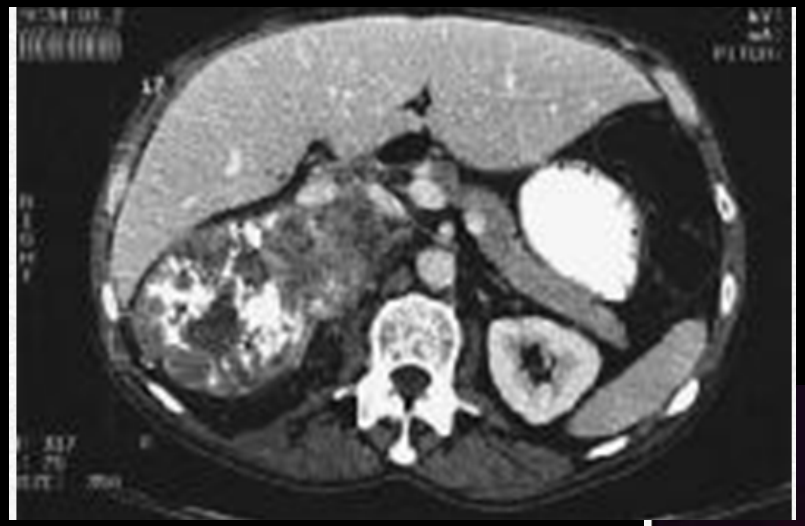
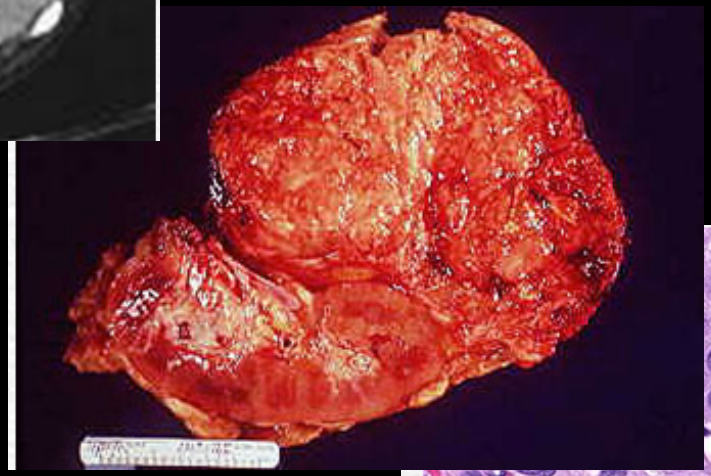
Quando l'oncologo ha bisogno dell'endocrinologo
Topics

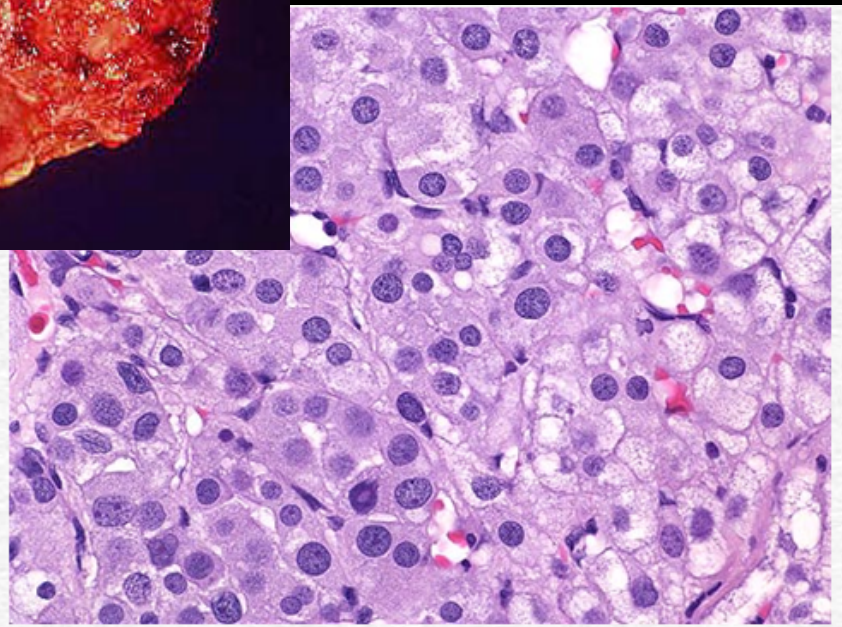
- ***Tumori del surrene***

Carcinoma della corteccia surrenalica



Incidenza 0,5-2/1.000.000/anno
Picco bimodale in età pediatrica e tra la 4° e la 5° decade
Rapporto maschi/femmine 1,5/1





Per lo piu' sporadico
Li-Fraumeni
MEN-1
Congenital adrenal hyperplasia
Familial polyposi colon

Carcinoma della corteccia surrenalica: 60-65% funzionanti

- *Cushing*
- *Virilizzazione*
- *Femminizzazione*
- *Iperaldosteronismo*

clinical practice guidelines

Annals of Oncology 23 (Supplement 7): vii131–vii138, 2012
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Adrenal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

A. Berruti[1], E. Baudin[2], H. Gelderblom[3], H. R. Haak[4], F. Porpiglia[5], M. Fassnacht[6] & G. Pentheroudakis[7] on behalf of the ESMO Guidelines Working Group*

Hormonal work-up	
Glucocorticoid excess (minimum 3 of 4 tests)	
Dexamethasone suppression test (1 mg, 23:00 h)	
Excretion of free urinary cortisol (24 h urine)	
Basal cortisol (serum)	
Basal ACTH (plasma)	
Sexual steroids and steroid precursors	
DHEA-S (serum)	
17-OH-progesterone (serum)	
Androstenedione (serum)	
Testosterone (serum)	
17-beta-estradiol (serum, only in men and postmenopausal women)	
24-h urine steroid metabolite excretion	
Mineralocorticoid excess	
Potassium (serum)	
Aldosterone/renin ratio (only in patients with arterial hypertension and/or hypokalemia)	
Catecholamine excess	
Normetanephrine, metanephrine and methoxytyramine (plasma)	
Alternatively: fractionated metanephrine excretion (24 h urine)	
Imaging	
CT or MRI of abdomen and CT thorax	
Bone scintigraphy (when suspecting skeletal metastases)	
FDG-PET (optional)	
MIBG scintigraphy, DOTA-TATE-PET, Dopa/Dopamine PET or FDG-PET if pheochromocytoma is proved	

Adapted according to the recommendation of the ACC working group of the European Network for the Study of Adrenal Tumors (www.ensat.org/acc.html), May 2005.

In patients with a clearly established diagnosis of an ACC, one can skip the workup on catecholamine excess (and conversely for established pheochromocytoma, one can skip the steroid analysis). DHEA, dehydroepiandrosterone

Carcinoma corticosurrenalico : chirurgia

TABLE 7. *Adrenocortical carcinoma: survival rates from reported series*

Study	Institution/group	Year	n	5-y Survival (%)		
				Overall	Complete resection	Incomplete resection
Soreide et al.[6]	Norway	1991	99	16	62	0
Icard et al.[16]	French Endocrine Surgeons	1992	156	34	42	0
Zografos et al.[17]	Roswell Park	1994	53	19	38	0
Haak et al.[18]	Holland	1995	96	27	49	9
Crucitti et al.[19]	ACC Italian Registry	1996	129	35	48	7

ACC, adrenal cortical carcinoma.

