UNIVERSITY
CHILDREN'S HOSPITAL
ZURICH
Children's Research Center CRC

ECFS-CLINICAL TRIALS NETWORK
Clinical Trials Network

Die neuen CFTR Modulatoren
Durchbruch in der CF-Therapie?

Prof. Dr. med. Alexander Moeller
Leiter Pädiatrische Pneumologie
und CF Zentrum

Inhalt

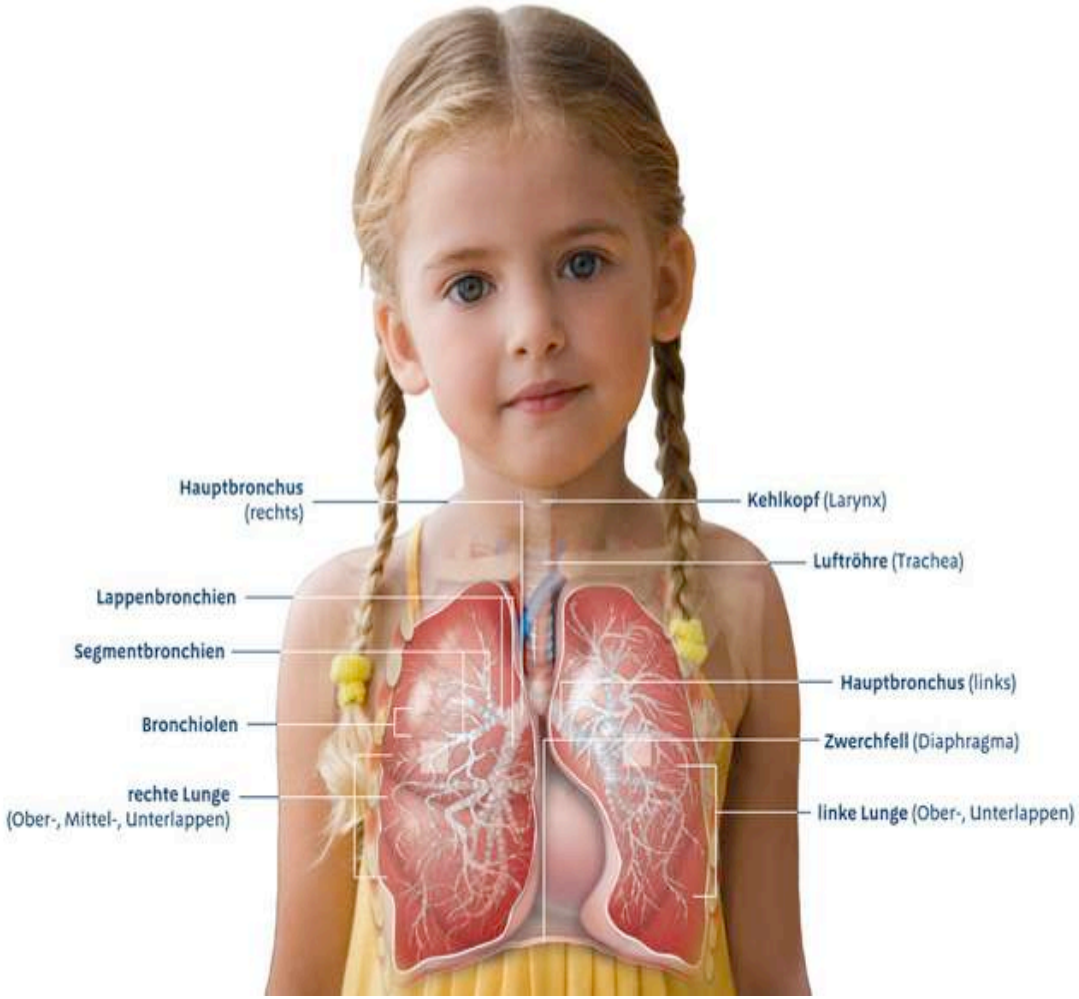
i. Hintergrund: vom Gen zur Krankheit

ii. Therapie bisher

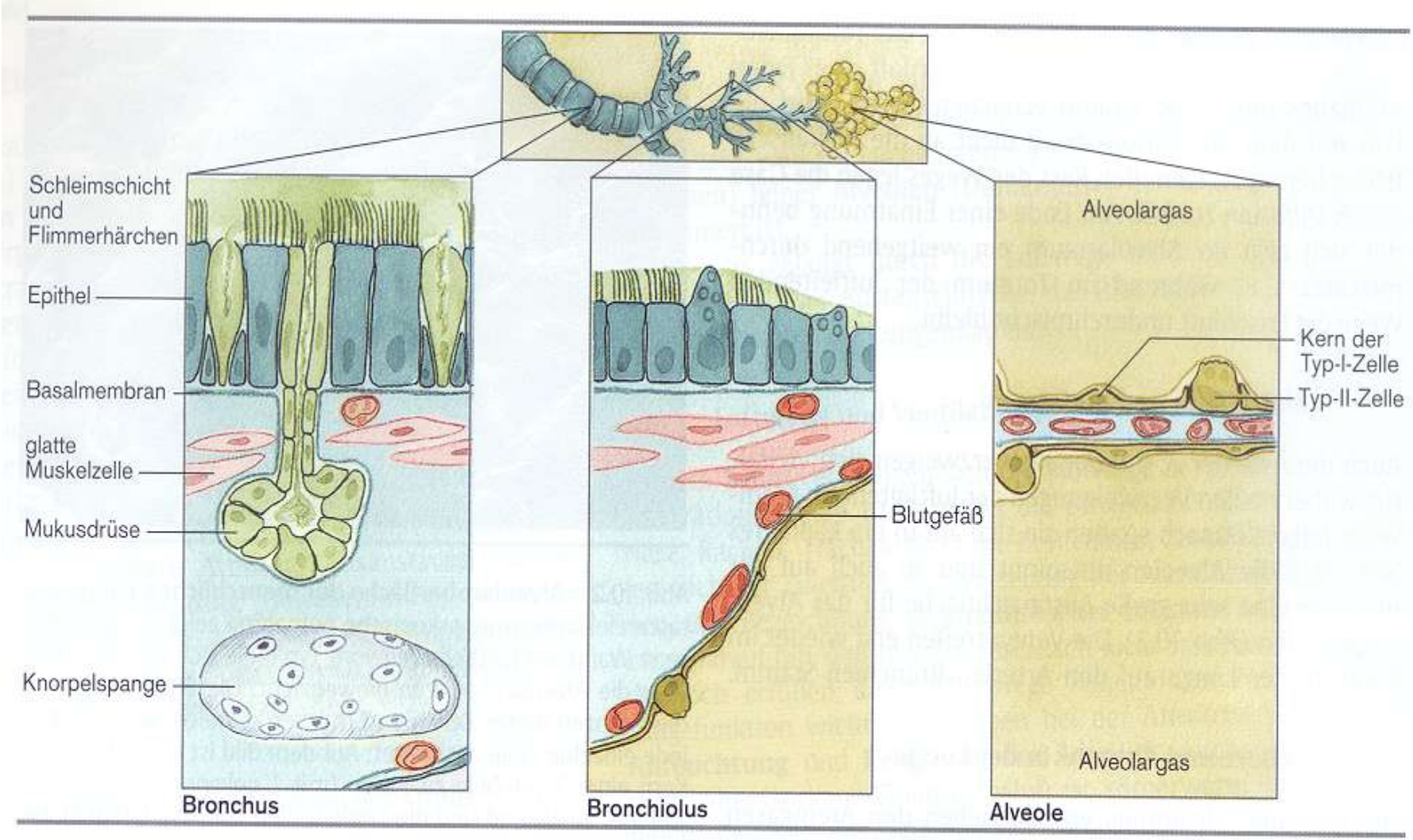
iii. Resultate der wichtigen Studien zu CFTR Modulator-Therapien

