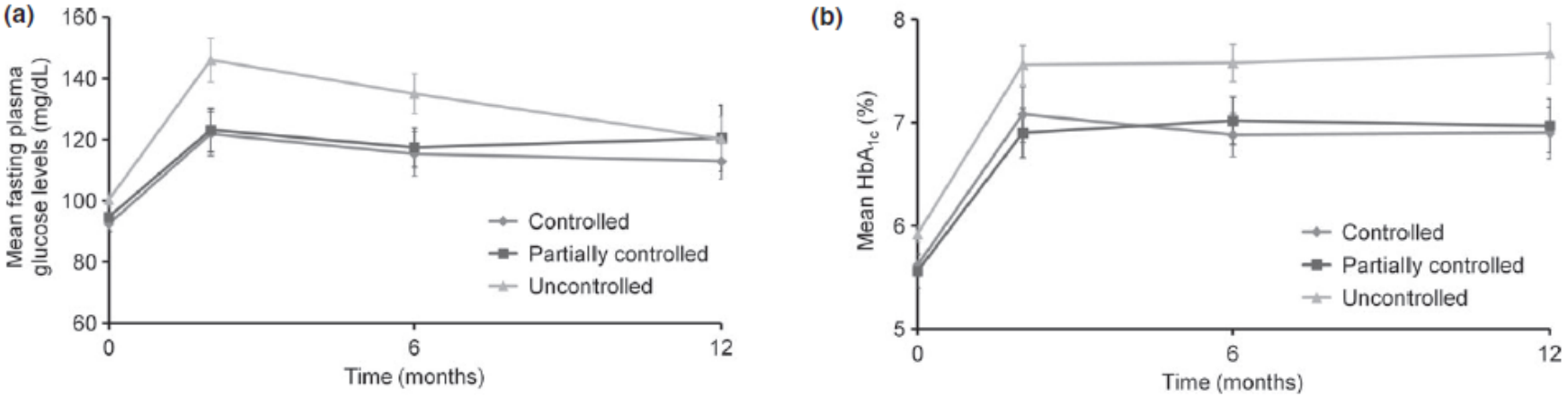
	Pasireotide 600µg bid		Pasireotide 900µg bid	
	n/N	% (95%CI)	n/N	% (95%CI)
Month 6				
Facial rubor	18/49	36.7 (23.2, 50.2)	28/47	59.6 (45.5, 73.6)
Supraclavicular fat pad	18/46	39.1 (25.0, 53.2)	20/47	42.6 (28.4, 56.7)
Dorsal fat pad	18/47	38.3 (24.4, 52.2)	18/46	39.1 (25.0, 53.2)
Month 12				
Facial rubor	14/35	40.0 (23.8, 56.2)	21/34	61.8 (45.4, 78.1)
Supraclavicular fat pad	18/35	51.4 (34.9, 68.0)	19/33	57.6 (40.7, 74.4)
Dorsal fat pad	18/34	52.9 (36.2, 69.7)	19/33	57.6 (40.7, 74.4)

95% confidence intervals are based on normal approximation to the binomial distribution.

N is the number of patients in the intention-to-treat population with measurements at month 6 or 12, and baseline. A patient had an improvement from baseline if the sign at month 6 or 12 was less severe than at baseline.

Pasireotide treatment significantly improves clinical signs and symptoms in patients with Cushing's disease: results from a Phase III study

Rosario Pivonello*, Stephan Petersenn†, John Newell-Price‡, James W. Findling§, Feng Gu¶, Mario Maldonado**, Andrew Trovato**, Gareth Hughes††, Luiz R. Salgado‡‡, André Lacroix§§, Jochen Schopohl¶¶ and Beverly M.K. Biller*** on behalf of the Pasireotide B2305 Study Group[1]