Chemioterapia : mitotane

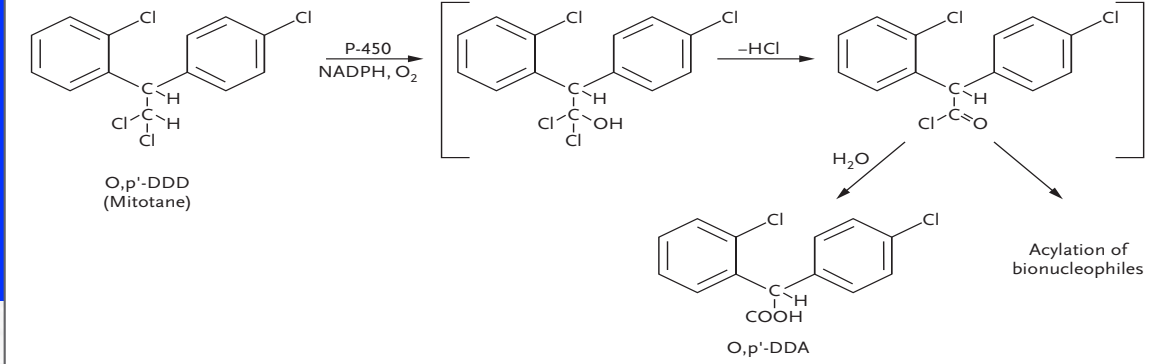

Figure 1. Metabolism of Mitotane.
Mitotane is hydroxylated at the β-carbon and transformed by dehydrochlorination into an acyl chloride. The acyl chloride either covalently binds to bionucleophiles in the target cells or is transformed to an acetic acid derivative for excretion.

Table 5. Effect of mitotane treatment on adrenal cortical cancer.

Study	Year	Institution	No.	Result/conclusion
Kasperlik-Zaluska [72]	1995	Poland	36	Suggested benefit of adjuvant mitotane
Haak [59]	1994	Netherlands	62	Response rate 21% (6/29) in setting of measurable disease
Vassilopoulou-Sellin [73]	1993	MDACC	13	No effect on survival
Pommier [26]	1992	MSKCC	29	PR 24%
Luton [74]	1990	France	37	PR 22%, no effect on survival
Venkatesh [75]	1989	MDACC	72	Stable disease or PR 29%
Karakousis [76]	1985	Roswell Park	10	Stable disease or response 40% (n = 4)
Van Slooten [77]	1984	Netherlands	34	Serum levels > 14 μg/ml associated with improved survival
Henley [61]	1983	Mayo Clinic	24	PR 4% (n = 1)

PR: partial response.

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Table 3. Mitotane dose regimen, glucocorticoid, and mineralocorticoid supplementation, blood level monitoring, and dose adjustment according to toxicity and blood level monitoring

Mitotane dose regimen[a]	• Start with 1.5 g/d and increase dose within 4–6 days to 6 g/days • After 3 weeks, adjust dosage according tolerability and blood level (see below) • Maximum dose 12 g/days, but most patients do not tolerate >8 g/days • Target mitotane blood level 14–20 mg/l. Using this regimen, ~50% of pat[illegible]ac[illegible]ve the target level within 3 months
Glucocorticoid and mineralocorticoid supplementation	• A total daily dose of 50 mg hydrocortisone (divided as 20–[illegible] mg) or 75 mg cortisone acetate and more may be needed. Glucocorticoid replac[illegible]ent is [illegible]est with careful clinical assessment • Fludrocortisone may be added depending [illegible] blo[illegible]ssure, serum potassium levels, and plasma renin activity
Recommended blood monitoring during mitotane therapy	• Mitotane serum leve[illegible] every [illegible]eks in the first 3 months [illegible] rea[illegible] a plateau, the interval can be extended (i.e. every [illegible] w[illegible] • Glutamate-Oxa[illegible]ic Transaminase (GOT), Glu[illegible]e Transaminase (GPT), bilirubin, Gamm[illegible]lutam[illegible]ansferase (GGT). In[illegible] weeks, later 6 months every 8 weeks. GGT is [illegible]ly elevated without clinical [illegible]es. If other liver enzymes are rapidly increasing (>3-fold [illegible]seline), there is a risk [illegible] fail[illegible]: stop mitotane • TSH, fT3, fT4 every 3–4 [illegible]on[illegible]yroid hormone replacement is recommended in patients with clinical symptoms [illegible] hyp[illegible]yroidism • Testos[illegible]or [illegible]ne, androstenedione, and sexual hormone binding globulin (SHBG) should be tested in male pati[illegible]ts [illegible]ptoms of hypogonadism [illegible] 3 months. If renin increases in the presence of symptoms suggestive of mineralocorticoid deficiency, fludrocortisones should be added • Cholesterol (High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL)), triglycerides every 3–4 months (in an adjuvant setting). If LDL/HDL cholesterol consistently increases, consider treatment with statins not metabolized by CYP3A4 (e.g. pravastatin, rosuvastatin) • Blood count every 3–4 months

Plasma mitotane level	CNS (grade 2)/GI side effects (grade 3/4)		Grade 3/4 CNS side effects
	Absent	Present	Present
<14 mg/l	Increase daily dose by 1 g[b]	Reduce daily dose by 1 g	Stop mitotane[c]
14–20 mg/l	Maintain dose	Reduce daily dose by 1.5 g	Stop mitotane[c]
>20 mg/l	Reduce daily dose to 50%–75% of the most recent dose	Stop mitotane[c]	Stop mitotane[c]

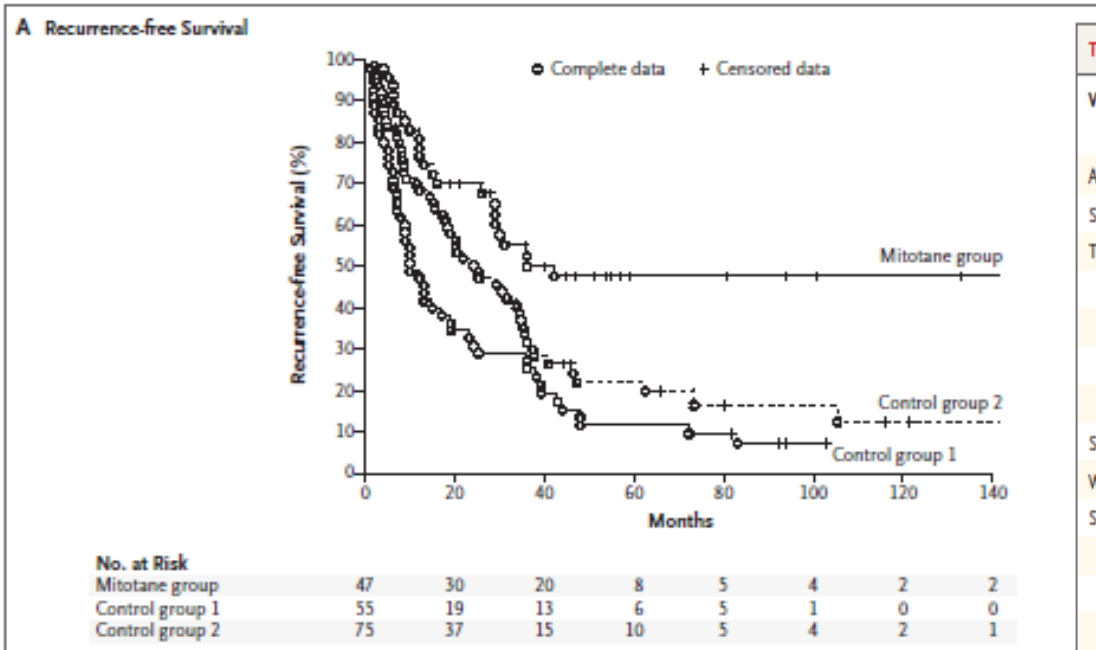

Figure 1. Kaplan–Meier Estimates of Recurrence-free Survival and Overall Survival.

Table 2. Predictive Factors for Recurrence-free Survival, According to Univariate and Multivariate Analyses.