iv. Eigene Erfahrungen und persönliche Beurteilung

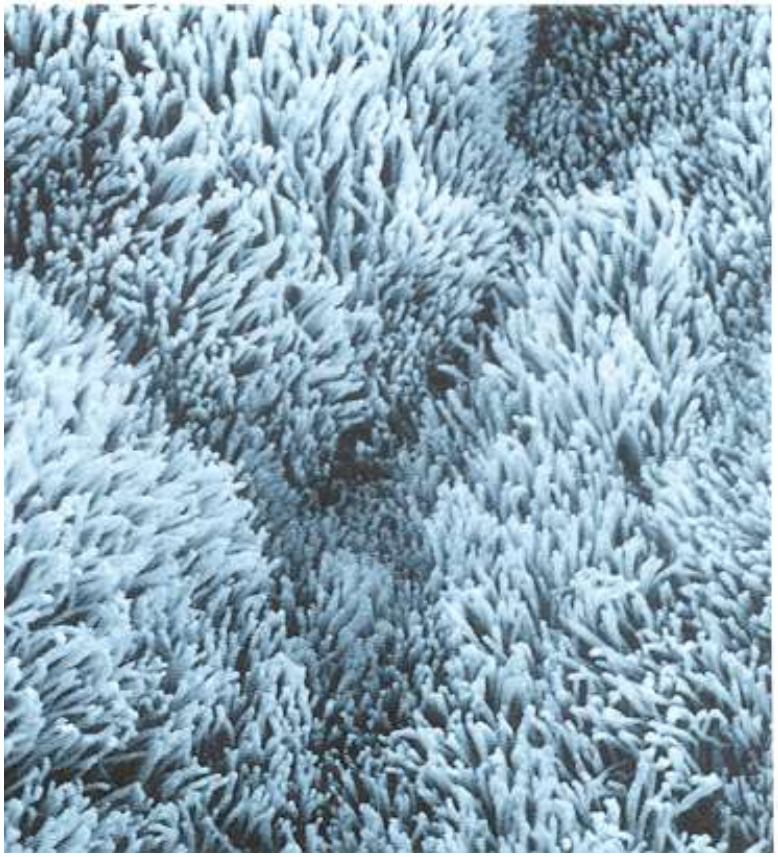
Atemwege und Atemwegsreinigung

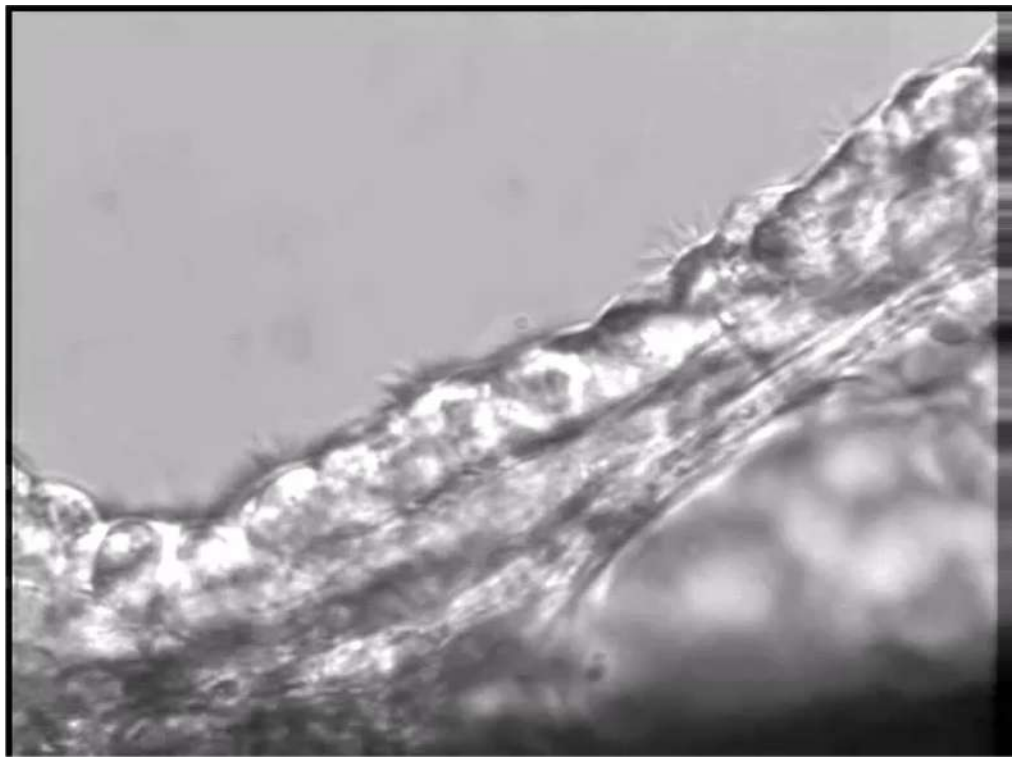


Atemwege und Atemwegsreinigung

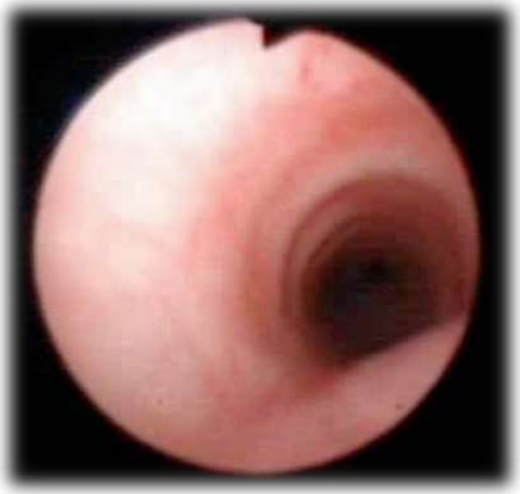


Atemwege und Atemwegsreinigung

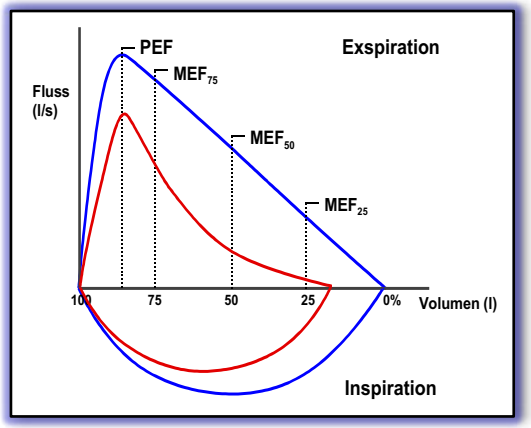




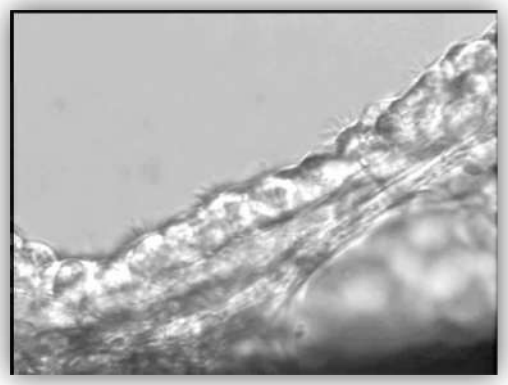
Mechanismen der Atemwegsreinigung: wenn alles gut läuft



