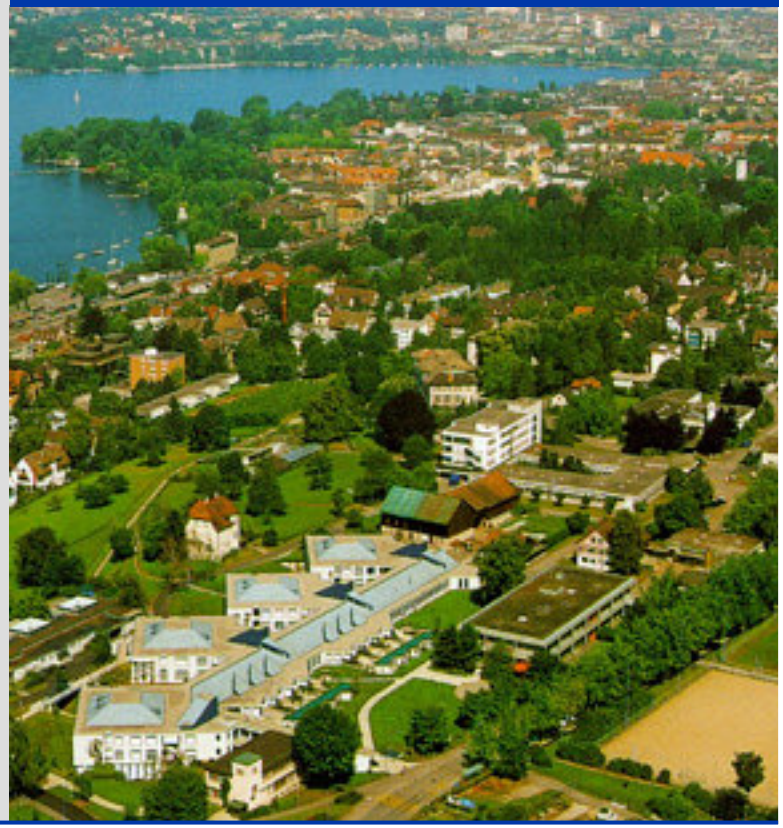
EPI

Schweizerisches Epilepsie-Zentrum

SAGB Jahrestagung 2012

Beeinflussung des Verlaufs einer tuberösen Sklerose durch mTOR-Inhibition



Dr. T. Dorn

Übersicht

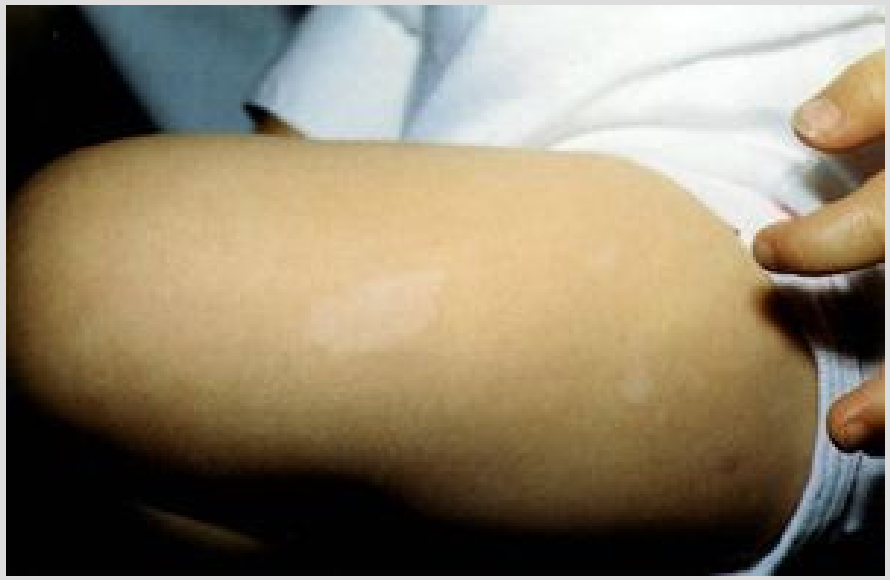
- Klinik und Genetik
- Pathophysiologie
- mTOR-Inhibition – Studien bei TSC
- Kasuistik 1: Eigene Erfahrung
- Kasuistik 2: Was nun?
- Fazit

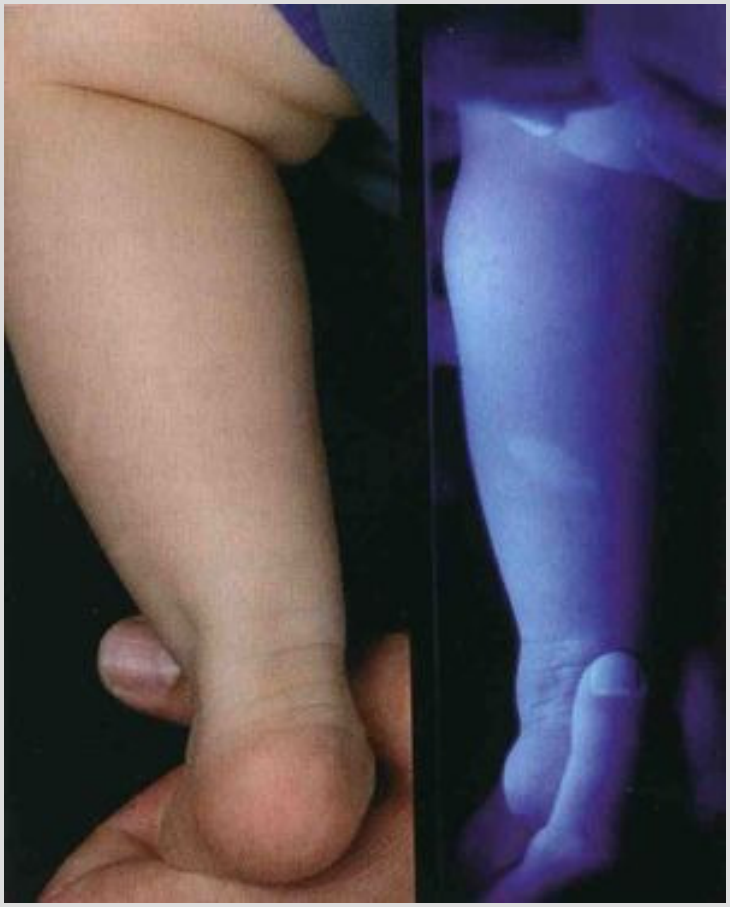
Klinik und Genetik der TS

- Neurokutane, genetisch bedingte Erkrankung mit charakteristischen tumorösen Manifestationen an ZNS, Haut und anderen Organen (u.a. Niere, Herz)
- Häufig epileptische Anfälle, geistige Behinderung
- Ursache: Mutationen in zwei Tumorsuppressor-Genen
  - TSC1 (Hamartin) (Chromosom 9)
  - TSC2 (Tuberin) (Chromosom 16)