Variable	Univariate Analysis			Multivariate Analysis*		
	Hazard Ratio	95% CI	P Value	Hazard Ratio	95% CI	P Value
Age†	0.98	0.96–0.99	<0.001	0.97	0.96–0.98	<0.001
Sex‡	1.20	0.83–1.72	0.33	1.08	0.74–1.58	0.67
Tumor stage			0.27			0.03
I	1			1		
II	1.91	0.92–3.95		2.10	1.00–4.28	
III	2.14	0.98–4.71		2.45	1.10–5.41	
IV	2.22	0.85–5.80		4.34	1.61–11.67	
Secreting tumor§	1.29	0.87–1.90	0.20			
Weiss score¶	0.96	0.61–1.50	0.85			
Study group						
Mitotane group	1		<0.001	1		<0.001
Control group 1	2.91	1.77–4.78		3.79	2.27–6.32	
Control group 2	1.97	1.21–3.20		2.93	1.74–4.94	

Adjuvant Mitotane Treatment for Adrenocortical Carcinoma

Massimo Terzolo, M.D., Alberto Angeli, M.D., Martin Fassnacht, M.D., Fulvia Daffara, M.D., Libuse Tauchmanova, M.D., Pier Antonio Conton, M.D., Ruth Rossetto, M.D., Lisa Buci, M.D., Paola Sperone, M.D., Erika Grossrubatscher, M.D., Giuseppe Reimondo, M.D., Enrico Bollito, M.D., Mauro Papotti, M.D., Wolfgang Saeger, M.D., Stefanie Hahner, M.D., Ann-Cathrin Koschker, M.D., Emanuela Arvat, M.D., Bruno Ambrosi, M.D., Paola Loli, M.D., Gaetano Lombardi, M.D., Massimo Mannelli, M.D., Paolo Bruzzi, M.D., Franco Mantero, M.D., Bruno Allolio, M.D., Luigi Dogliotti, M.D., and Alfredo Berruti, M.D.

N Engl J Med 2007;356:2372-80.

Linee guida ESMO 2012

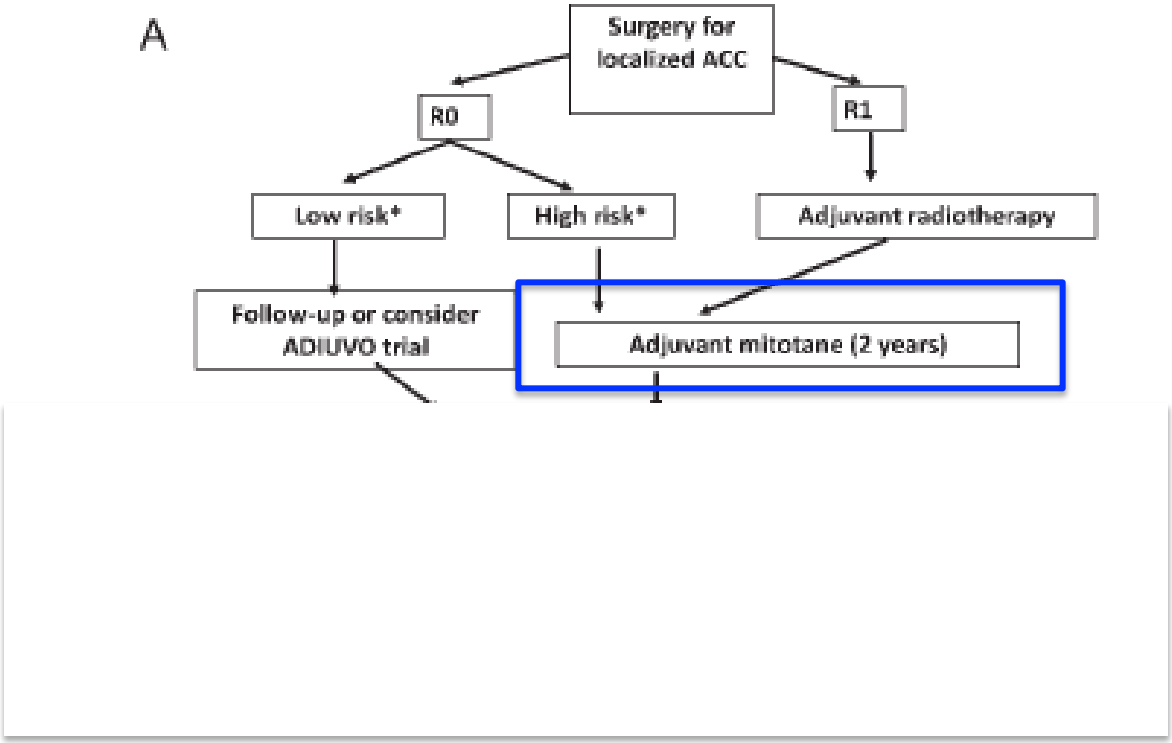

Figure 1 Algorithm on management according to stage, risk factors, and disease characteristics for adrenocortical carcinoma (ACC) (A) and pheochromocytoma (B). *Low-risk ACC is defined stage I–II and Ki67 expression in ≤10% of neoplastic cells, high-risk ACC: stage III or Ki67 expression in >10% of neoplastic cells.

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Chemioterapia : oltre il mitotane

Table 6. Effect of chemotherapy on adrenal cortical cancer.

Series	Year	Institution	Regimen	No.	Response
Williamson [83]	2000	SWOG	ECM[a]	45	PR 5
Abraham [84]	1999	NCI	MEDV	28	CR 1, PR 4
Berruti [85]	1998	Italy	MEDP	28	CR 2, PR 13
Zidan [86]	1996	Israel	EP[b]	1	PR 1
Bukowski [87]	1993	SWOG	MP	37	PR 11
Berruti [88]	1992	Italy	EDP	2	PR 2
Schlumberger [89]	1991	France	DP5-FU	13	CR 1, PR 2
Hesketh [90]	1987	Boston University	EPB	4	CR 1, PR 1
Johnson [91]	1986	Vanderbilt	EC	2	PR 2

5-FU: 5-fluorouracil; B: bleomycin; CR: complete response; D: doxorubicin; E: etoposide; M: mitotane; NCI: National Cancer Institute; P: cisplatin; PR: partial response; SWOG: Southwest Oncology Group; V: vincristine.

[a]Mitotane given only after disease progression on EC and only to patients who had not received mitotane previously.

[b]Mitotane failure.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combination Chemotherapy in Advanced Adrenocortical Carcinoma

Martin Fassnacht, M.D., Massimo Terzolo, M.D., Bruno Allolio, M.D., Eric Baudin, M.D., Harm Haak, M.D., Alfredo Berruti, M.D., Staffan Welin, M.D., Carmen Schade-Brittinger, André Lacroix, M.D., Barbara Jarzab, M.D., Halfdan Sorbye, M.D., David J. Torpy, M.D., Vinzenz Stepan, M.D., David E. Schteingart, M.D., Wiebke Arlt, M.D., Matthias Kroiss, M.D., Sophie Leboulleux, M.D., Paola Sperone, M.D., Anders Sundin, M.D., Ilse Hermsen, M.D., Stefan
Antoine Tabarin, M.D., Marcus
Martin Schlumberger, M.D.,
Felix Beuschlein, M.D., Han
Monica Sender, M.D., Mau
Tito Fojo, M.D., Hans-He
for the