Atemwegs-Reinigung



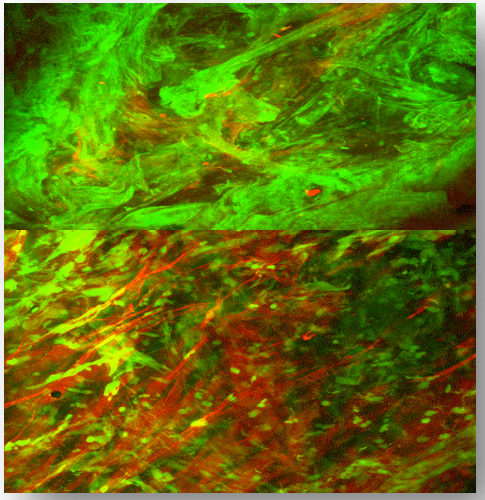
Lungenfunktion



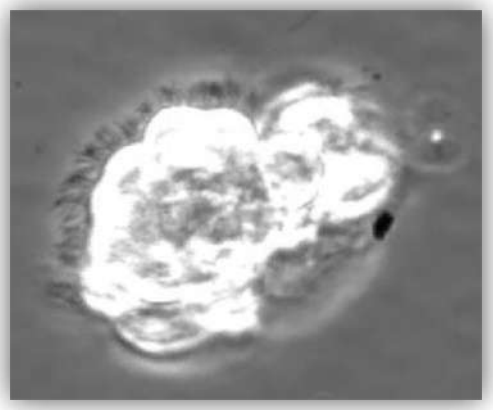
Ciliäre-Funktion

Husten-Funktion

Mechanismen der Atemwegsreinigung: wenn etwas falsch läuft



Zäher Schleim
(Cystische Fibrose



Ziliendyskinesie

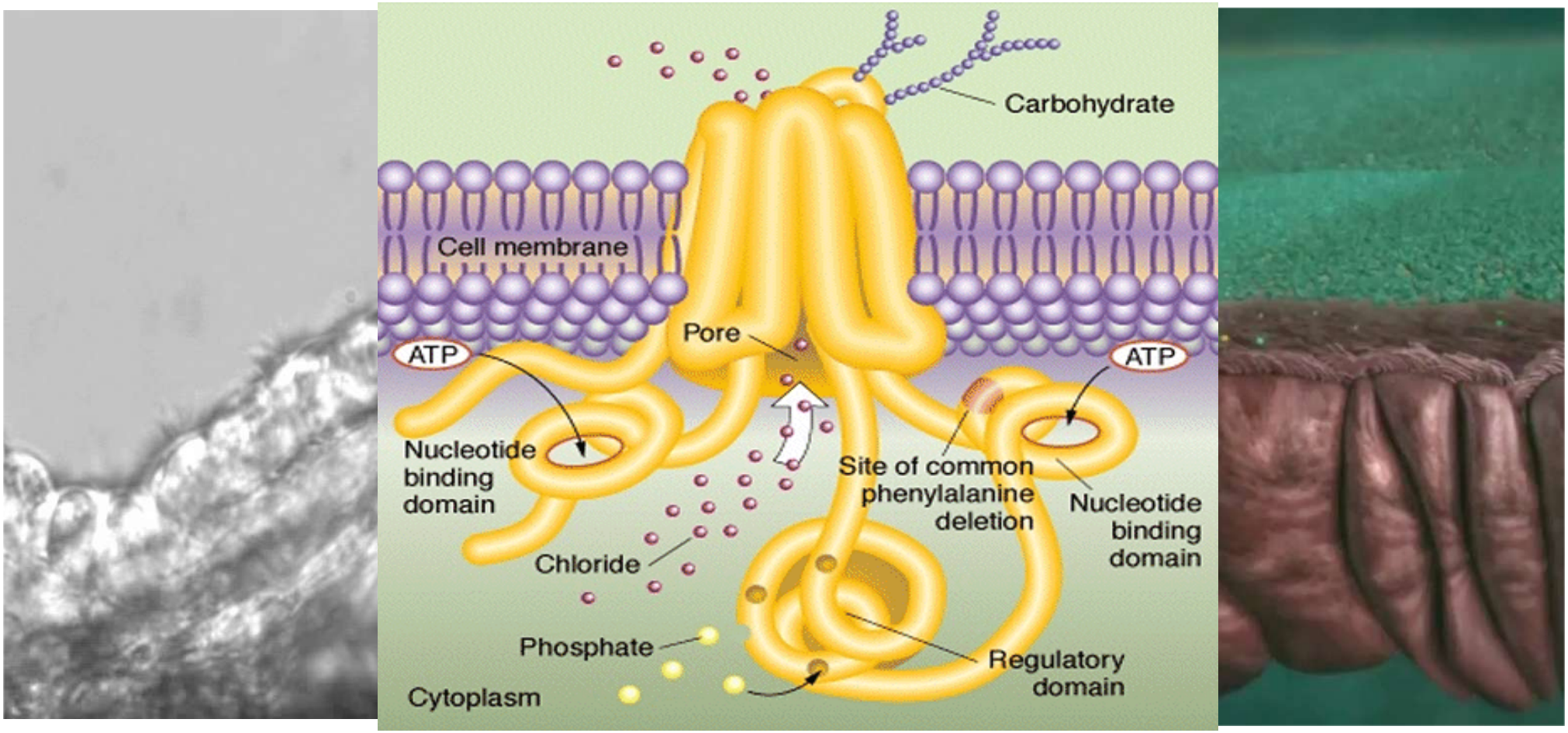
Atemwegs-
Obstruktion

Bronchiektasie

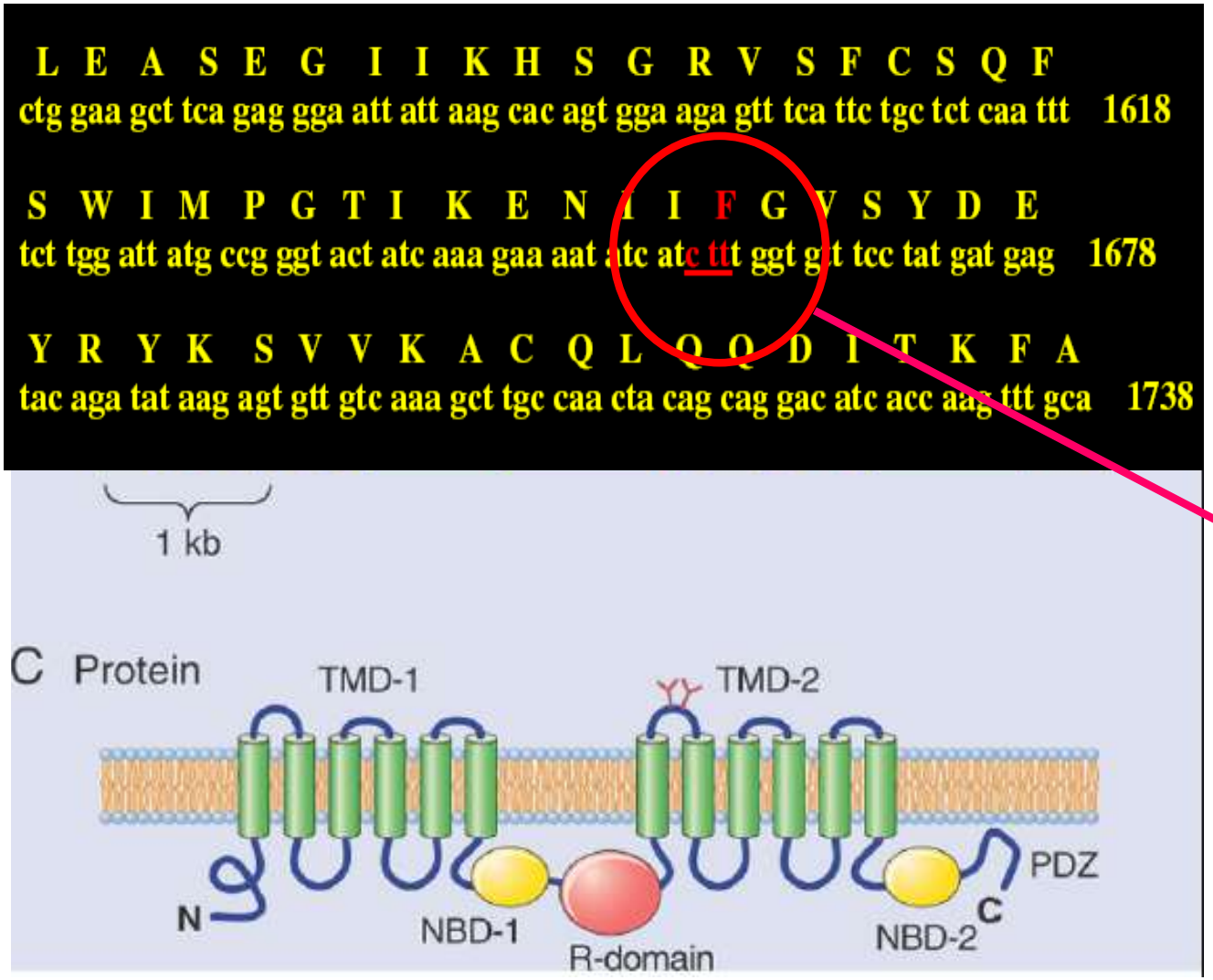
Schwacher
Hustenstoss
(Muskelkrankheiten)