Klinik und Genetik der TS – TSC2

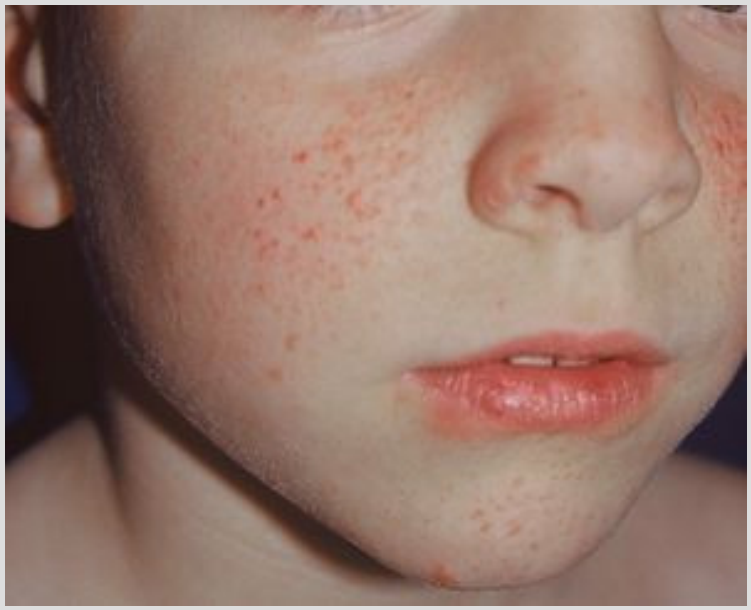
Hypomelanotische Flecken

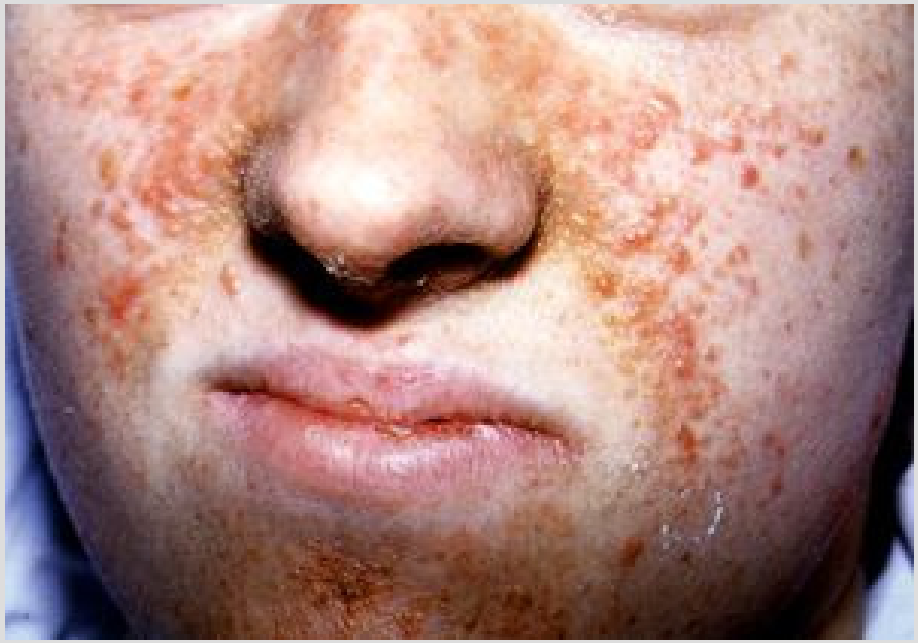




Klinik und Genetik der TS – TSC2

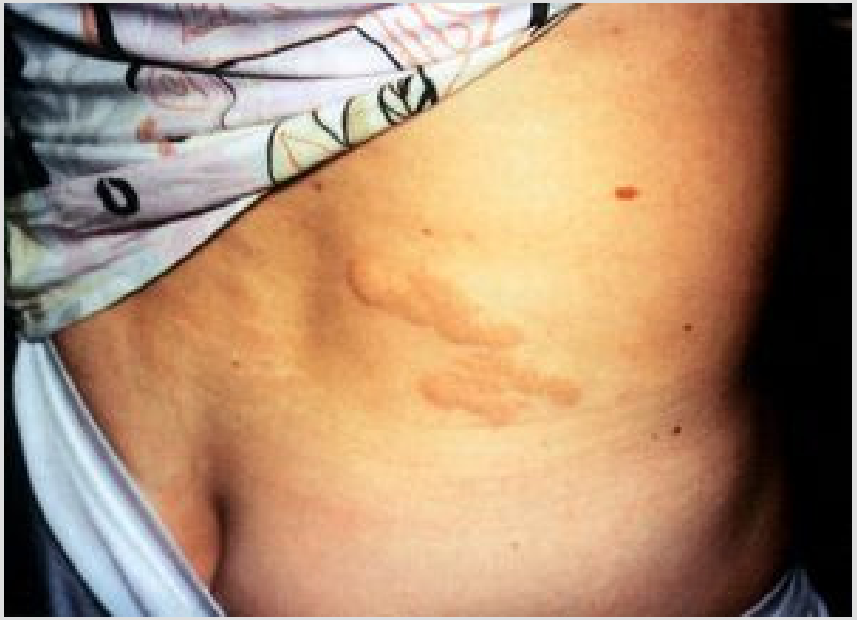
Angiofibrome des Gesichts



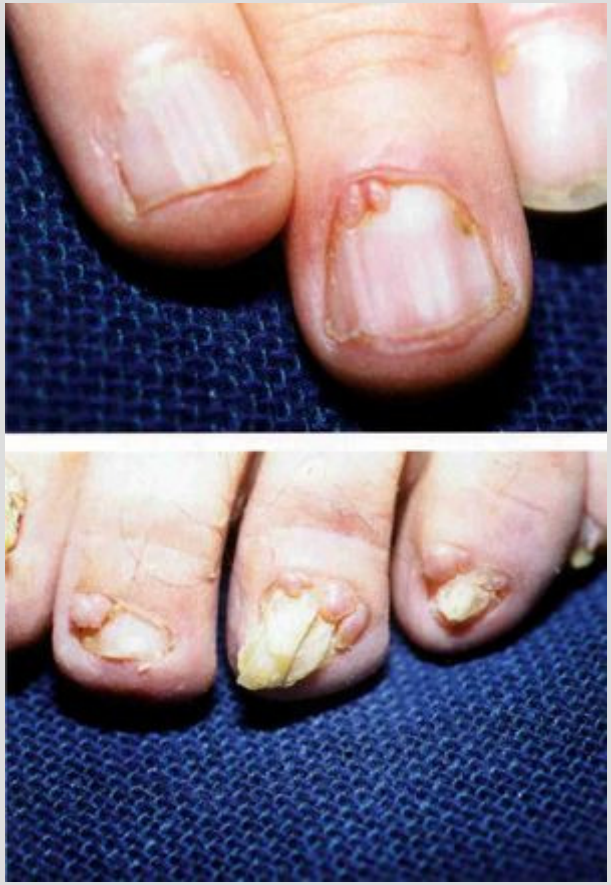


Klinik und Genetik der TS – TSC2

Pflasterstein-Nävus

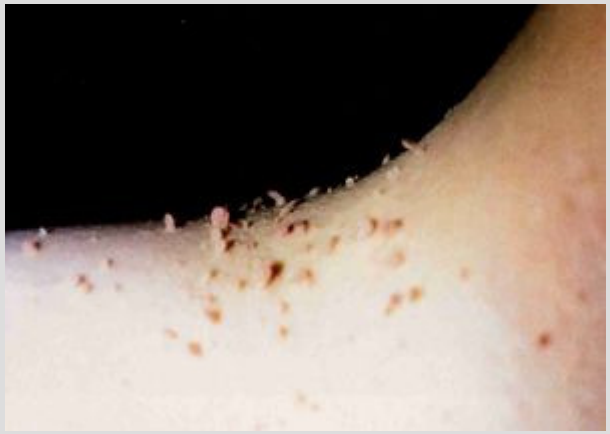


Nagelfalz-Fibrome (Koenen-Tumore)

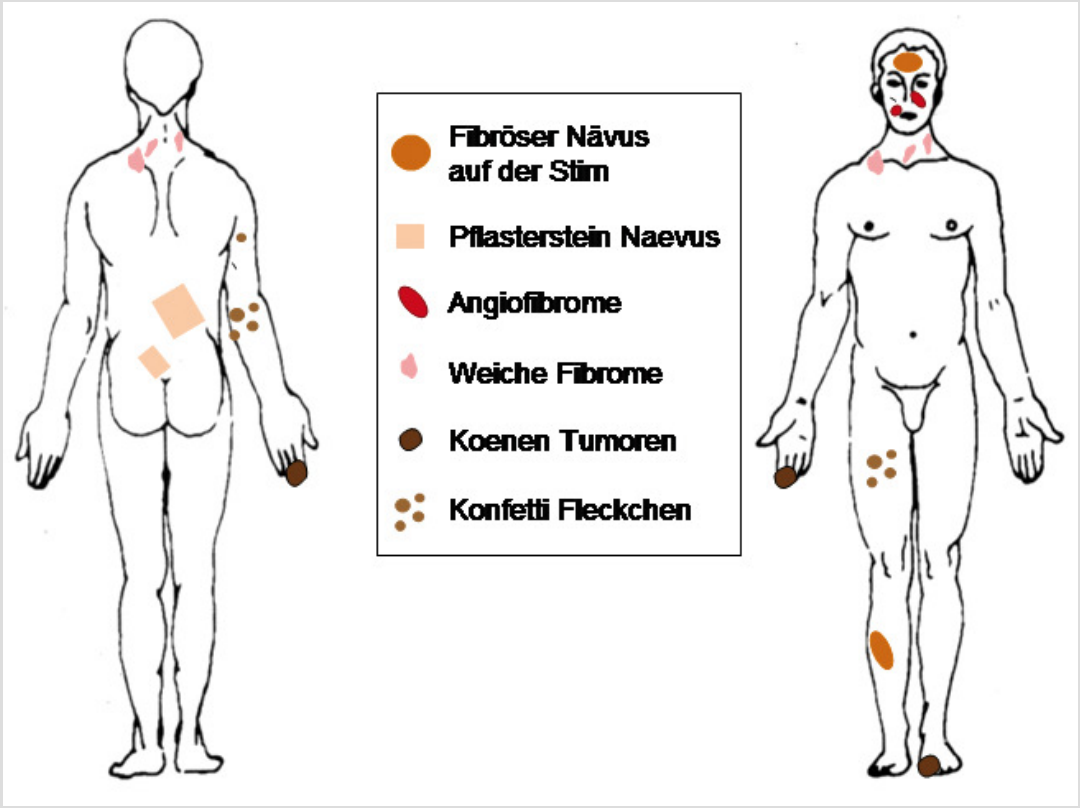


Klinik und Genetik der TS – TSC2

Pendel-Fibrome



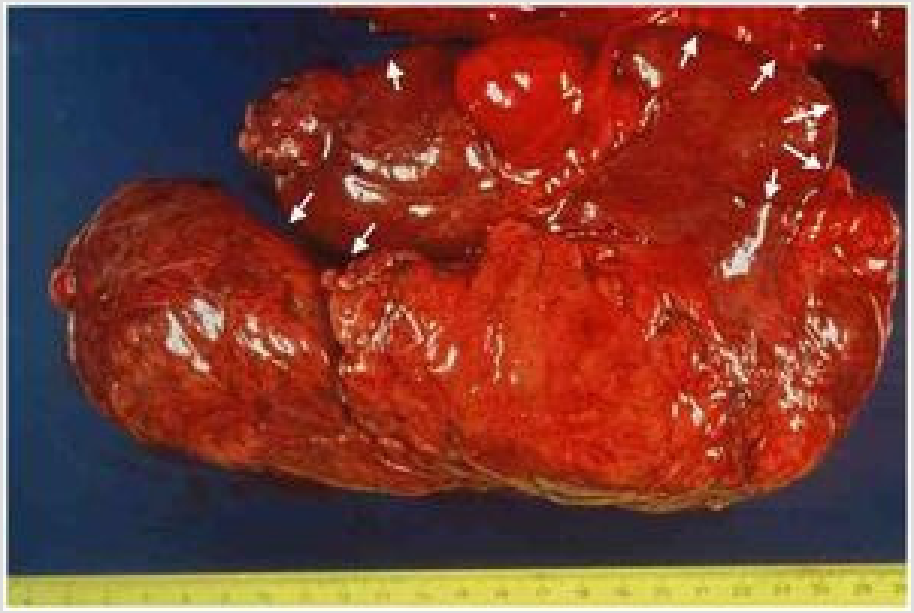
Übersicht Hautveränderunge



Klinik und Genetik der TS – TSC2

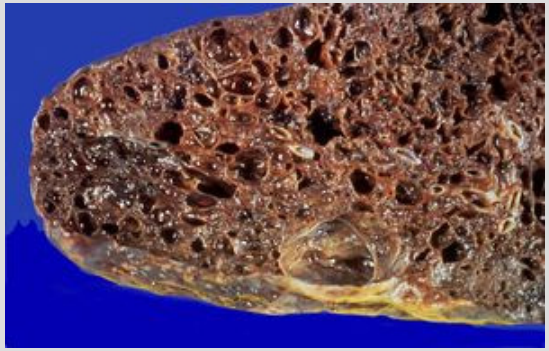
Angiomyolipome und Komplikationen

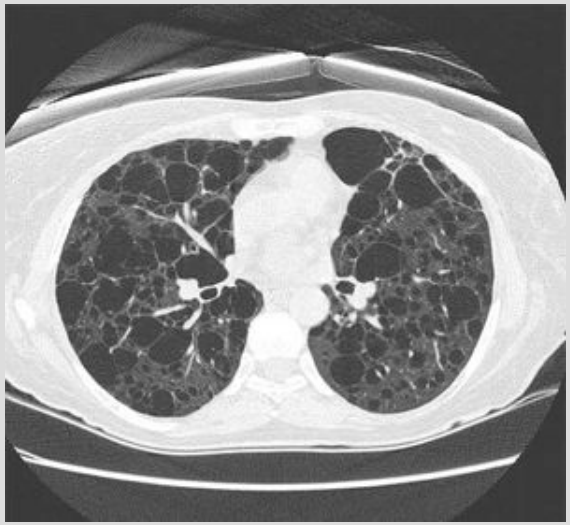
- Blutungen (> 4 cm)
- Renale Hypertonie
- Keine direkte pathogenetische Beziehung zu Nierenzell-CA, die bei TSC gehäuft vorkommen
- Lymphangiomyomatose (v.a. bei Frauen)
- Therapie:
  - OP (ggf. Nephrektomie)
  - Ggf. Embilusation