N ENGL J MED 366;23 NEJM.ORG JUNE 7, 2012

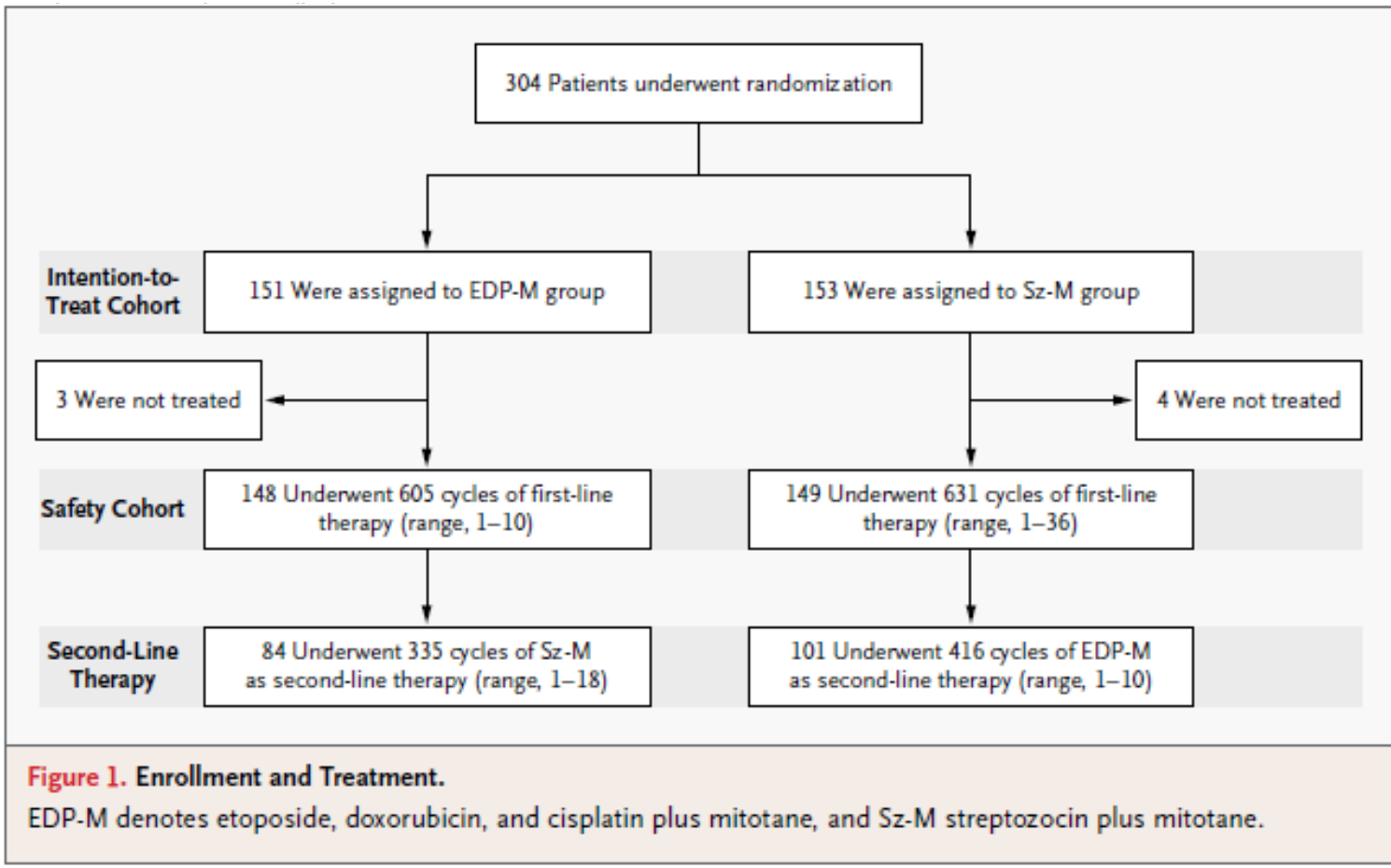
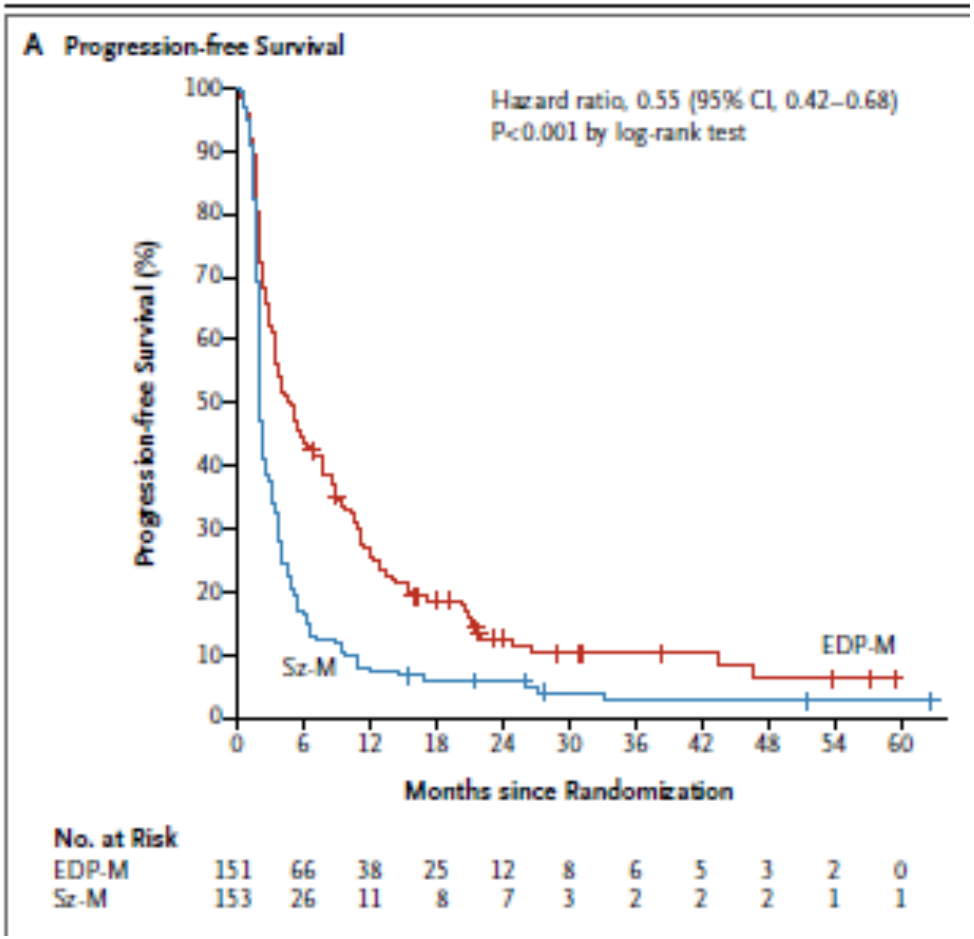


Figure 1. Enrollment and Treatment.

EDP-M denotes etoposide, doxorubicin, and cisplatin plus mitotane, and Sz-M streptozocin plus mitotane.


A Progression-free Survival
Hazard ratio, 0.55 (95% CI, 0.42–0.68)
P<0.001 by log-rank test
Progression-free Survival (%)
100
90
80
70
60
50
40
30
20
10
0
EDP-M
Sz-M
0 6 12 18 24 30 36 42 48 54 60
Months since Randomization
No. at Risk
EDP-M 151 66 38 25 12 8 6 5 3 2 0
Sz-M 153 26 11 8 7 3 2 2 2 1 1