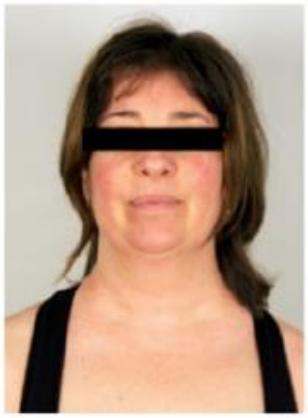
Clinical Endocrinology 2014

Pituitary
DOI 10.1007/s11102-013-0539-4

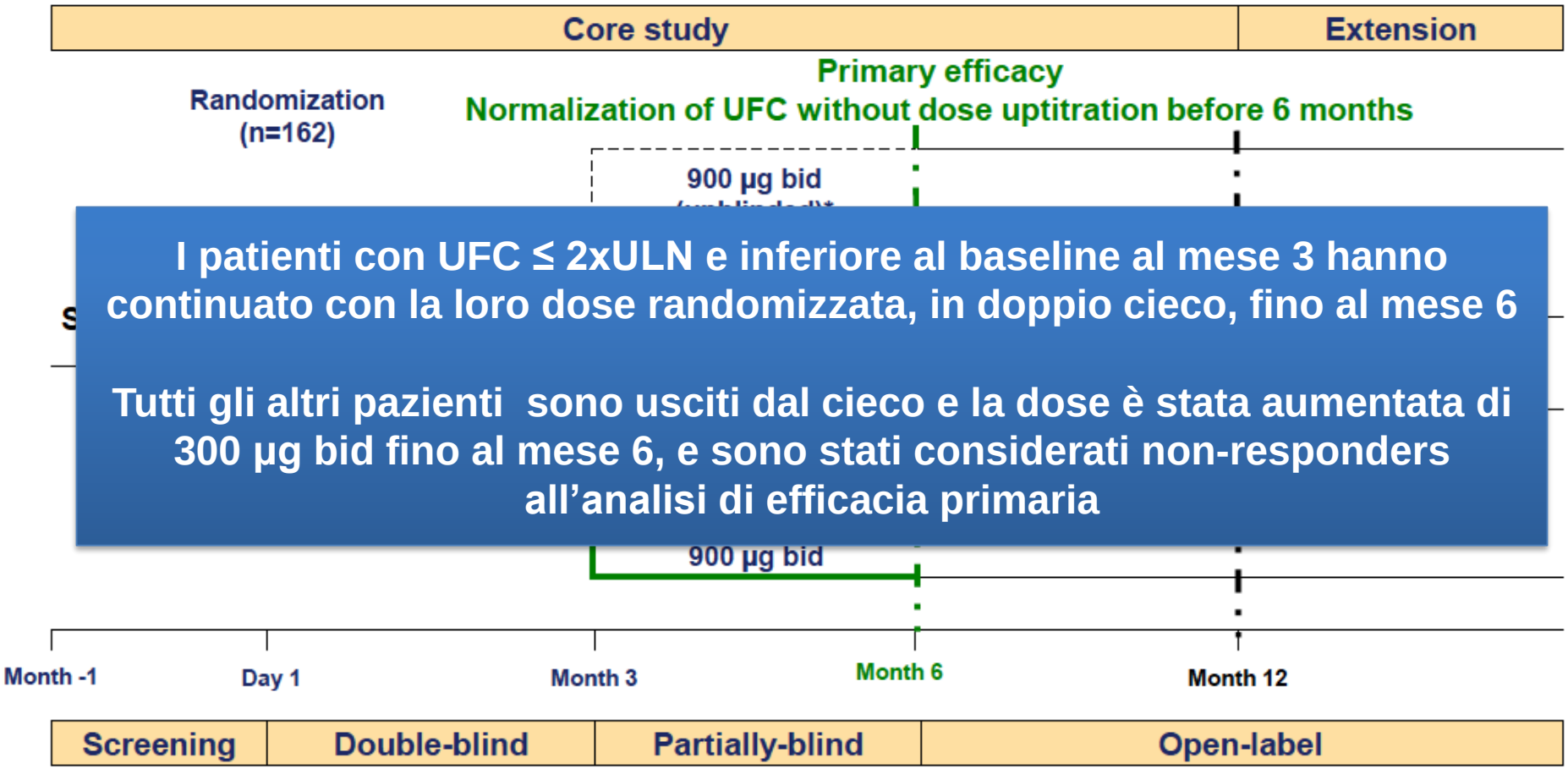
Pasireotide monotherapy in Cushing's disease: a single-centre experience with 5-year extension of phase III Trial