Klinik und Genetik der TS – TSC2

Lymphangiomyomatose



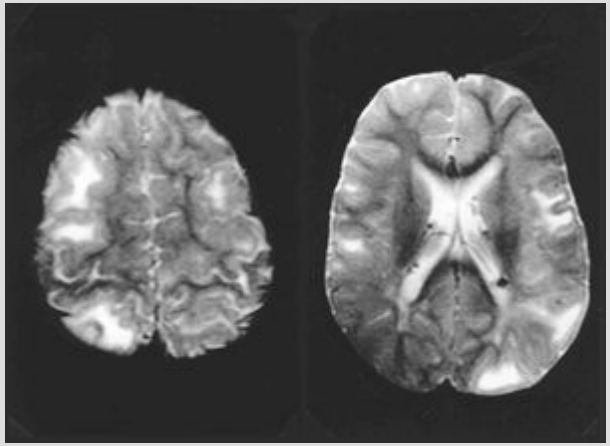


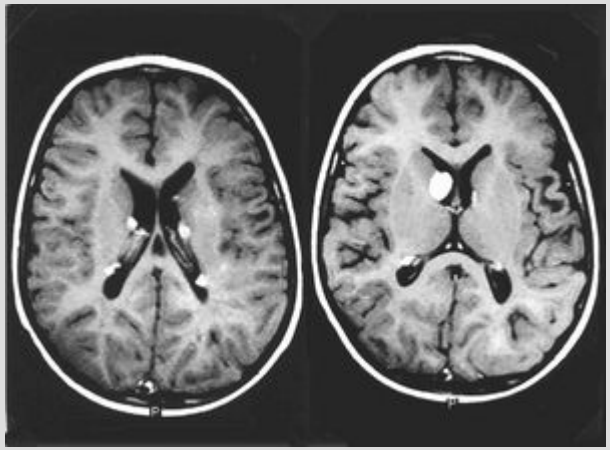
- Fast nur bei Frauen, v.a. TSC 2
- Therapie:
  - Ovarektomie
  - Lungentransplantation

Klinik und Genetik der TS – TSC2

Gehirnbeteiligung

Kortikale Tubera

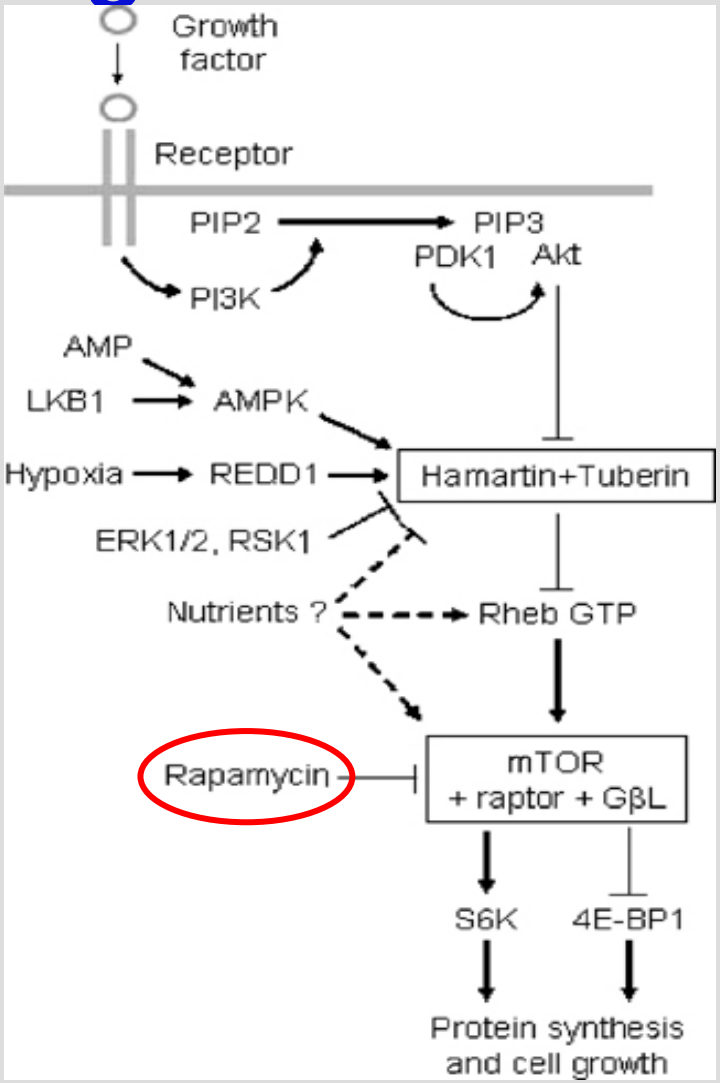




Gliaknötchen,
Subependymale
Riesenzellastrozytome

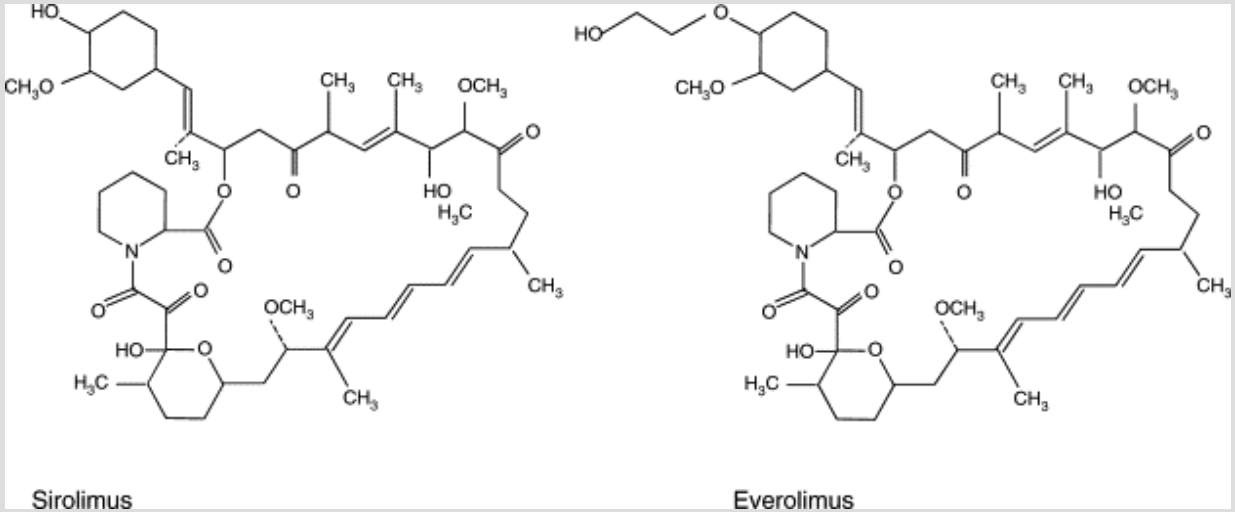
- Epilepsie
  - BNS-Anfälle
  - fokale Anfälle
  - meist Pharmakotherapie-resistenz
  - Epilepsiechirurgie möglich
- Geistige Behinderung
- Autismus
- Hydrocephalus

Pathophysiologie



Yates JRW European Journal of Human Genetics 2006; 14: 1065–1073.

mTOR-Inhibition - Studien



Sirolimus = Rapamycin (Rapamune®),

- aus Streptomyces hygropicus aus der Erde der Osterinsel Rapa Nui 1975
- (Antimykotikum)
- Immunsuppression nach Organtransplantation
- Tumortherapie
- **TSC (off label)**

Evorlimus (Votubia®)

- Derivat von Rapamycin
- Evtl. grössere onkologische Bedeutung als Rapamycin
- **TSC (für SEGA, evtl. Angiomyolipome)**

Nach Otto, T, Hrsg. mTOR-Inhibotoren Update 2011, Uni-Med Verlag AG, Bremen 2011

mTOR-Inhibition – Studien - SEGA

Everolimus for Subependymal Giant-Cell Astrocytomas in Tuberous Sclerosis

Darcy A. Krueger, M.D., Ph.D., Marguerite M. Care, M.D., Katherine Holland, M.D., Ph.D., Karen Agricola, F.N.P., Cynthia Tudor, P.N.P., Prajakta Mangeshkar, M.S., Kimberly A. Wilson, M.S., Anna Byars, Ph.D., Tarek Sahmoud, M.D., Ph.D., and David Neal Franz, M.D.

Table 2. Response of Primary Subependymal Giant-Cell Astrocytomas (SEGAs) to Everolimus Therapy at 6 Months, among the 28 Patients, According to Type of Assessment.*

SEGA Volume	Local Investigator's Assessment		Independent Central Review	
	Baseline	6 Mo	Baseline	6 Mo
Mean — cm^3	2.25±1.66	1.24±0.90	2.45±2.81	1.30±1.48
Median — cm^3	2.00	0.96	1.74	0.93
Range — cm^3	0.35–7.10	0.19–3.40	0.49–14.23	0.31–7.98
Reduction from baseline				
Mean — cm^3	1.01±1.04		1.15±1.42	
Median (95% CI) — cm^3	0.92 (0.5–1.4)		0.80 (0.4–1.2)	
P value	<0.001		<0.001	
Percent reduction — no. (%)				
≥50	11 (39)		9 (32)	
≥30	21 (75)		21 (75)	
>0	28 (100)		28 (100)	

* Plus–minus values are means ±SD. At 6 months (i.e., the end of the core treatment phase), 1 of the 28 patients had discontinued therapy; the 6-month data for this patient were obtained from the magnetic resonance imaging performed at 3 months, according to the last-observation-carried-forward approach. CI denotes confidence interval.

Table 1. Baseline Characteristics of the 28 Patients Receiving Everolimus.*

Characteristic	Value
Age — yr	
Median	11
Range	3–34
Age group — no. (%)	
3 to <12 yr	16 (57)
≥12 to <18 yr	6 (21)
≥18 yr	6 (21)
Sex — no. (%)	
Male	17 (61)
Female	11 (39)
No. of SEGA lesions — no. (%)	
1	15 (54)
2	13 (46)
Bilateral SEGAs — no. (%)	12 (43)
Hydrocephalus — no. (%)	6 (21)
Facial angiofibroma — no. (%)	25 (89)
Previous therapy or surgery for SEGA — no. (%)	5 (18)
Surgery	4 (14)
Systemic therapy	2 (7)
No. of antiepileptic drugs in use at baseline — no. (%)	23 (82)
1	10 (36)
2	10 (36)
≥3	3 (11)

* SEGA denotes subependymal giant-cell astrocytoma.