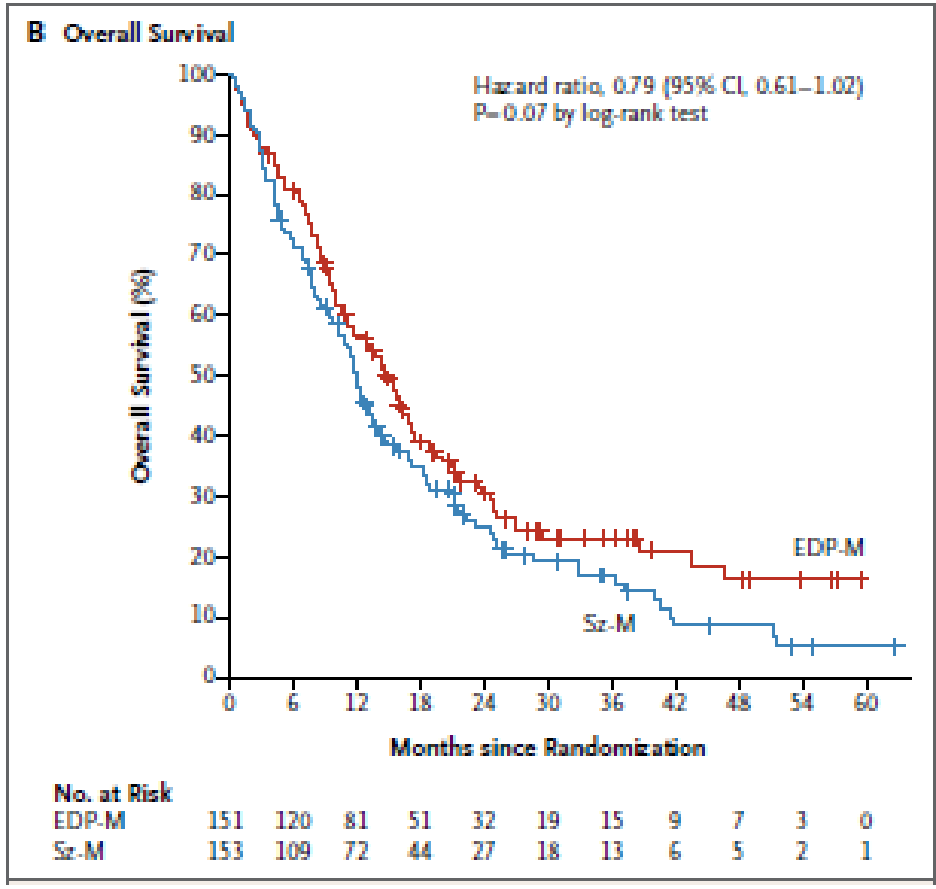

B Overall Survival
Hazard ratio, 0.79 (95% CI, 0.61–1.02)
P=0.07 by log-rank test
Overall Survival (%)
100
90
80
70
60
50
40
30
20
10
0
EDP-M
Sz-M
0 6 12 18 24 30 36 42 48 54 60
Months since Randomization
No. at Risk
EDP-M 151 120 81 51 32 19 15 9 7 3 0
Sz-M 153 109 72 44 27 18 13 6 5 2 1

Table 3. Serious Adverse Events during First-Line Therapy.

Event	EDP-M (N = 148)	Sz-M (N = 149)
	no. of patients (%)	
Any serious adverse event	86 (58.1)	62 (41.6)
Adrenal insufficiency	5 (3.4)	1 (0.7)
Bone marrow toxicity	17 (11.5)	3 (2.0)
Cardiovascular or thromboembolic event	10 (6.8)	0
Fatigue or general health deterioration	8 (5.4)	7 (4.7)
Gastrointestinal disorder	6 (4.1)	12 (8.1)
Impaired liver function	0	7 (4.7)
Impaired renal function	1 (0.7)	6 (4.0)
Infection	10 (6.8)	4 (2.7)
Neurologic toxicity	5 (3.4)	4 (2.7)
Respiratory disorder	9 (6.1)	5 (3.4)
Other	15 (10.1)	13 (8.7)

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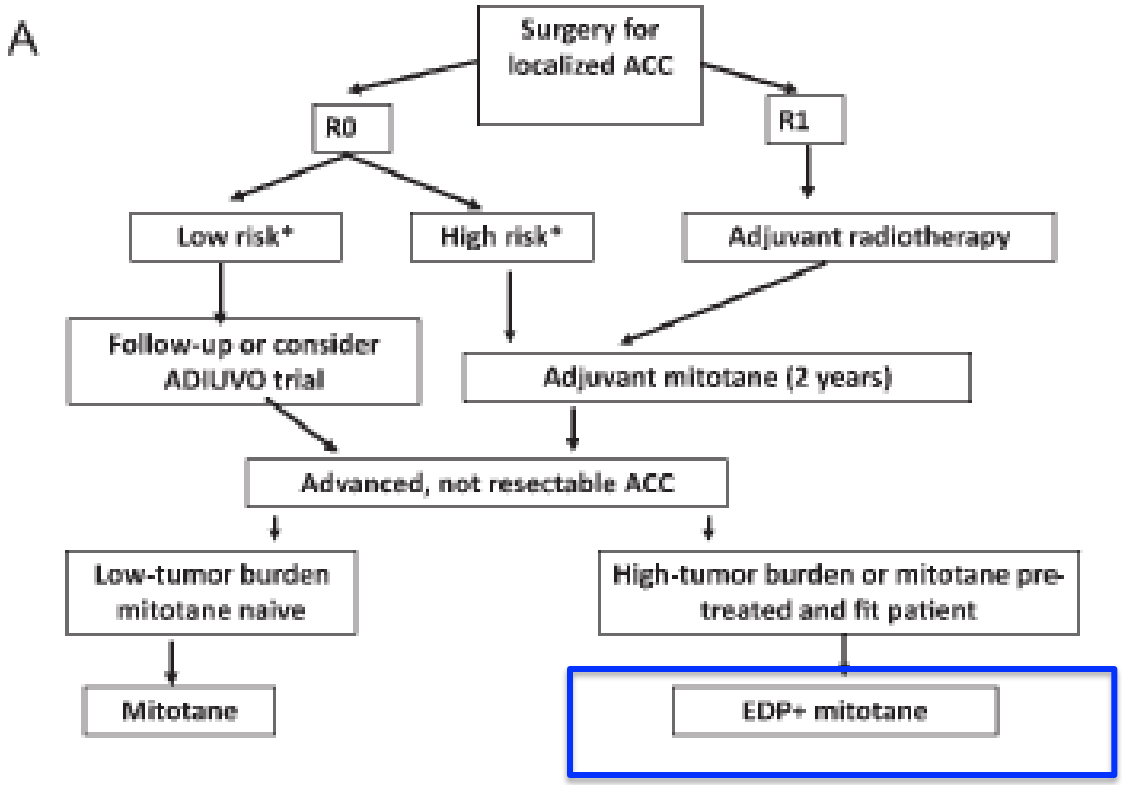

Figure 1 Algorithm on management according to stage, risk factors, and disease characteristics for adrenocortical carcinoma (ACC) (A) and pheochromocytoma (B). *Low-risk ACC is defined stage I–II and Ki67 expression in ≤10% of neoplastic cells, high-risk ACC: stage III or Ki67 expression in >10% of neoplastic cells.

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Table 4: Ongoing Clinical Trials that test the Target Therapies.

Study	Target	ID	Purpose	Status
Mitotane with or without *IMC-A12* in treating patients with recurrent, metastatic, or primary adrenocortical cancer that cannot be removed by surgery	*IGF1R*	NCT00778817	This randomized phase II trial compares the combination of mitotane and IMC-A12 with mitotane alone in the treatment of recurrent, metastatic, or primary adrenocortical cancer that cannot be removed by surgery	Recruiting
A study of *OSI-906* in patients with locally advanced or metastatic adrenocortical carcinoma (GALACCTIC)	*IGF1R*	NCT00924989	A multicenter, randomized, double-blind, placebo-controlled, phase III study of single-agent OSI-906 in patients with locally advanced/metastatic adrenocortical carcinoma who received at least 1 but no more than 2 prior drug regimens	Ongoing not recruiting
Phase II trial of *ZD1839* (*Iressa*) in patients with nonresectable adrenocortical carcinoma	*VEGFR*	NCT00215202	This phase II trial investigates the effect of Iressa in patients with nonresectable adrenocortical cancer who have previously been treated with one other form of systemic therapy (either Mitotane or chemotherapy).	Completed
Phase II Study of *Axitinib* (AG-013736) With Evaluation of the VEGF-Pathway in Metastatic, Recurrent or Primary Unresectable Adrenocortical Cancer	*Multikinase* (i) *VEGFR* (ii) *PDGFR* (iii) *KIT*	NCT01255137	To evaluate the effectiveness of axitinib in individuals who have adrenocortical cancer that is inoperable and has not responded to standard treatments	Recruiting
Sunitinib in Refractory Adrenocortical Carcinoma (SIRAC)	*Multikinase* (i) *VEGFR* (ii) *PDGFR* (iii) *KIT*	NCT00453895	The primary objective of this trial is to estimate the response (defined as progression-free survival of $\geq$12 weeks) rate associated with Sunitinib treatment in patients advanced ACC progressing after cytotoxic chemotherapy	Unknown
Sorafenib Plus Paclitaxel in adreno-cortical-cancer patients (PAXO)	*Multikinase* (i) *RAF* (ii) *VEGFR* (iii) *PDGFR* (iv) *KIT*	NCT00786110	The aim of this phase II trial is to evaluate the clinical benefit and toxicity of the combination of Sorafenib plus metronomic chemotherapy in patients with locally advanced or metastatic ACC who progressed after first or second line chemotherapy.	Unknown
Clinical trial of *Dovitinib* in first-line metastatic or locally advanced non-resectable adrenocortical carcinom	*FGFRs*	NCT01514526	Non-randomized, phase II clinical trial, that investigates the use of Dovitinib in adult patients with metastatic or locally advanced non-resectable adrenocortical carcinoma, confirmed histologically	Recruiting
Cixutumumab in treating patients with relapsed or refractory solid tumors	*IGF1R*	NCT00831844	Phase II trial that studies the side effects and how well cixutumumab works in treating patients with relapsed or refractory solid tumors, including ACC	Recruiting