Unkoordinierter
Hustenstoss
(Hirnerkrankungen

Flüssigkeitsregulation durch den CFTR Kanal



CFTR Kanal: vom Gen zur Krankheit



7 q31.2
230 Kb
27 Exons

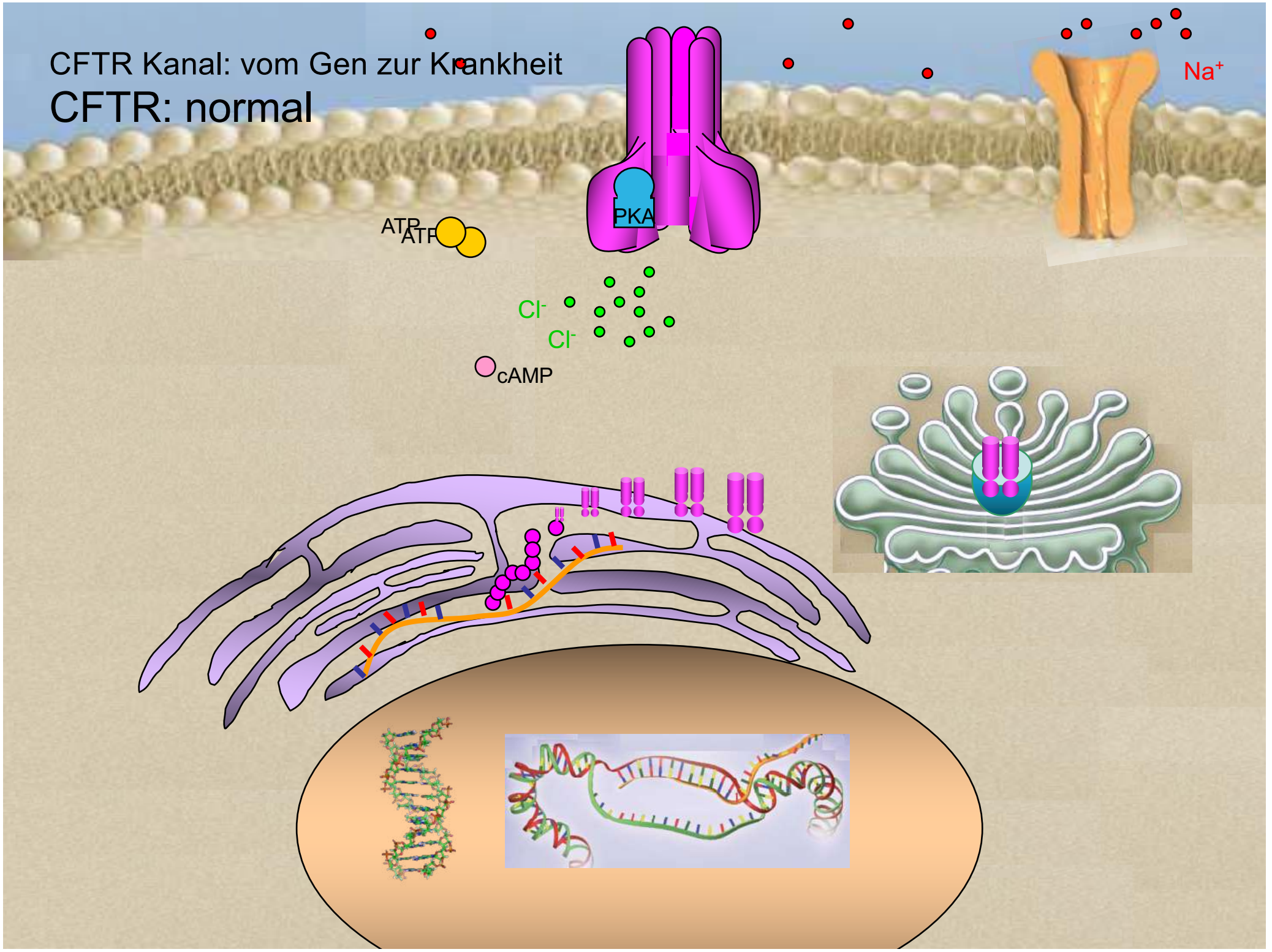
6.5kB

F508del

1480 AS

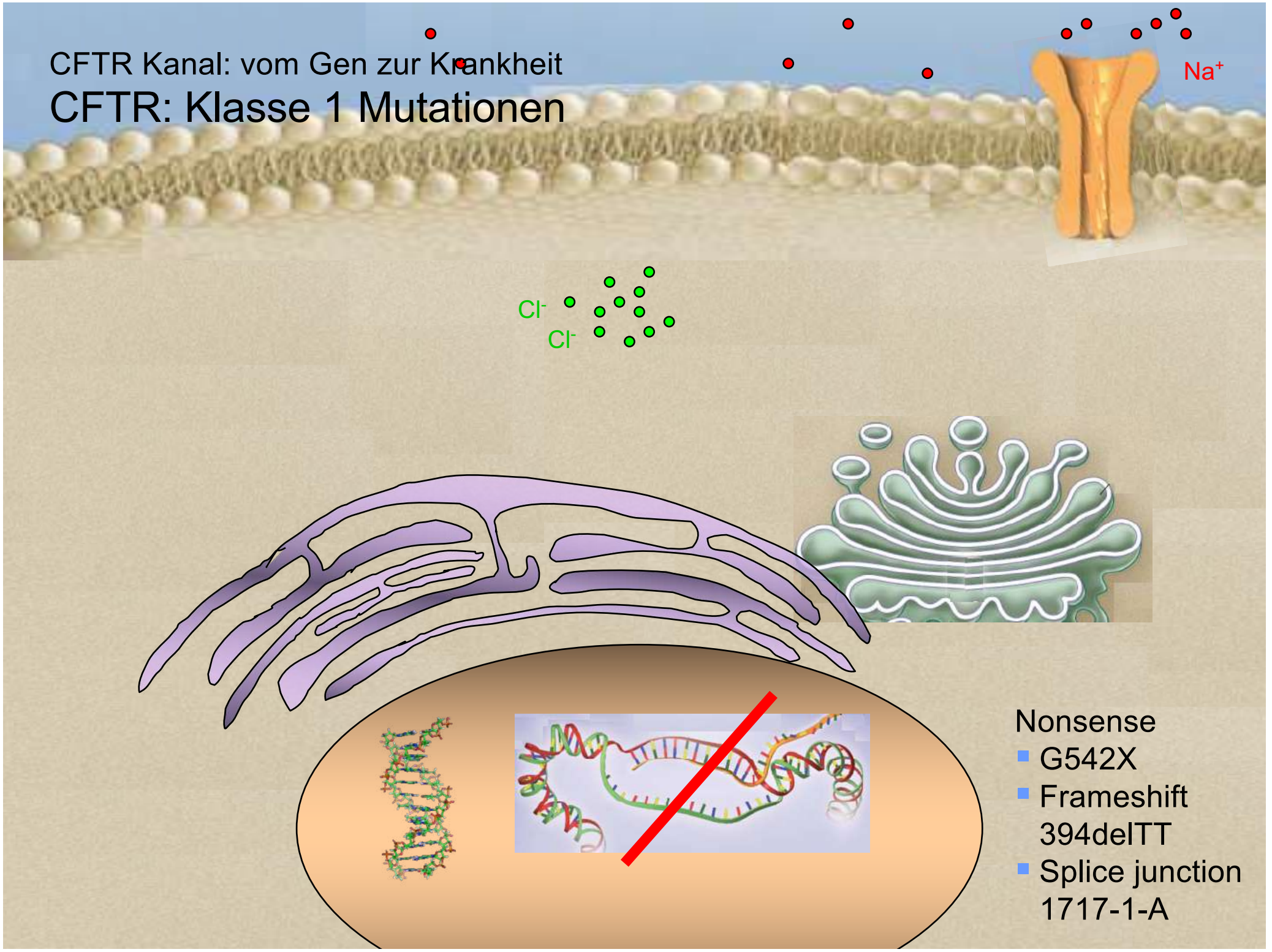
CFTR Kanal: vom Gen zur Krankheit

CFTR: normal



CFTR Kanal: vom Gen zur Krankheit

CFTR: Klasse 1 Mutationen

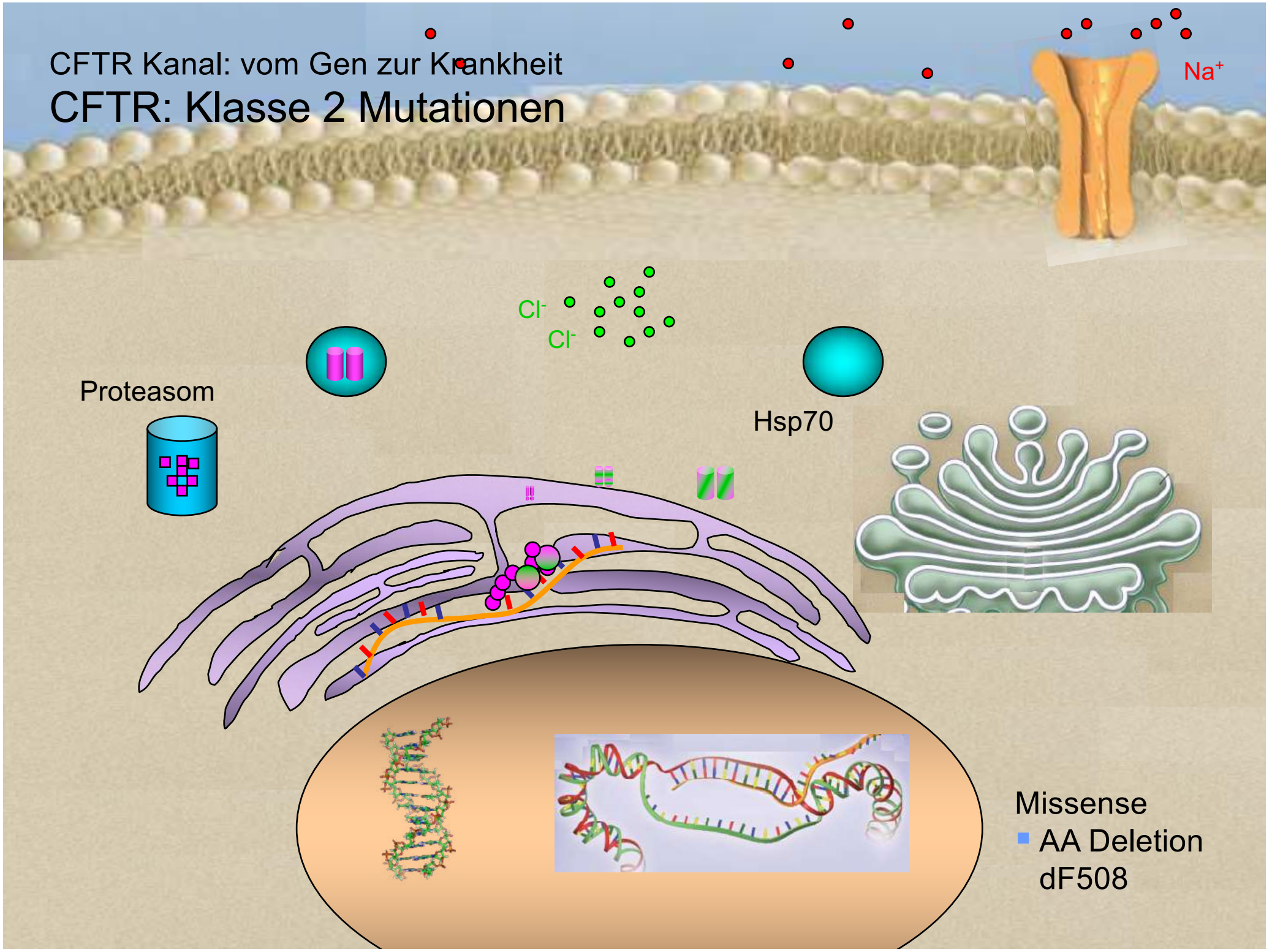


Nonsense

- G542X
- Frameshift 394delTT
- Splice junction 1717-1-A

CFTR Kanal: vom Gen zur Krankheit

CFTR: Klasse 2 Mutationen

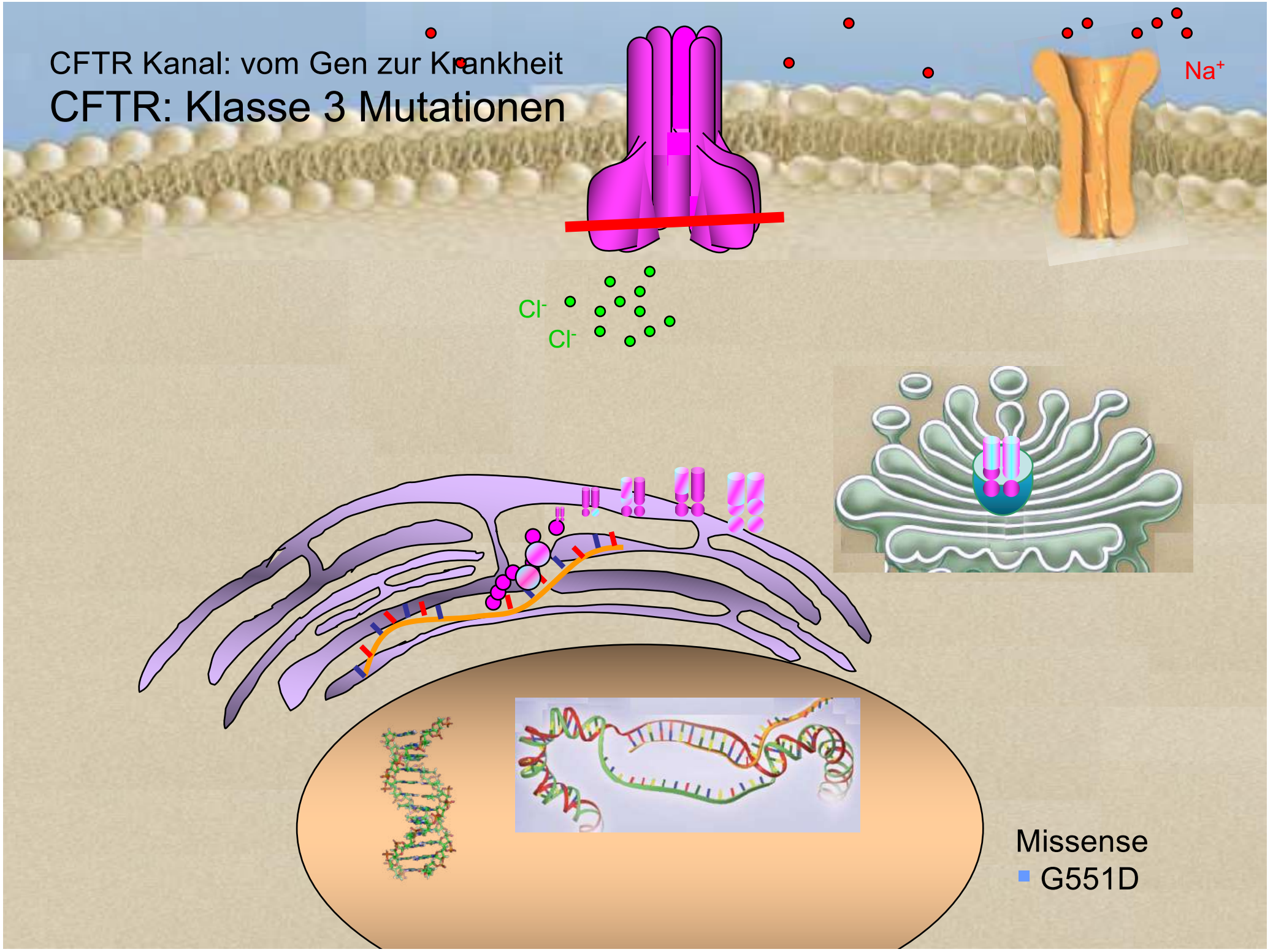


Missense

- AA Deletion dF508

CFTR Kanal: vom Gen zur Krankheit

CFTR: Klasse 3 Mutationen



CFTR Kanal: vom Gen zur Krankheit

≈ 2000 CFTR Mutationen und Regionale Verteilung

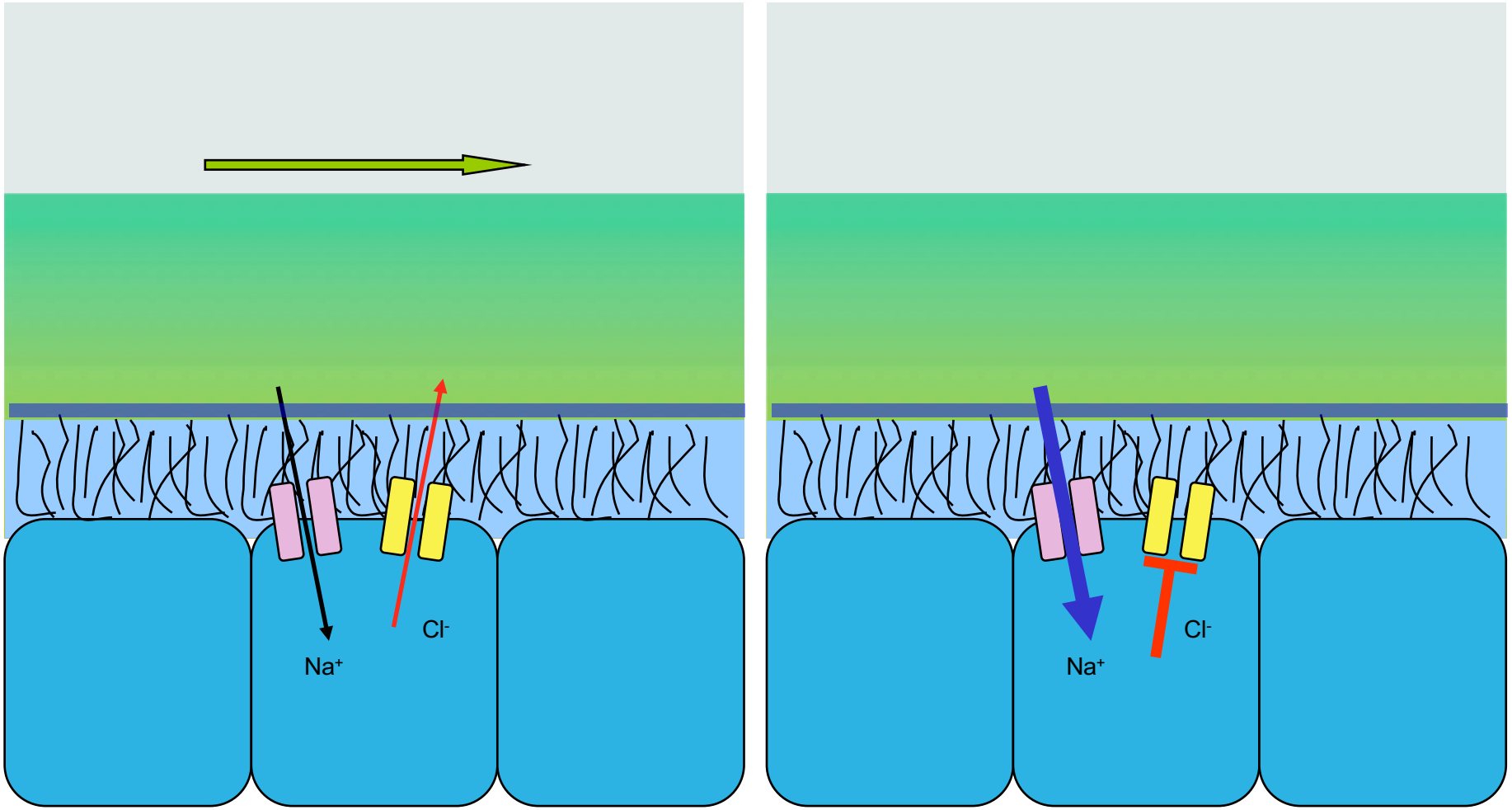
Geographical distribution of the most common mutations

E60X	Southern European	S549N	Indian