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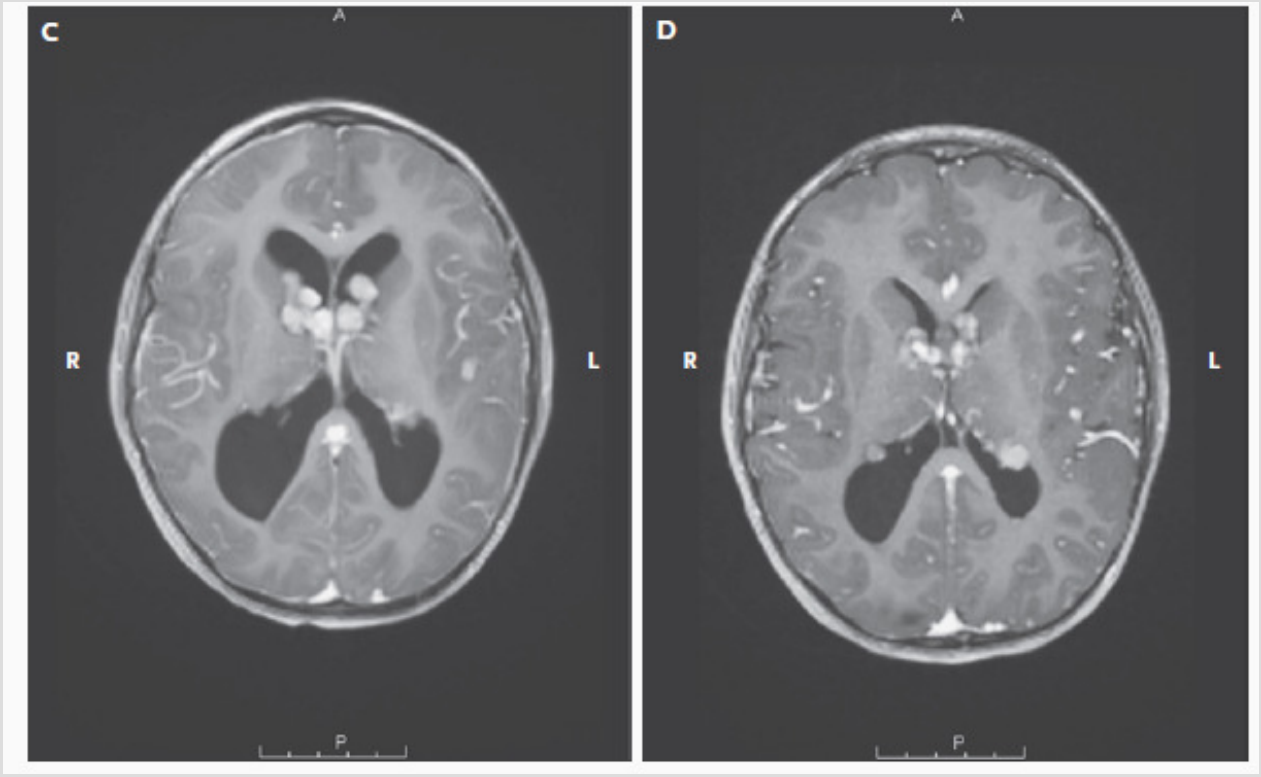

Krueger DA et al.. New England Journal of Medicine 2010;363:1801- 1811

mTOR-Inhibition – Studien - SEGA

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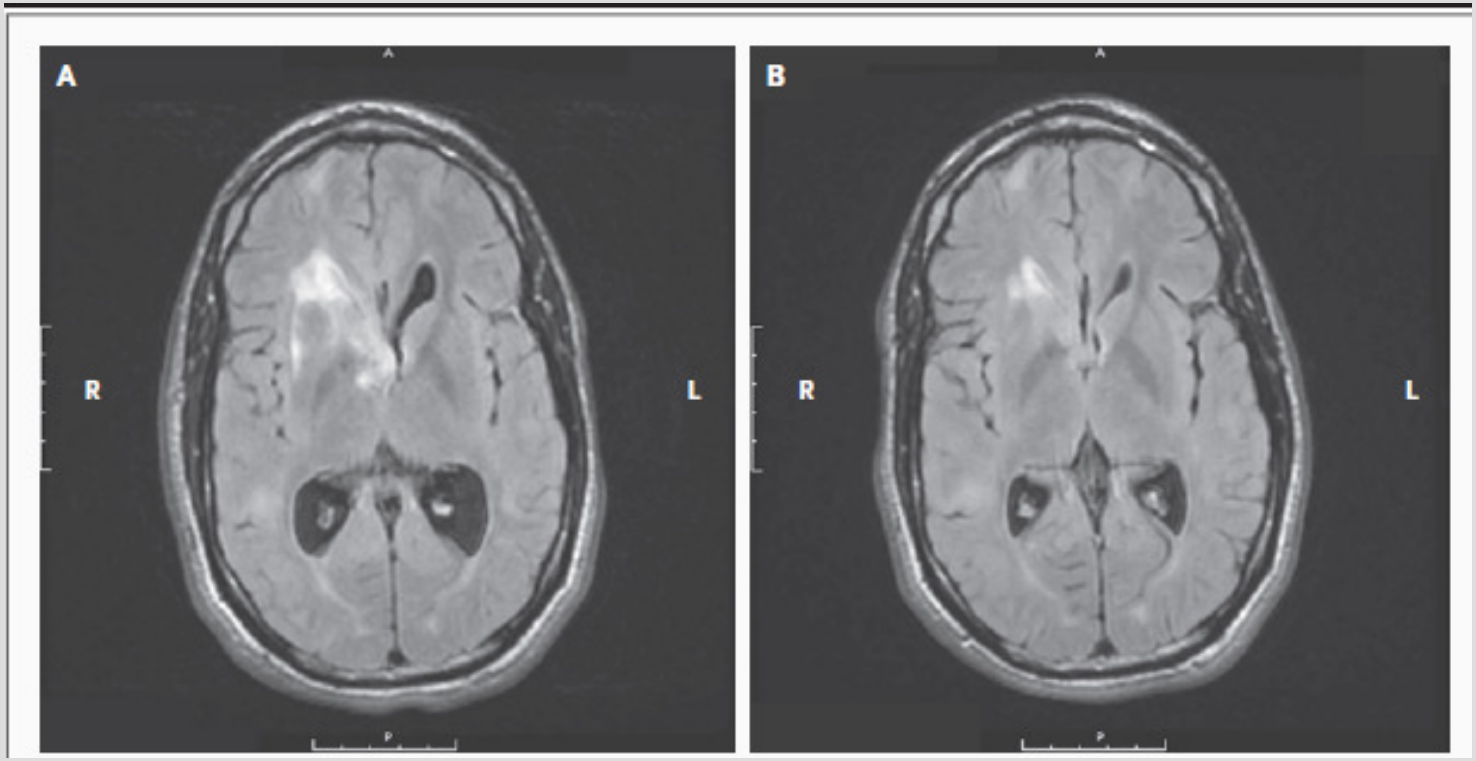

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Sekundärer Endpunkt Epilepsie

- 24-Video-EEG bei 16 von 28 Patienten vor und 6 Monate nach Behandlungsbeginn
- Anfallsfrequenz rückläufig bei 9 Patienten, gleichbleibend bei 6, zunehmend bei 1 Patient
- Bei 15 Patienten CYP-3A4 – induzierende AED (z.B. CBZ) → niedrigere Everolimus-Konzentrationen, höhere AED-Konzentrationen(?)

Sekundärer Endpunkt Lebensqualität und Kognition

- QOLCE (Qulity of Life in Children with Epilepsy) verbessert sich signifikant
- Neuropsychologische Verlaufsuntersuchungen bei 24 Patienten zeigten keine Veränderung

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Table 4. Adverse Events in the 28 Patients.

Event*	Adverse Event		Adverse Drug Reaction	
	Any	Grade 3 or 4	Any	Grade 3†
	number (percent)			
Any	28 (100)	11 (39)	28 (100)	5 (18)
Stomatitis	22 (79)	1 (4)	22 (79)	1 (4)
Upper respiratory tract infection	22 (79)	0	22 (79)	0
Sinusitis	11 (39)	1 (4)	11 (39)	1 (4)
Otitis media	10 (36)	0	10 (36)	0
Pyrexia	10 (36)	0	8 (29)	0
Convulsion	7 (25)	3 (11)	0	0
Acneiform dermatitis	7 (25)	0	7 (25)	0
Diarrhea	7 (25)	0	6 (21)	0
Vomiting	6 (21)	1 (4)	2 (7)	0
Cellulitis	6 (21)	0	6 (21)	0
Body tinea	5 (18)	0	4 (14)	0
Cough	5 (18)	0	3 (11)	0
Headache	5 (18)	0	1 (4)	0
Rash	5 (18)	0	1 (4)	0
Personality change	5 (18)	0	0	0
Dizziness	4 (14)	1 (4)	0	0
Gastroenteritis	4 (14)	0	4 (14)	0
Otitis externa	4 (14)	0	4 (14)	0
Skin infection	4 (14)	0	3 (11)	0
Allergic rhinitis	4 (14)	0	0	0
Contact dermatitis	4 (14)	0	0	0
Acne	3 (11)	0	3 (11)	0
Gastric infection	3 (11)	0	3 (11)	0
Dry skin	3 (11)	0	1 (4)	0
Constipation	3 (11)	0	0	0
Skin disorder	3 (11)	0	0	0
Laboratory abnormalities reported as adverse events				
Decreased white-cell count	3 (11)	1 (4)	3 (11)	1 (4)
Hypertriglyceridemia	3 (11)	0	3 (11)	0

* Each adverse event is listed as the preferred term of the *Medical Dictionary for Regulatory Activities* (MedDRA).
† No grade 4 adverse drug reactions were reported. Grade 3 adverse drug reactions not listed here include single cases of pneumonia, viral bronchitis, and tooth infection.