Adrenocortical Carcinoma: Current Therapeutic State-of-the-Art
Journal of Oncology
Volume 2012, Article ID 234726, 11 pages
dot:10.1155/2012/234726

Amir H. Lebastchi, John W. Kunstman, and Tobias Carling

Department of Surgery, Yale Endocrine Neoplasia Laboratory, Yale School of Medicine, .

Suspected diagnosis	Confirmatory test	Diagnostic test	Preoperative managment	Postoperative management
Pheochromocytoma	Plasma metanephrines	24-h urine metanephrines. Clonidine suppression test. MRI may be considered in some selected cases	α−Blocker +/− β−blocker +/− calcium channel blocker. Additional imaging studies as clinically indicated.	Monitor blood pressure and glucose levels. Intravenous fluid to treat hypotension. Discontinue or adjust antihypertensive therapy.

Table 2. — Chemotherapy Trials for Treating Malignant Pheochromocytoma

Trial	Year	No. of Patients	Median Survival (mos)*	Biochemical Response Rate (%)	Radiologic Response Rate (%)	Chemotherapy Regimen
Nomura et al[21]	2009	19	216	52	N/D	CVD
Huang et al[22]	2008	18 **	78	72	56	CVD
Rao et al[23]	2000	9	N/D	56	N/D	CVD
Patel et al[24]	1995	13	67	N/D	46	CDD
Averbuch et al[25]	1988	14 **	65	79	57	CVD

CVD = cyclophosphamide, vincristine, and dacarbazine, CDD = cyclophosphamide, doxorubicin, and dacarbazine, N/D = no data.
* No study has shown an overall survival benefit with any chemotherapy regimen.
** The 2008 study by Huang et al[22] is a 22-year follow-up by the National Institutes of Health of the original study published by Averbuch et al[25] in 1988.

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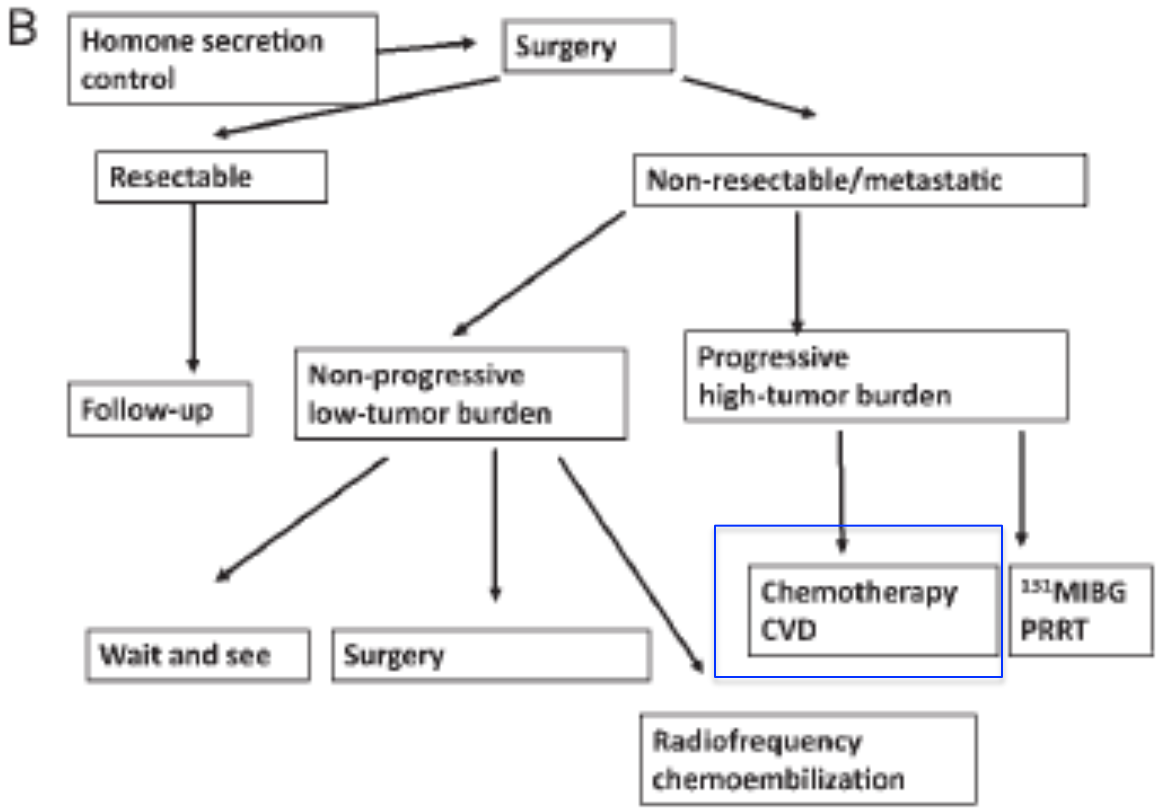

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doi:10.1093/annonc/mds231

Changing Paradigms in the Treatment of Malignant Pheochromocytoma

Raymon H. Grogan, MD, Elliot J. Mitmaker, MD, and Quan-Yang Duh, MD

Table 1. — Gene Mutations Associated With Malignant Pheochromocytoma and Paraganglioma

Gene	Chromosome	Exon	Protein	Germline Mutation Rate (%)*	Malignancy Rate (%)
VHL[5-8]	3p25-26	3	pVHL19 and pVHL30	2–11	5
SDHB[6,7,9,10]	1p36.13	8	Catalytic iron-sulfur protein	3–10	50
SDHD[6,7,9,10]	11q23	4	CybS (membrane-spanning subunit)	4–7	< 3
RET[6,7]	10q11.2	21	Tyrosine-kinase receptor	< 5	3
NF1[7]	17q11.2	59	Neurofibromin	Unknown	11
KIF1BBeta[11]	1p36.2	41	Kinesin family member 1B (microtubule motor)	Unknown	Unknown

* The rate of germline mutations found in apparently sporadic mutations. Dotted line separates the HIF pathway mutations (above) from the RNA regulation pathway (below). Reprinted from the *Lancet*, Vol. No. 366(9486), Lenders JW, Eisenhofer G, Mannelli M, et al. Phaeochromocytoma; pages 665-675.