CFTR	Slavic — Eastern European	G551D	United Kingdom, Central Europe
R75X	Southern European, US-Hispanic	Q552X	Southern European, Italian
394delTT	Nordic — Baltic sea region	R553X	Central European
G85E	Southern Europe	A559T	African-American
406-1G>A	US-Hispanic	R560T	Northern Irish
R117H	European-derived populations	1811+1.6kbA>G	Spanish, US-Hispanic
R117C	Northern European	1898+1G>A	United Kingdom, Central Europe
621+1G>T	Southern European	1898+5G>T	East Asian populations
711+1G>T	French, French Canadian	2143delT	Slavic — Eastern European
711+5G>A	US-Hispanic	2183delAA>G	Southern Europe, Middle Eastern, Iranian, Latin American
L206W	Spanish and US-Hispanic	2184delA	European-derived populations
V232D	Spanish and US-Hispanic	2789+5G>A	European-derived populations
1078delT	French Brittany	Q890X	Southern European
R334W	Southern European, Latin American	3120+1G>A	African, Arabian, African-American, Southern Europe
1161delC	Indian	3272–26A>G	European-derived populations
R347P	European-derived, Latin America	3659delC	Scandinavian
R347H	Turkish	3849+10kbC>T	Ashkenazi-Jewish, Southern European, Middle Eastern, Iranian, Indian
A455E	Dutch	R1066C	Southern European
1609delCA	Spanish, US-Hispanic	Y1092X (C>A)	Southern European
I506T	Southern European, Spanish	M1101K	US-Hutterite
I507del	European-derived populations	3905insT	Swiss
F508del	European-derived populations	D1152H	European-derived populations
1677delTA	Southern European, Middle Eastern	R1158X	Southern European
1717–G>A	European-derived populations	R1162X	Italian, Amerindian, Latin America
V520F	Irish	S1251N	European-derived populations
G542X	Southern European, Mediterranean	W1282X	Ashkenazi-Jewish, Middle Eastern
S549R(T>G)	Middle Eastern	N1303K	Southern European, Middle Eastern