Krueger DA et al.. New England Journal of Medicine 2010;363:1801- 1811

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EXIST-1 Trial

Results from a Double-Blind, Placebo-Controlled, Phase 3 Trial of Everolimus in Subependymal Giant Cell Astrocytomas Associated with Tuberous Sclerosis Complex

D.N. Franz, E. Belousova, P. Curatolo, P. de Vries, V. Whittemore, E. Thiele, S. Sparagana, B. Korf, R. Kuperman, O. Witt, J. Y. Wu, J. P. Ford, G. Shah, H. Cauwel, P. Edrich, T. Sahmoud, S. Jozwiak

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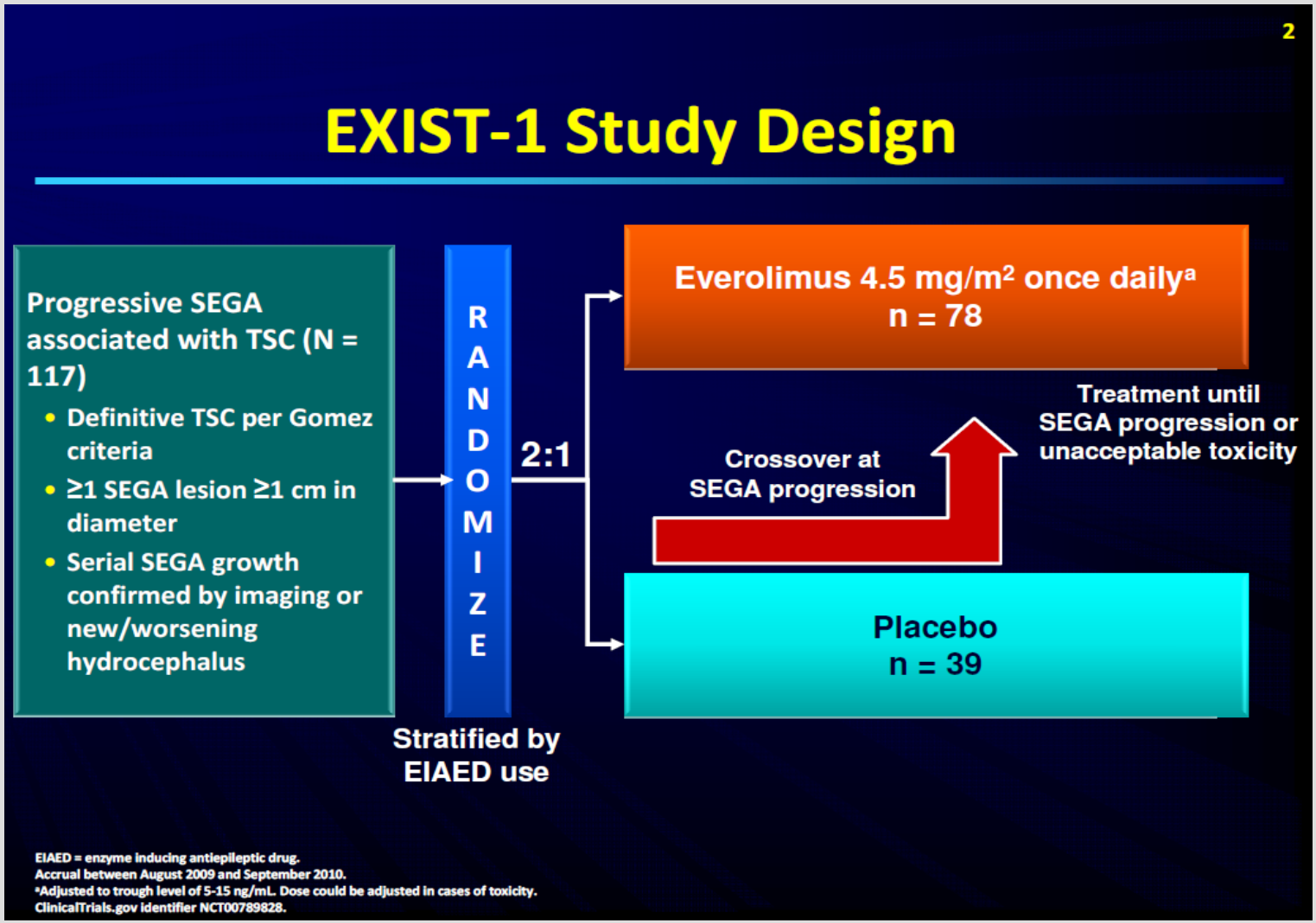

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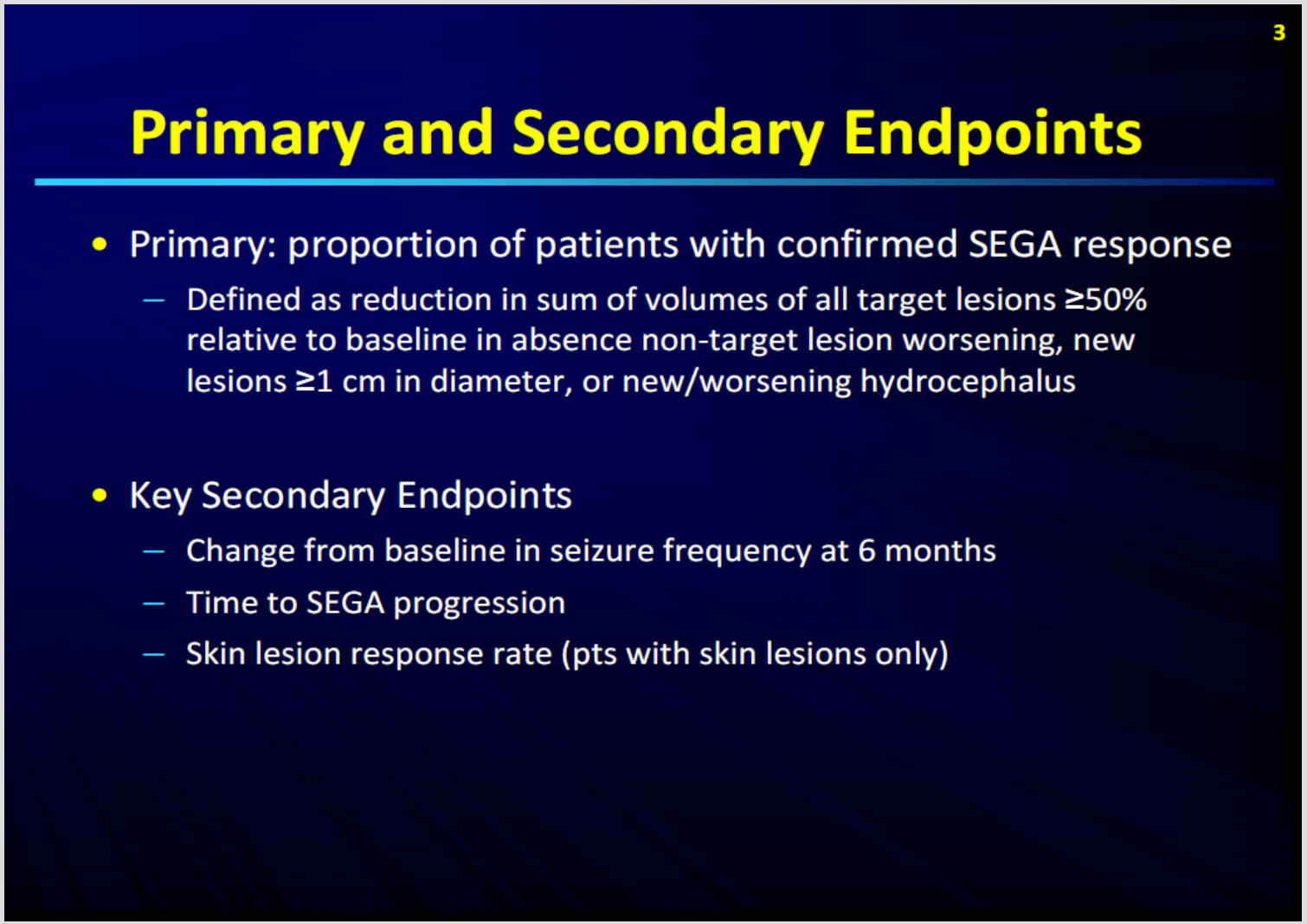

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SEGA Best Overall Response Rate

	Everolimus	Placebo
Full Analysis Set, n	78	39
Response (95% CI), %	35 (24-46)	0 (0-9)
P-value	<0.0001	

*P-value is obtained from the one sided exact Cochran-Mantel Haenszel test, stratified by the protocostratification factor EIAED use vs EIAED non-use

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Change in Median Seizure Frequency per 24 Hours

	Everolimus		Placebo	
	Baseline	Week 24	Baseline	Week 24
All Patients	n = 78		n = 39	
Frequency[a], median (range)	0.00 (0.0, 42.6)	0.00 (0.0, 31.6)	0.00 (0.0, 78.9)	0.0 (0.0, 91.5)
Change from baseline, median (95% CI)	0.00 (0.0, 0.0)		0.00 (0.0, 0.0)	
P-value for treatment effect	0.2004			
With Seizures at Baseline	n = 24		n = 11	
Frequency, median (range)	5.85 (1.0, 42.6)	3.99 (0.0, 31.6)	10.98 (1.0, 78.9)	6.78 (0.0, 91.5)
Change from baseline, median (95% CI)	–2.92 (–4.00, –1.00)		–4.06 (–10.89, 5.78)	
P-value for treatment effect	0.2988			

[a]Missing values imputed using LOCF (Last observation carried forward) method.
Seizures captured during 24-hour video EEG.
P-value obtained from Rank ANCOVA (one sided-test) with baseline seizure frequency as covariate, stratified by use of EIAED at randomization

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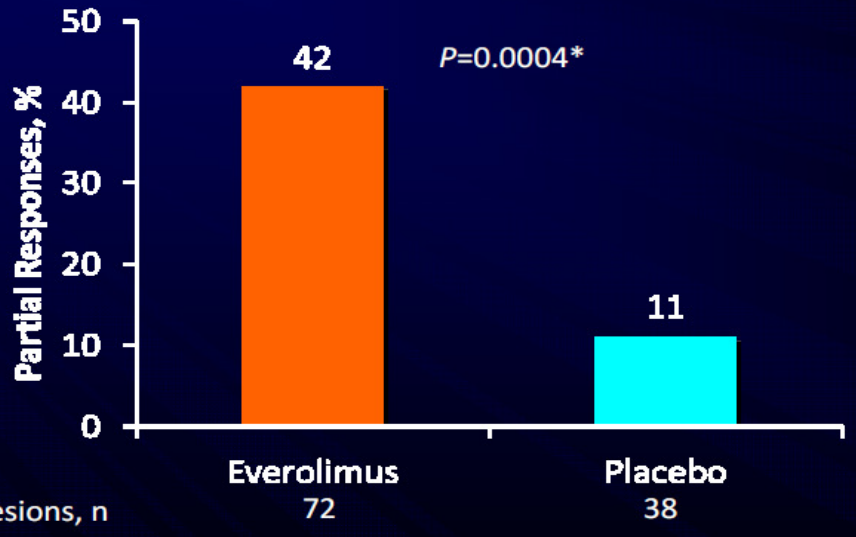
15