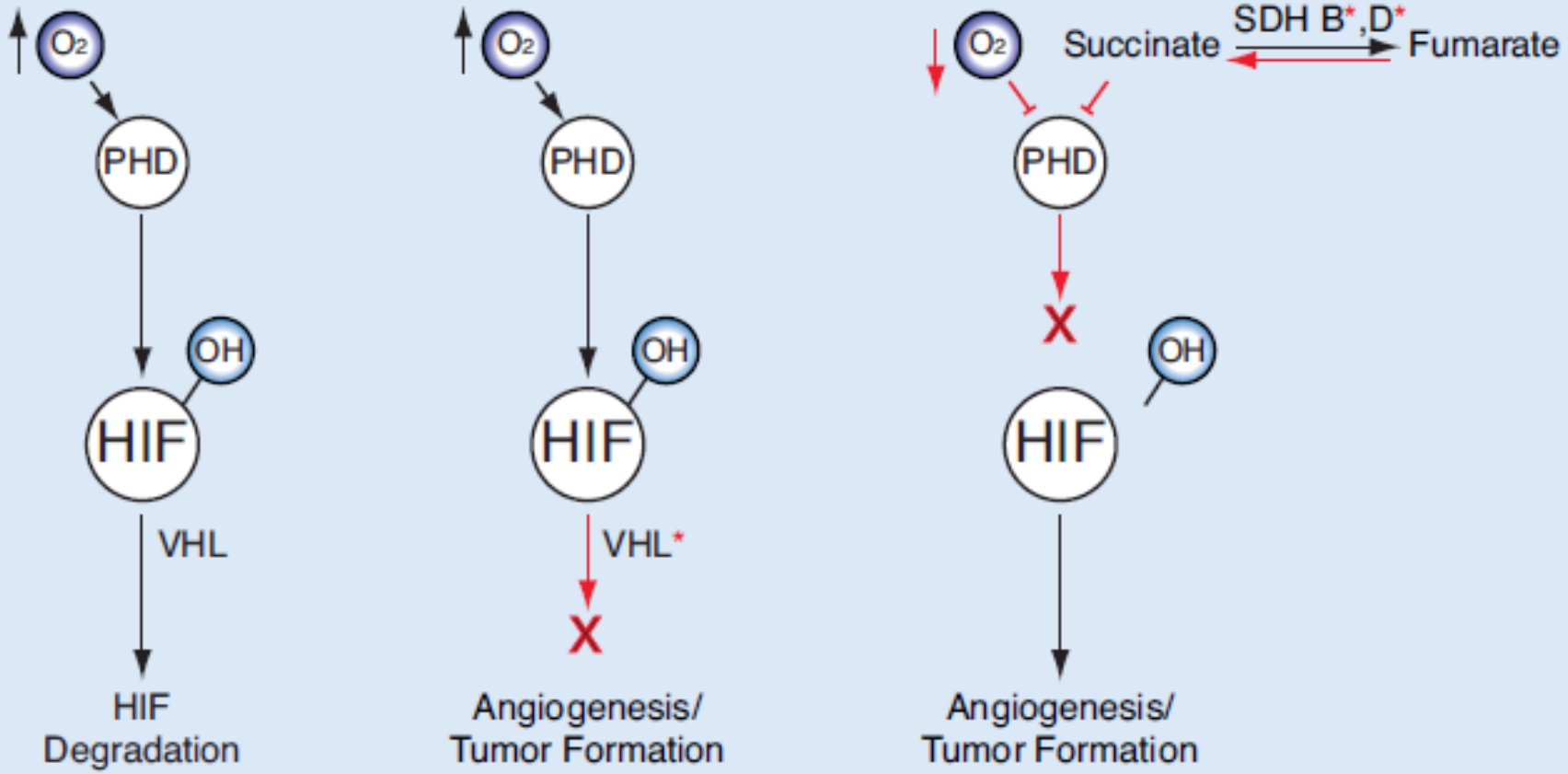


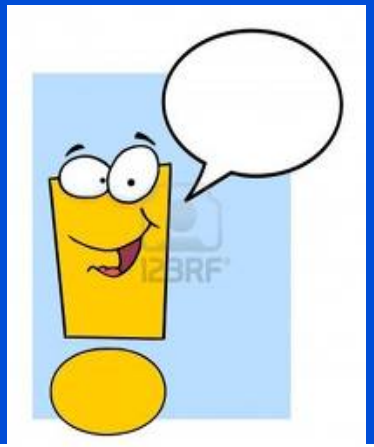
Figure. — Three HIF pathway mutations are associated with pheochromocytoma. The HIF protein regulates cellular responses to oxygen tension by acting as a transcriptional regulator for multiple proangiogenic factors. Under normal normoxic conditions, HIF is hydroxylated by PHDs allowing it to be degraded by a VHL-mediated process (left). Mutations of VHL prevent HIF degradation, causing increased HIF accumulation, unregulated angiogenesis, and tumor formation (middle). Mutations of SDHB and SDHD genes cause succinate to accumulate. Excess succinate prevents PHDs from hydroxylating HIF, which also leads to HIF accumulation, activation, and tumor formation. Under normal hypoxic conditions HIF is activated via the PHD pathway to promote angiogenesis (right). VHL = von Hippel-Lindau, PHD = prolyl hydroxylase domain, HIF = hypoxia-inducible factor, SDHB = succinate dehydrogenase B subunit gene, SDHD = succinate dehydrogenase D subunit gene.

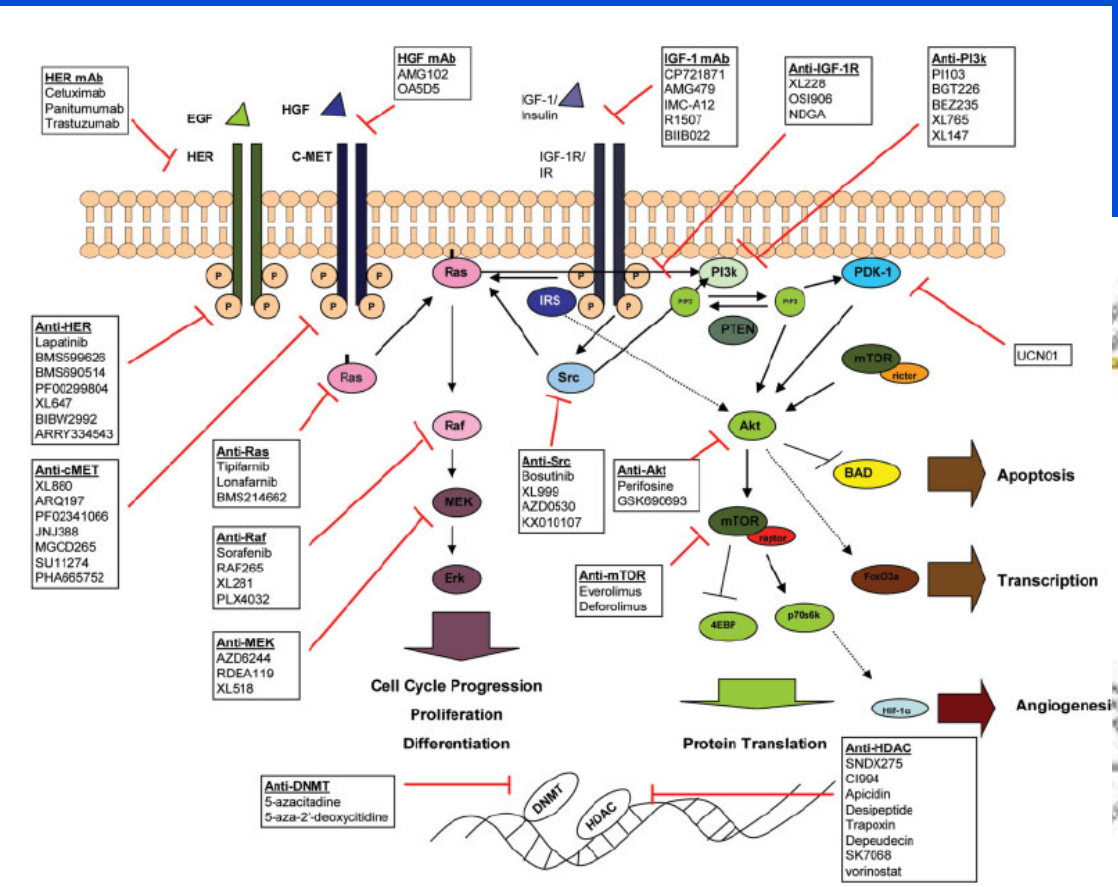
Table 3. — Molecular Targets and Current (or Potential) Cytostatic Therapies for Malignant Pheochromocytomas or Paragangliomas