Castellani C. J Cystic Fibrosis 7 (2008) 179–196

CFTR Kanal: vom Gen zur Krankheit

Konsequenzen der gestörten CFTR Funktion

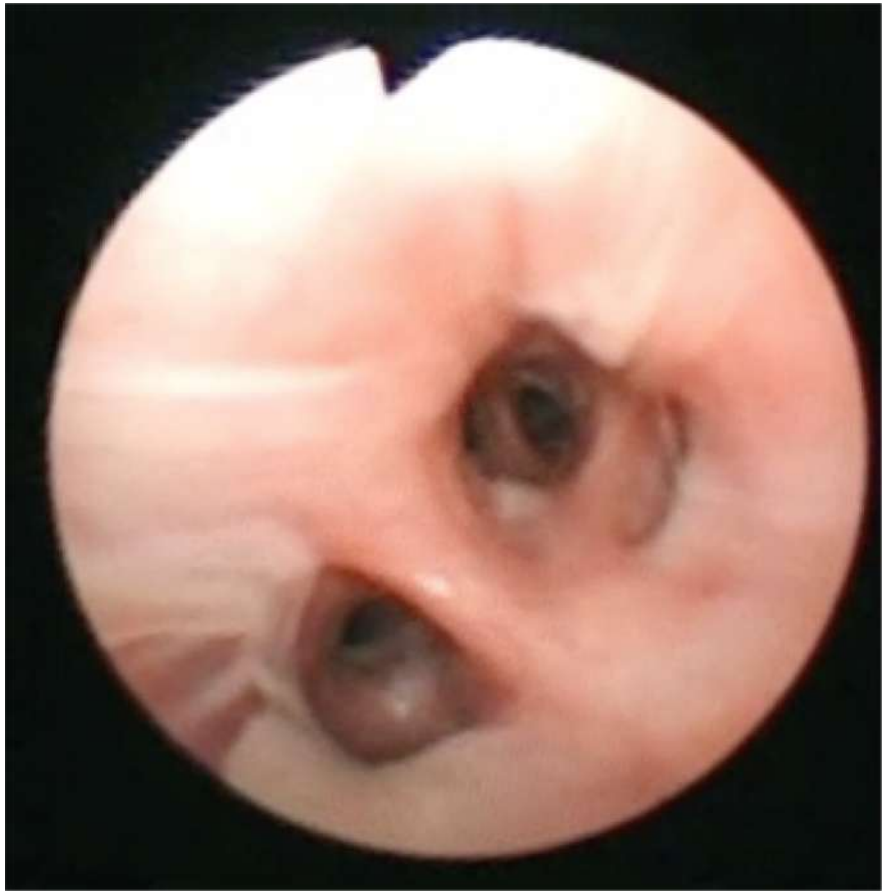


Gesund

CF

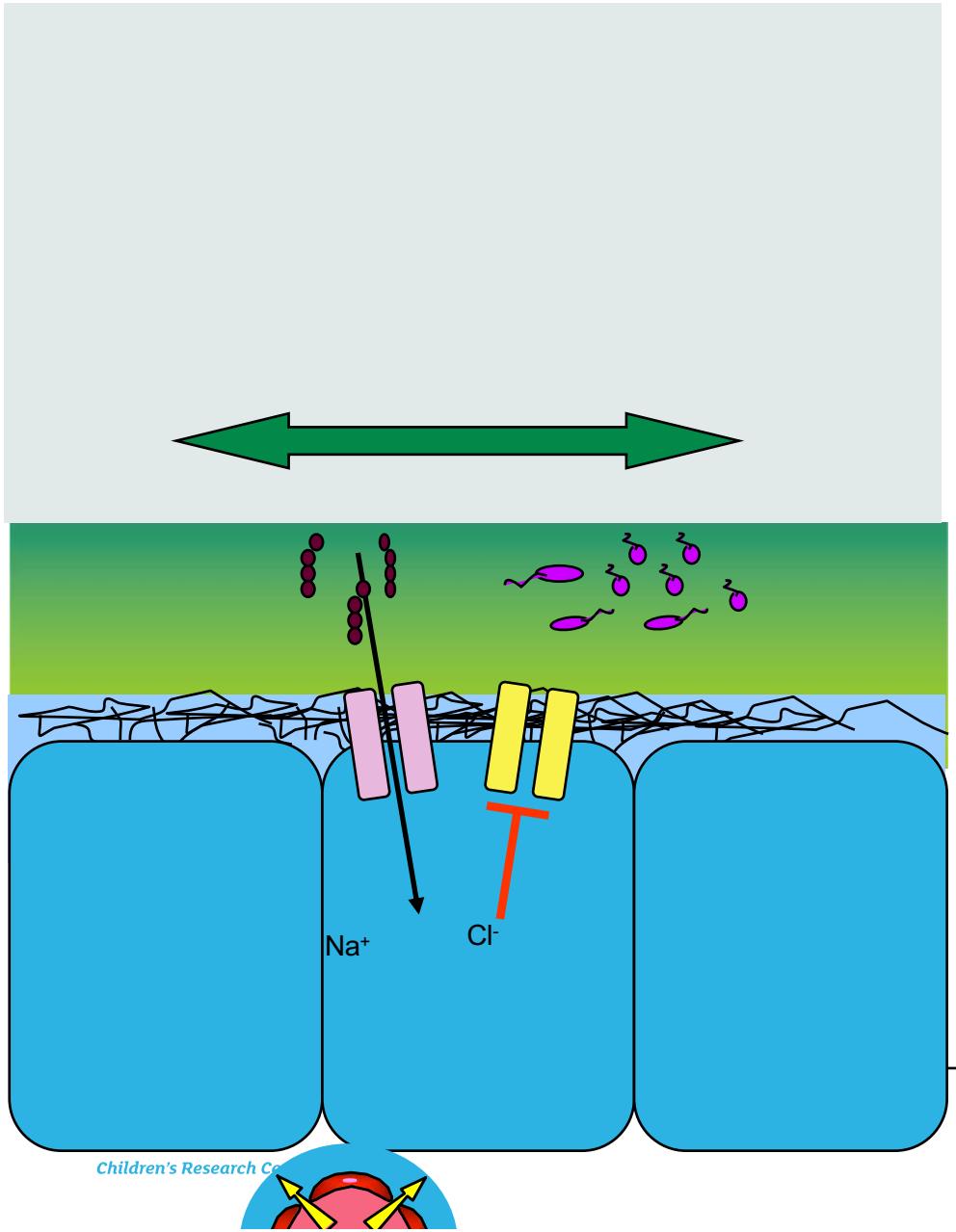
CFTR Kanal: vom Gen zur Krankheit

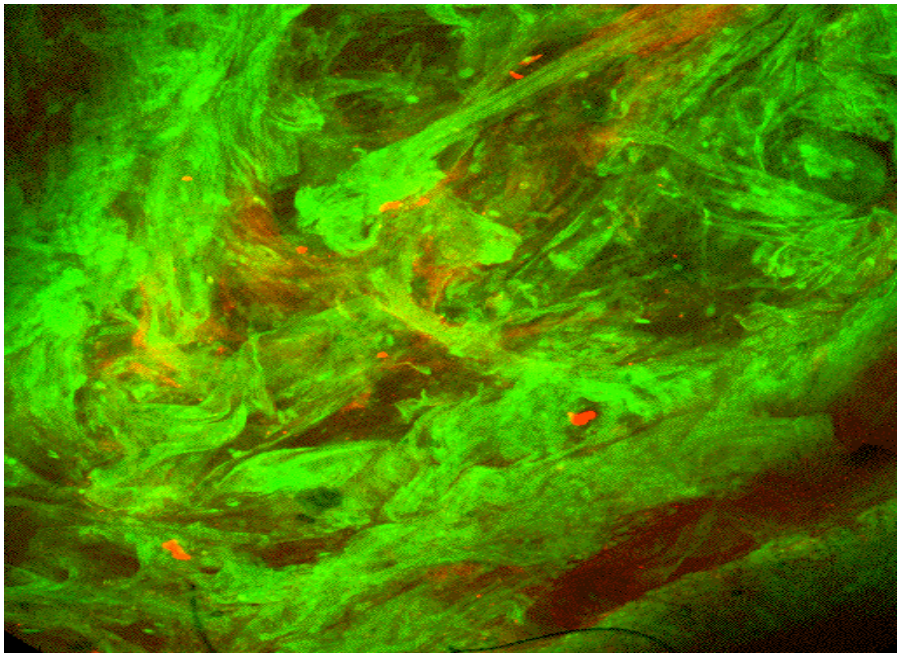
Konsequenzen der gestörten CFTR Funktion