Skin Lesion Response Rate

- 110 patients had ≥1 skin lesion at baseline
- The best response observed was partial response



Skin lesions were assessed using Physician's Global Assessment of Clinical Condition tool every 3 months
* P-value is obtained from the one sided exact Cochran-Mantel Haenszel test, stratified by the protocol stratification factor EIAED use vs EIAED non-use

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Serious Adverse Events

- No deaths were reported
- Serious AEs thought to be study drug-related observed in 5% of everolimus and 0% of placebo recipients
  - Included viral gastroenteritis and pneumonia (3% each), and pyrexia, bronchopneumonia, febrile infection, upper respiratory tract infection, and dehydration (1% each)

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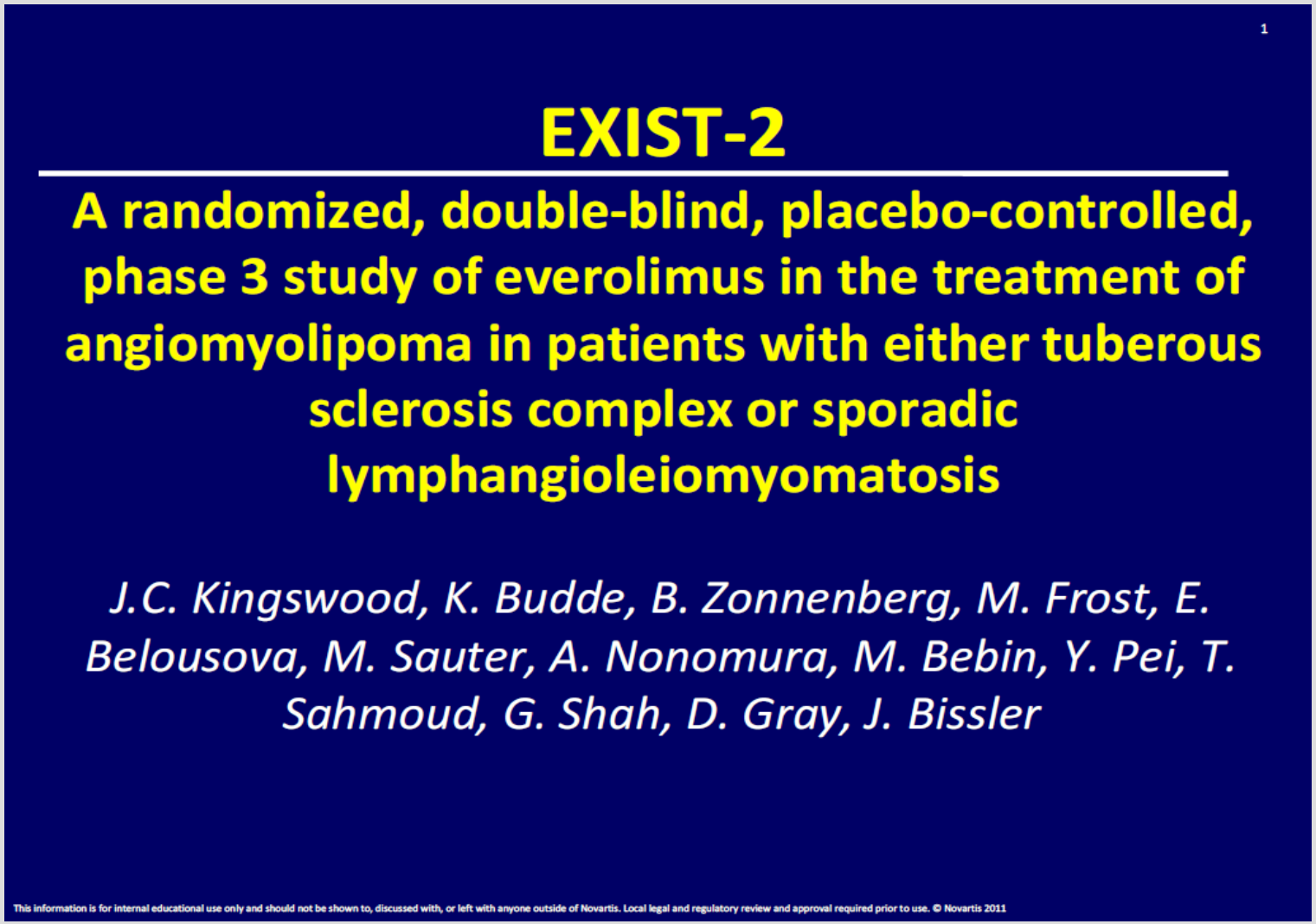
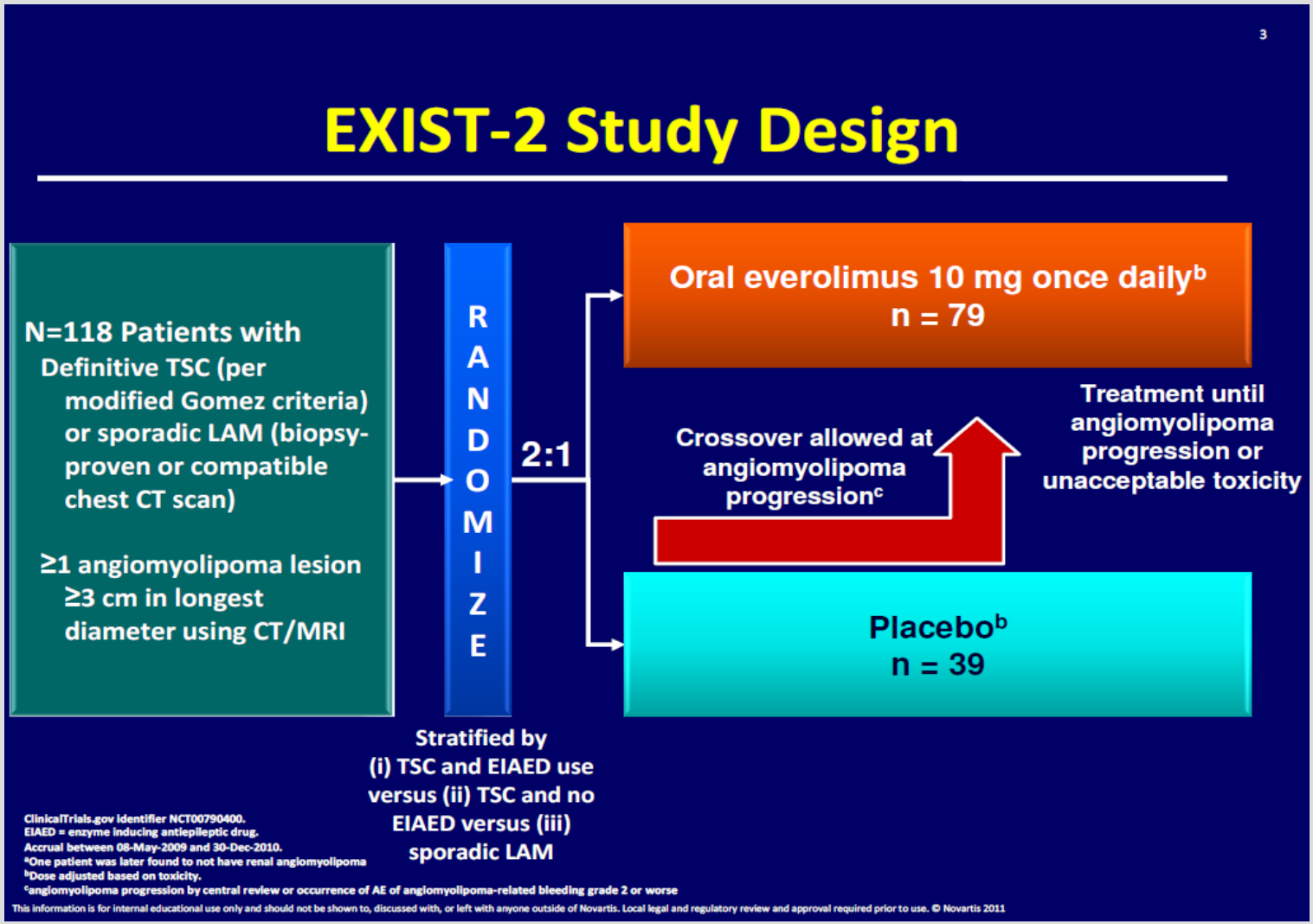