Reference	Molecular Target	Potential Targeted Therapy	Trial Phase
Kulke et al[54]	Vascular endothelial growth factor (VEGF)	Thalidomide	I/II
Kulke et al[54]	Basic fibroblast growth factor (bFGF)	Thalidomide	I/II
Gross et al[56] Joshua et al[58] Jimenez et al[60]	Receptor tyrosine kinase (RTK): KIT, PDGF-R, and ABL VEGF, PDGFR-β, c-KIT, FLT3, and RET	Imatinib mesylate Sunitinib	I/II
Yao et al[38] Druce et al[43]	Mammalian target of rapamycin (mTOR)	Everolimus (RAD001)	I/II
Welsh et al[45,46]	Hypoxia-inducible factor 1-alpha (HIF-1α)	PX-478 PX-12	N/A
Choi et al[47] Temes et al[48]	Prolyl hydroxylase	KRH102053 R59949	N/A
Saeger et al[61]	ERBB-2 (HER-2/neu)	Trastuzumab	N/A

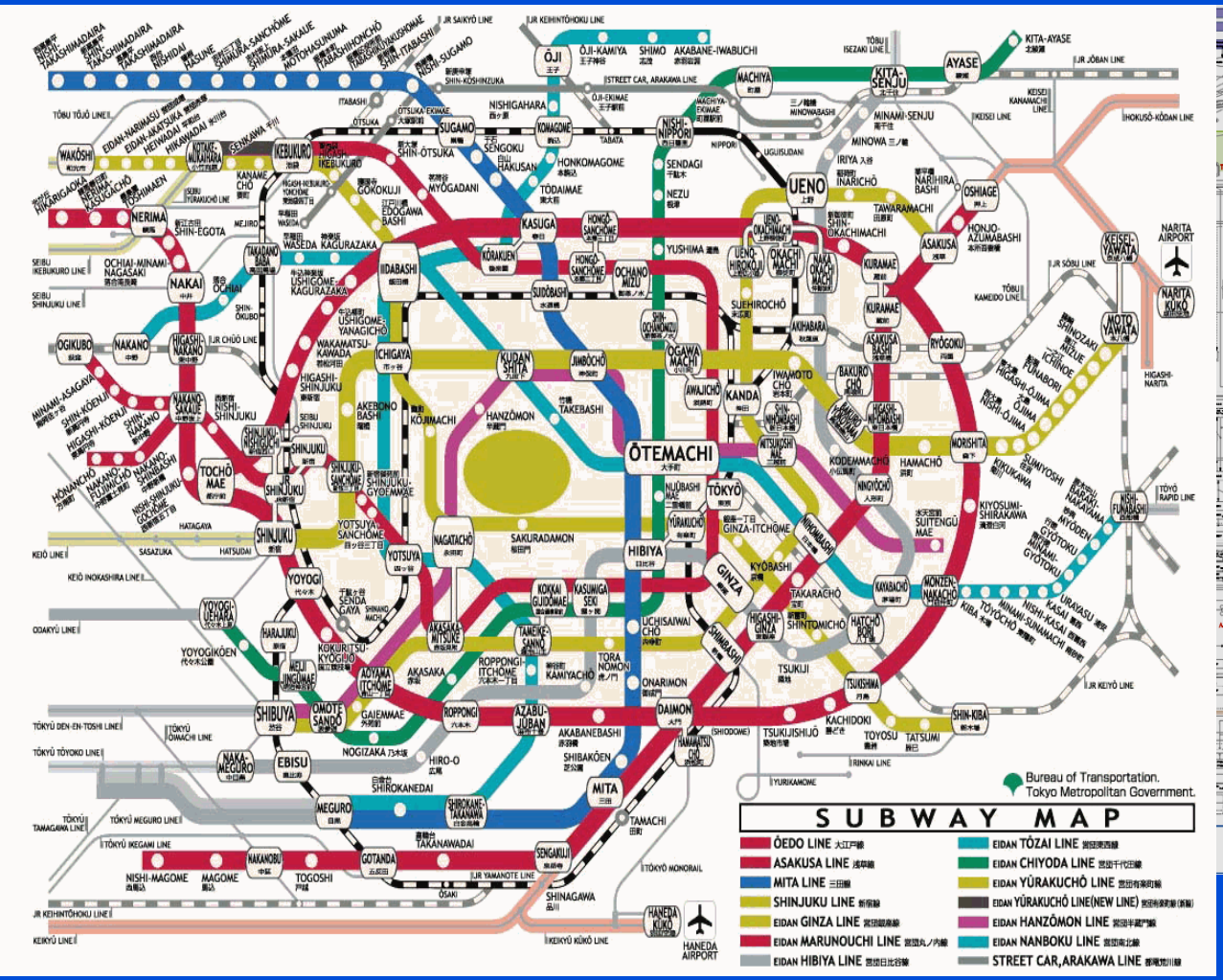
Take home messages

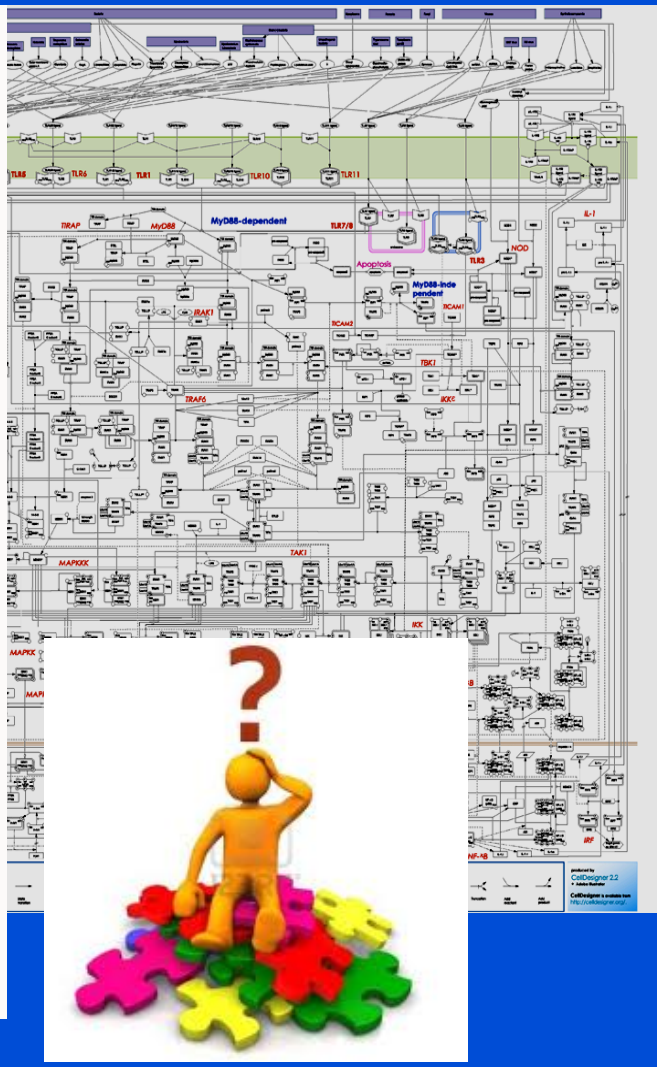
Take home messages





Take home messages





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"REGINA APOSTOLORUM"