Jessica MacKenzie Feder · Isabelle Bourdeau · Sophie Vallette · Hugues Beauregard · Louis-Georges Ste-Marie · André Lacroix

Time (m)	Weight (kg)	BMI (kg/m^2)	Blood pressure (mmHg)	Muscle Strength[a]	T-score spine	T-score hip	% body fat	Karnofsky score
Patient 1								
0	60.9	23.7	122/76	1	−1.7	−1.5	37.6	90
12	54.9	21.4	115/73	0	−1.4	−1.5	32.5	90
24	52.3	20.4	130/83	0	−1.4	−1.9	32.4	90
36	54.5	21.2	121/73	0	−0.8	−1.4	33	100
48	54.1	21.1	104/71	0	−1	−1.2	32.9	100
60	55.9	21.8	103/67	0	−0.8	−1.3	33.2	100
Patient 2								
0	56.5	22.8	149/93	1	−0.3	0	31.5	90
12	58.4	23.6	137/87	0	−0.4	−0.5	39.1	100
24	55	22.2	114/85	0	−0.4	0	35.8	100
36	53	21.4	129/88	0	−0.5	0	34.7	100
48	55.7	22.5	113/80	0	−0.3	−0.6	37.1	100




B2305 study design



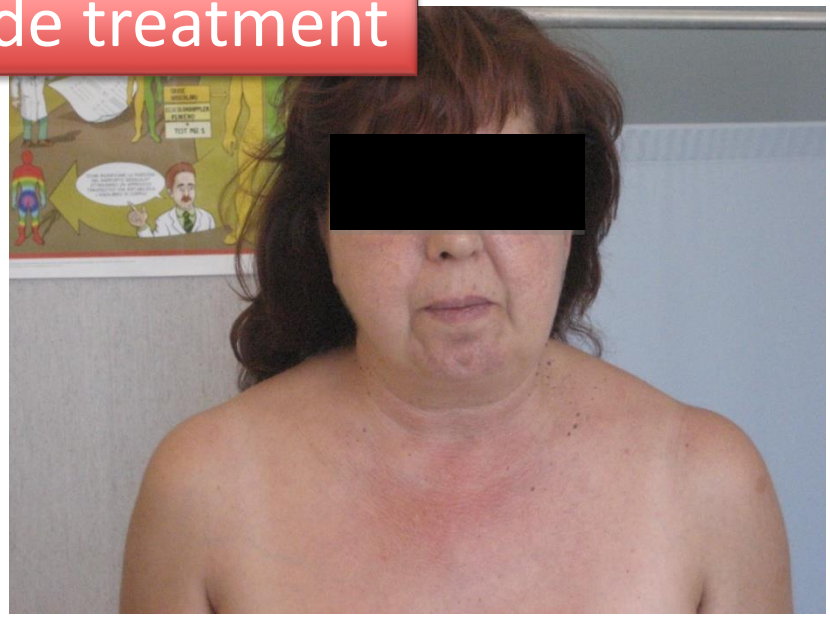
I patienti con UFC ≤ 2xULN e inferiore al baseline al mese 3 hanno continuato con la loro dose randomizzata, in doppio cieco, fino al mese 6