mTOR-Inhibition – Studien - AML



mTOR-Inhibition – Studien - AML

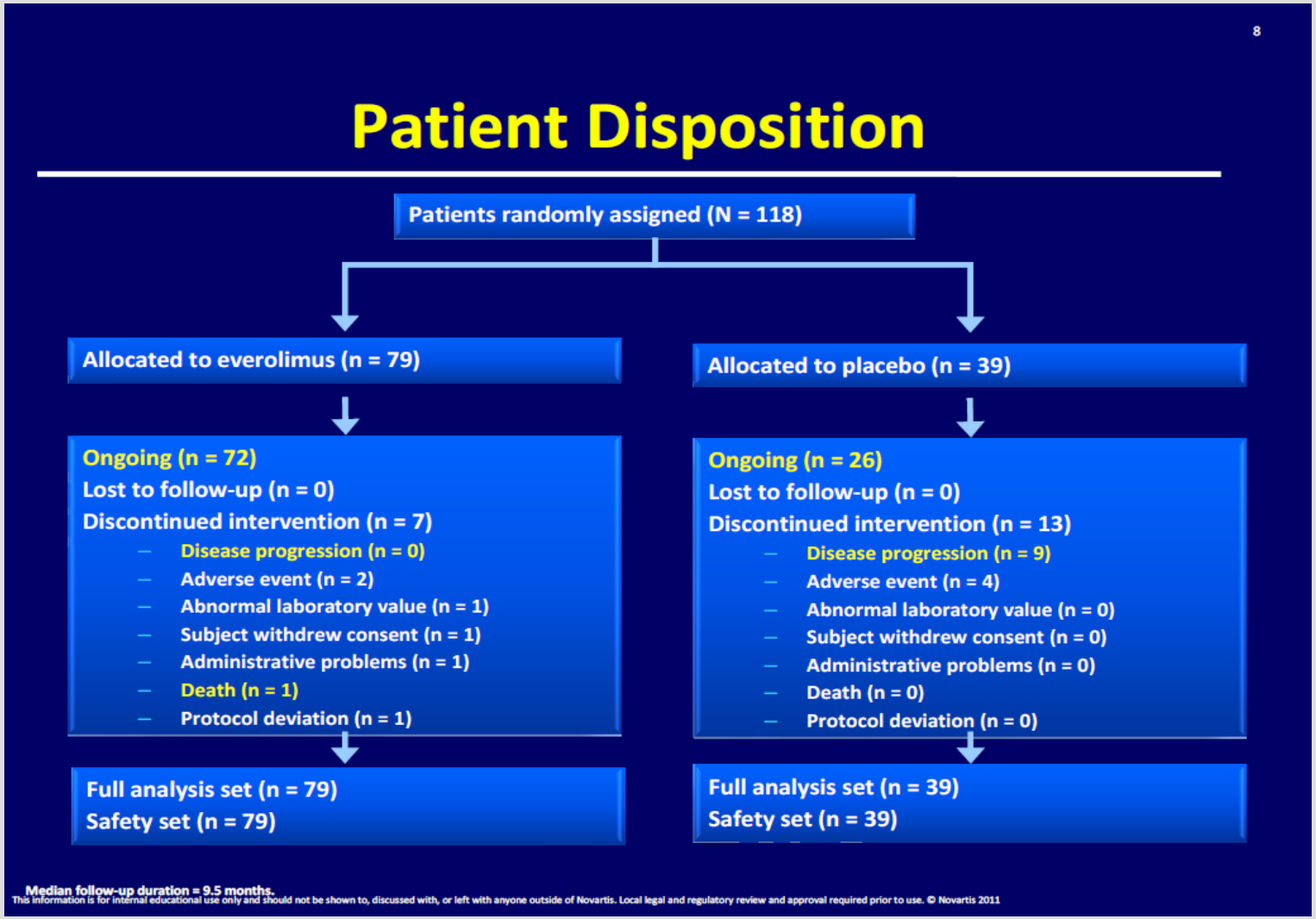
5

Primary and Secondary Endpoints

- Primary endpoint
  - Angiomyolipoma response rate: Proportion of patients with best overall confirmed response (**reduction in sum of volumes of all target angiomyolipoma lesions ≥50%**) relative to baseline and in absence of: new lesions ≥1 cm in longest diameter, kidney volume increase >20% from nadir, and angiomyolipoma-related bleeding grade ≥2)
- Key secondary endpoints
  - Time to angiomyolipoma progression
  - Skin lesion response rate (improvement in PGA score ≥50%)
  - Change from baseline in levels of plasma angiogenic molecules (results not yet available)
  - Renal function assessed using calculated creatinine clearance[1]
  - Safety
- Additional secondary endpoints in everolimus arm
  - Characterise pharmacokinetics of everolimus
  - Time to angiomyolipoma response, duration of angiomyolipoma response, duration of skin lesion response

1. Cockcroft DW, et al. *Nephron* 1976;16:31-41.

mTOR-Inhibition – Studien - AML



mTOR-Inhibition – Studien - AML

9

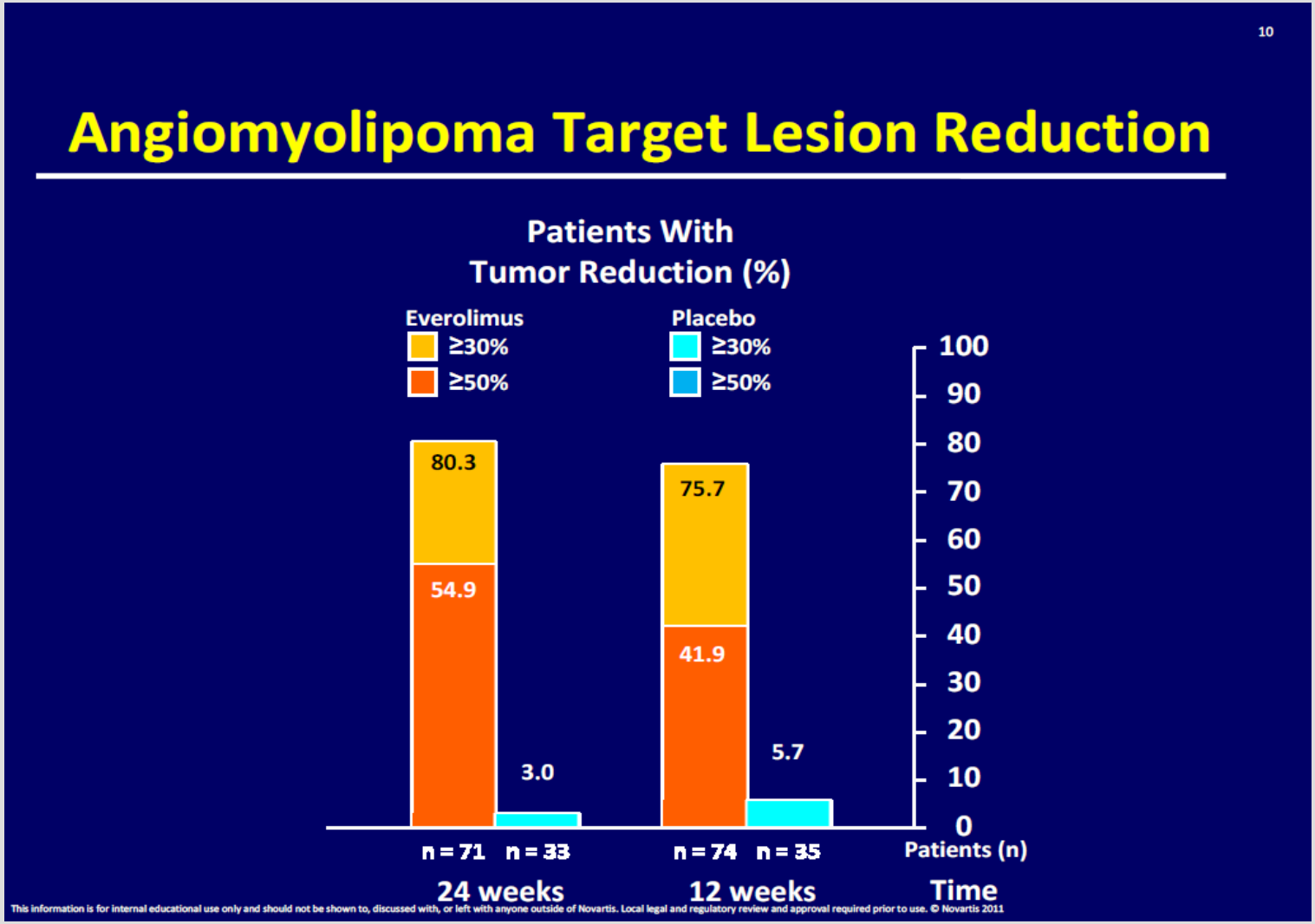
Angiomyolipoma Response Rate

Response, n (%)	Everolimus n = 79	Placebo n = 39
Primary analysis		
Angiomyolipoma response rate[a]	33 (41.8)	0
[95% CI]	[30.8, 53.4]	[0.0, 9.0]
P-value[b]	< 0.0001	
Difference % (95% CI)	41.8 (23.5, 58.4)	
Best overall angiomyolipoma response		
Response	33 (41.8)	0
Stable disease	32 (40.5)	31 (79.5)
Progression	1 (1.3)	2 (5.1)
Not evaluable	13 (16.5)	6 (15.4)

[a] By central review.

[b] P-value is obtained from the one-sided exact Cochran-Mantel-Haenszel test, stratified by the modified stratification factor (use of EIAED vs. non-use of EIAED).

mTOR-Inhibition – Studien - AML



mTOR-Inhibition – Studien - AML

15

Drug-Related Adverse Events Observed in >10% of Patients

AE, %	Everolimus n = 79	Placebo n = 39
Any AE suspected to be drug-related	76 (96.2)	25 (64.1)
Stomatitis	38 (48.1)	1 (2.6)
Hypercholesterolaemia	16 (20.3)	1 (2.6)
Aphthous stomatitis	14 (17.7)	3 (7.7)
Mouth ulceration	13 (16.5)	2 (5.1)
Acne	12 (15.2)	2 (5.1)
Fatigue	10 (12.7)	3 (7.7)
Anaemia	9 (11.4)	1 (2.6)
Blood lactate dehydrogenase increased	8 (10.1)	2 (5.1)
Leukopenia	8 (10.1)	3 (7.7)
Nausea	8 (10.1)	1 (2.6)

mTOR-Inhibition – Studien - AML

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Selected Adverse Events: Amenorrhea

- Amenorrhea was reported in 7 of 52 females (13.5%) on the everolimus arm (including 2 cases of Grade 3) versus 1 of 26 females (3.8%) in the placebo arm
  - Duration of amenorrhea ranged from 1 to 66 weeks, with no treatment modification in any cases
  - 3 cases of amenorrhea are ongoing on the everolimus arm, while 4 have resolved without intervention

mTOR-Inhibition – Studien - AML

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Conclusions

- Everolimus demonstrated superiority over placebo for best overall angiomyolipoma response rate (50.8% everolimus vs 0% placebo)
- Everolimus provided statistically significant improvement in secondary endpoints (time to angiomyolipoma progression and skin lesion response rate)
- AE profile was consistent with previously reported tolerability profile of everolimus in patients with TSC; most AEs were of grade 1 or 2 severity

Everolimus – Indikation Schweiz

Votubia®: Indikationen/Anwendungsmöglichkeiten

Behandlung von Patienten ab einem Alter von 3 Jahren mit subependymalem Riesenzellastrozytom (SEGA) in Verbindung mit tuberöser Sklerose, für welche eine chirurgische Behandlung nicht angemessen ist.

Tabletten zu 2,5 und 5 mg (Preis für 30 Tabl, a 2,5 mg CHF2318.85)

Certican®: Indikationen/Anwendungsmöglichkeiten

Certican ist indiziert zur Prophylaxe von Organabstossungen bei erwachsenen Patienten mit kleinem bis mittlerem immunologischen Risiko, die ein allogenes Nieren- oder Herztransplantat erhalten haben. Certican sollte in Kombination mit Ciclosporin Mikroemulsion und Kortikosteroiden verwendet werden.

Tabletten zu 0,25, 0,5, 0,75 mg und 1 mg.

Dispergierbare Tabletten zu 0,1 und 0,25 mg.