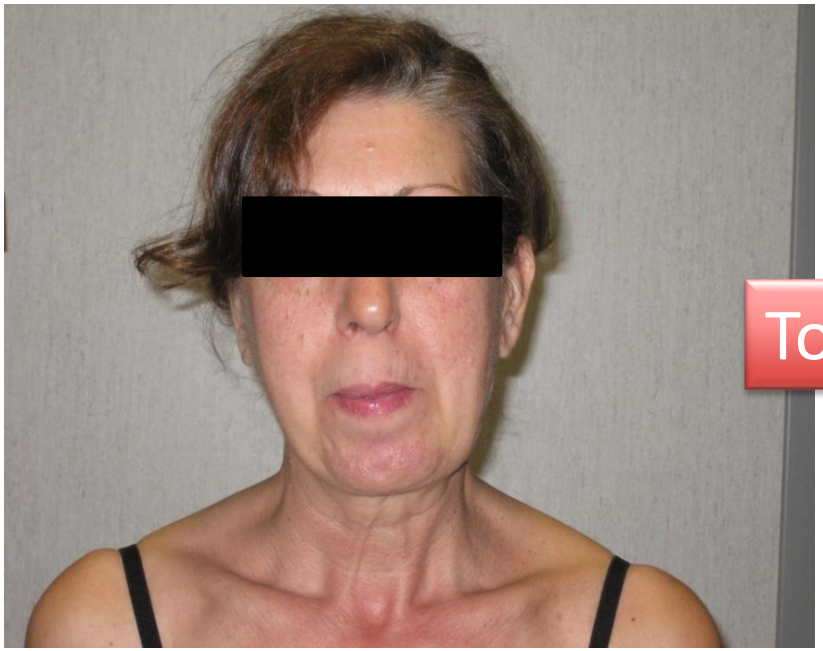
Tutti gli altri pazienti sono usciti dal cieco e la dose è stata aumentata di 300 µg bid fino al mese 6, e sono stati considerati non-responders all'analisi di efficacia primaria

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

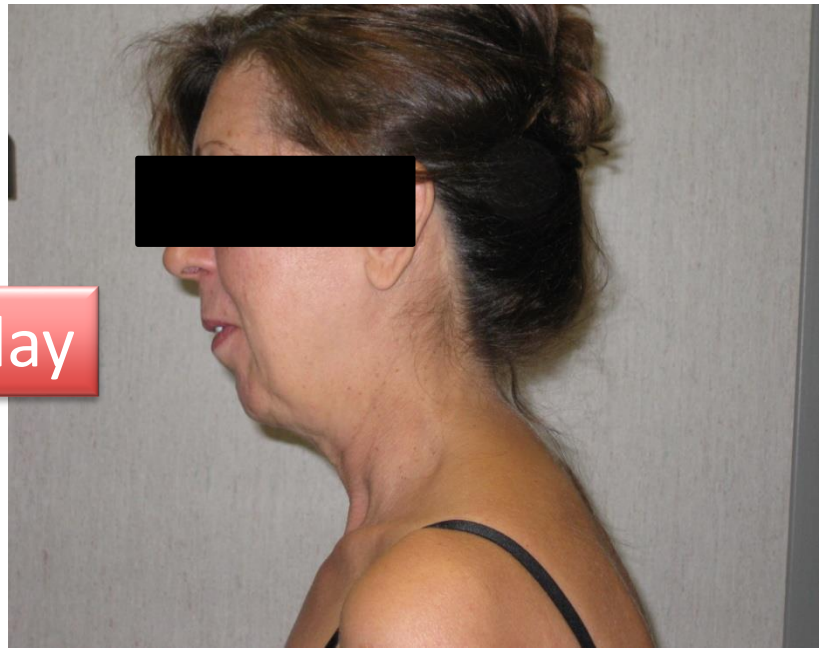
For patients who had a mean baseline UFC 1.5-2xULN with a 3-month UFC above their baseline UFC