Afinitor®: Indikationen/Anwendungsmöglichkeiten

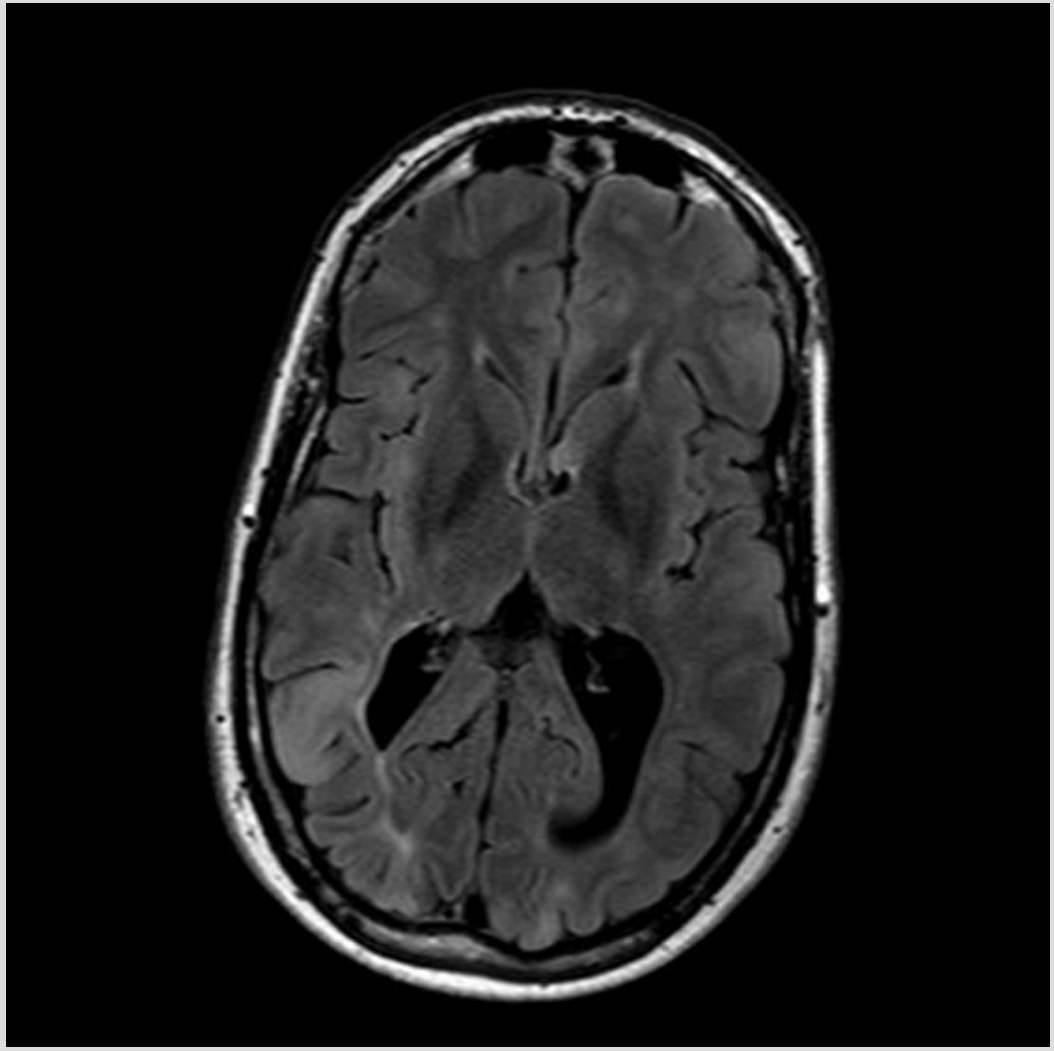
Behandlung von Patienten mit fortgeschrittenen, progredienten, gut oder mässig differenzierten neuroendokrinen Tumoren pankreatischen Ursprungs; fortgeschrittenem Nierenzellkarzinom nach Versagen einer Behandlung mit Sunitinib oder Sorafenib.

Tabletten zu 5 und 10 mg

Kasuistik 1 (m, * 1978): Eigene Erfahrung

- Mittelgradige geistige Behinderung
- Fokale Epilepsie seit 6. Lbj
  - einfach-fokale, komplex-fokale und sekundär generalisierte Anfällen
  - pharmakotherapieresistent, z. Zt LTG+LEV
- SEGA
- AML

Kasuistik 1 (m, * 1978): Eigene Erfahrung



MRI 02.05.2011

Kasuistik 1 (m, * 1978): Eigene Erfahrung

- **Nephrologische Indikation "off label" für Everolimus:** "Betreffend der renalen Situation sind bei Herrn…. multiple renale Angiomyolipome bekannt, welche aufgrund der erheblichen Grösse bei zunehmender Angiomyolipomgrösse im Bereich der linken Niere mittels *Nierenteilresektion im Juni '06* behandelt werden musste. Infolge ist es zu einem *erneuten Wachstum* aller in den Nieren detektierten Angiomyolipomen gekommen (das grösste Angiomyolipom vergrösserte im Vergleich zur einer Voruntersuchung 2005 im August 2010 auf *5cm*)"
- **Therapie mit Everolimus von 11/11 – 4/12**

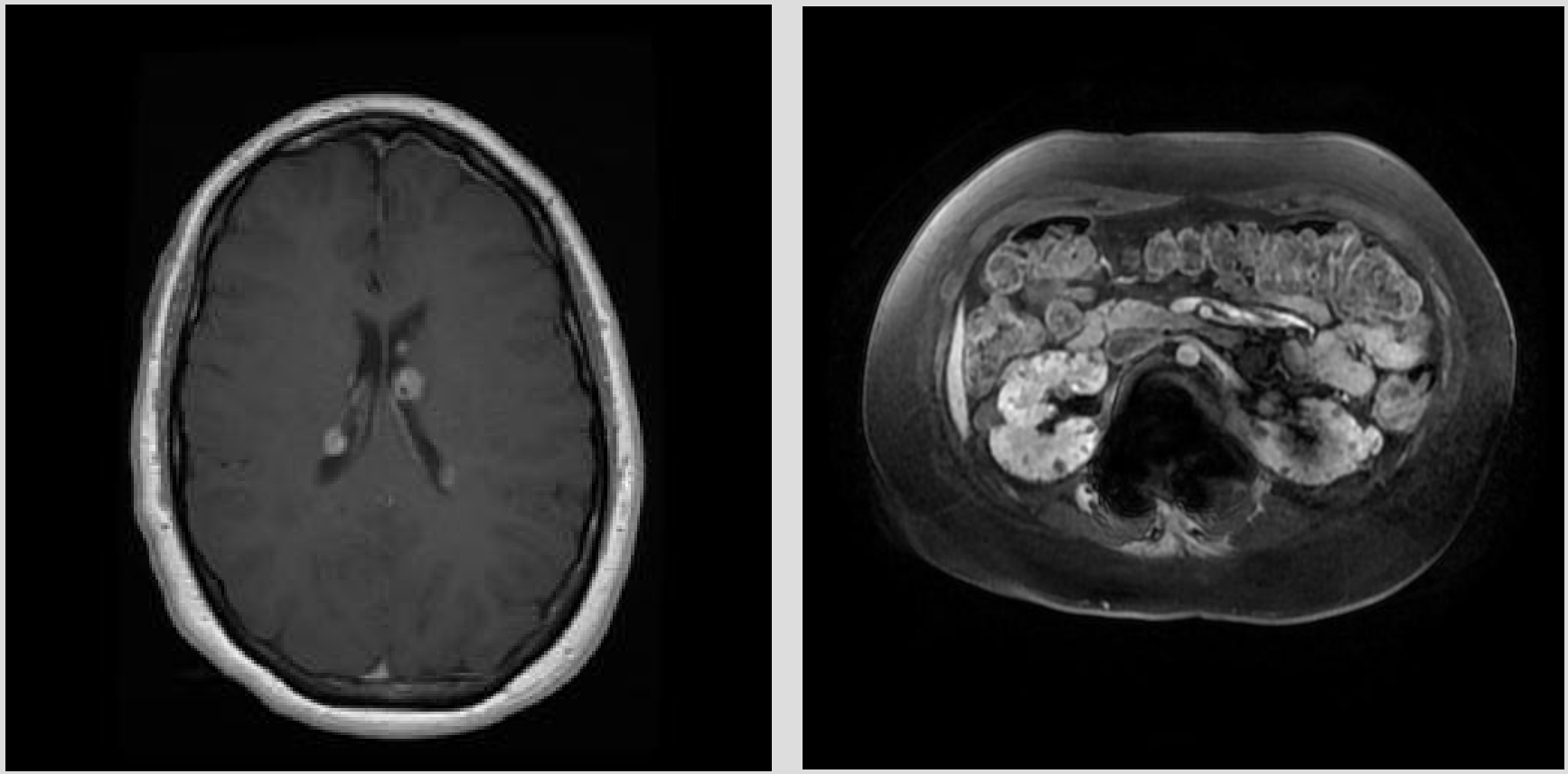
Kasuistik 1 (m, * 1978): Eigene Erfahrung

- **Ergebnis der Behandlung – Stand 4/12:**
  - Nierenfunktion stabil gehalten
  - Nieren-CT: Angiomyolipome etwas kleiner (um 1/3)
  - Fibrome im Gesicht unverändert
  - Epilepsie unverändert
  - cMRI: gegenüber 5/11 keine Veränderung
  - Nebenwirkungen:
    - Hypercholesterinämie,
    - orale Aphtosis - störend
    - Akne – lokal gut beherrschbar

Kasuistik 2 (w, * 1986): Was tun?

- Schwere geistige Behinderung
- Autismus
- Epilepsie seit 1987
  - Komplex-fokale und sekundäre generalisierte Anfälle
  - Bisher resistent gegenüber PB, VPA, CBZ, LTG, LTG + TPM (0-3 Anfälle/Monat)
  - Systematische Therapieführung wegen aggressiven Verhaltens und Interaktionen im Umfeld erschwert
- SEGA
- AML
- Mutter fürchtet Entwicklung eines Hydrocephalus, denkt über Everolimus aufgrund von Informationen aus der Selbsthilfe nach

Kasuistik 2 (w, * 1986): Was tun?



MRI 23.11.11 in Narkose

Fazit

- Die TS ist eine komplexe und dynamische Multisystemerkrankung.
- Betroffene müssen in einem multidisziplinäre ärztlichen Team betreut werden (“integrierte Versorgung”)
- Everolimus hemmt das Wachstum von SEGA und AML. Die Indikation (aktuell nur zur Therapie der SEGU zugelassen) muss sorgfältig geprüft werden. Im Falle eines Einsatzes ist eine sorgfältige multidisziplinäre/multiprofessionelle Dokumentation und Beurteilung erwünschter und unerwünschter Therapieeffekte vonnöten