Before Pasireotide treatment



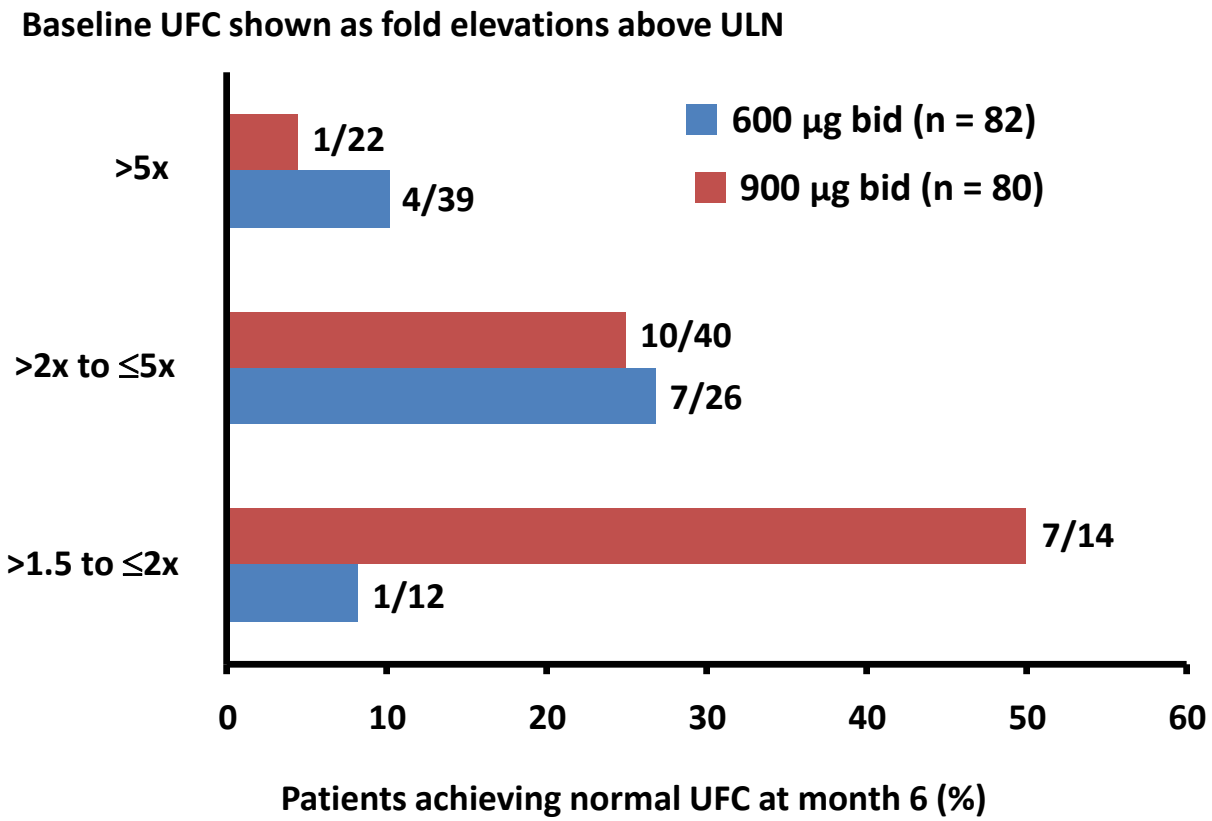


Today



Risposta della cortisoluria in base ai valori basali di UFC

Higher rate of UFC normalization with lower baseline UFC



Colao et al. N Engl J Med 2012

MARINA, 51 anni

diagnosi di M. di Cushing. RMN ipofisi: microadenoma ipofisario
Operata per via TNS → Istologia: conferma adenoma ACTH+ remissione
recidiva dopo 3 anni di ipercorticismo
esclusi reintervento e radioterapia

TERAPIA COMBINATA
CABERGOLINA 3.5 mg/settimana + KETOCONAZOLO 400 mg/die

- **controllo della cortisoluria: 153 e 67 nmol/24h (vn 30-193)**
- **non ripresa ritmo circadiano del cortisolo**
- **persistono habitus cushingoide, obesità centrale (circonferenza vita 106 cm), miglioramento della ipertensione arteriosa, alterazione dei parametri coagulativi, alterato tono umore**

PASIREOTIDE 900 mcg s.c. x 2/die

dopo 24 mesi :
- **Normale CLU: 67 nmol/24h (vn 16-168)**
- **Ripristino ritmo cortisolosalivare**
- **Calo di 8 kg, risolta ipertensione arteriosa, circonferenza vita →96 cm, permane in buon controllo glicemico**