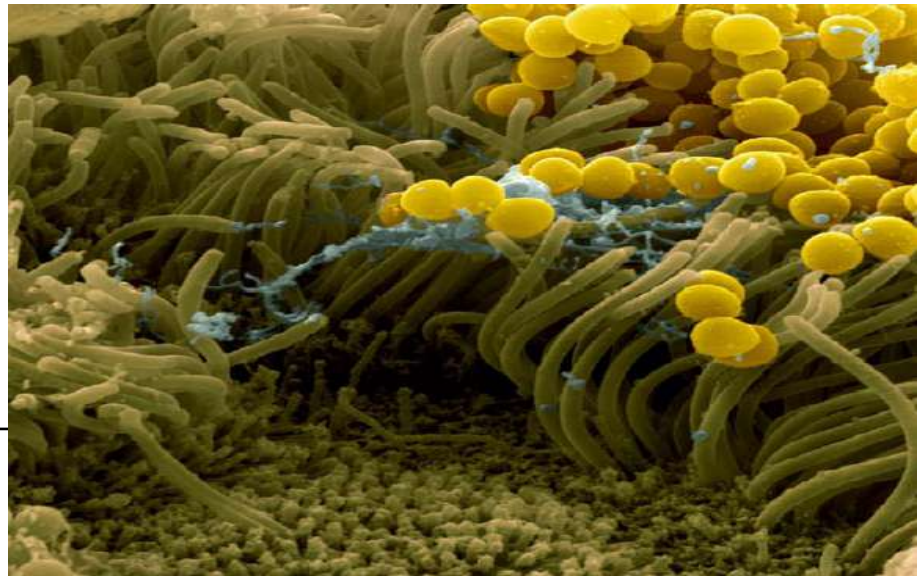


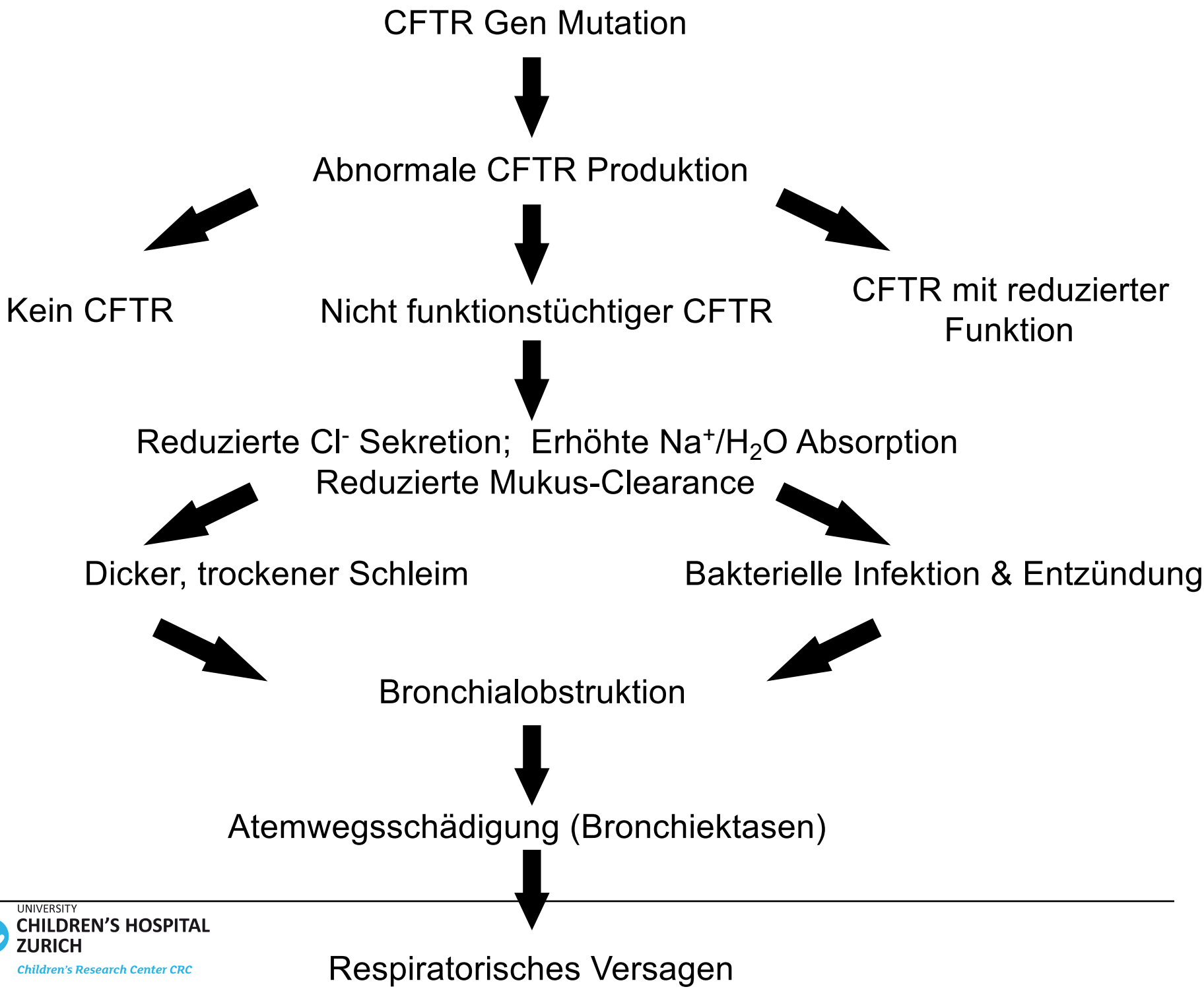
CFTR Kanal: vom Gen zur Krankheit

Konsequenzen der gestörten CFTR Funktion

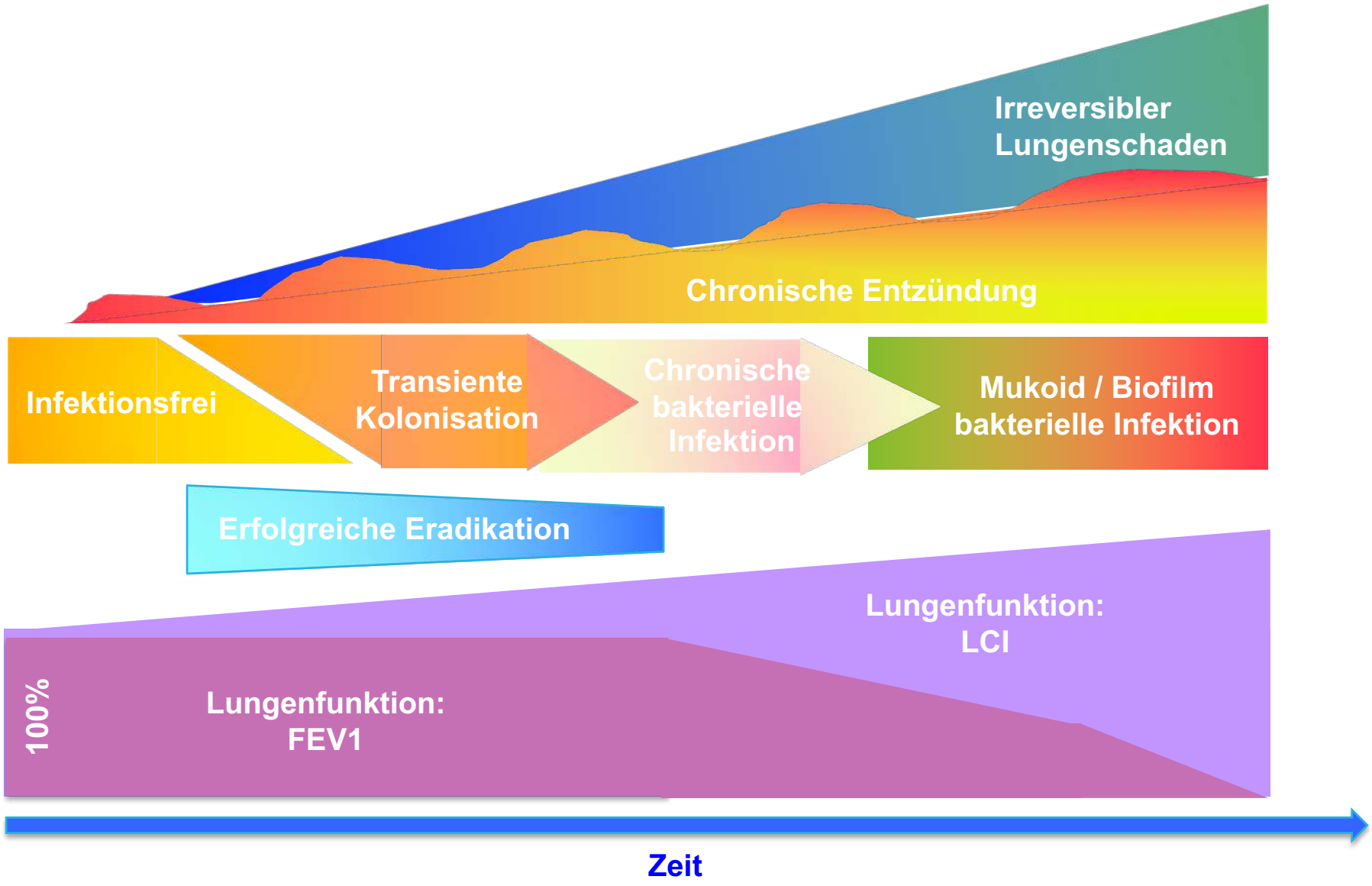






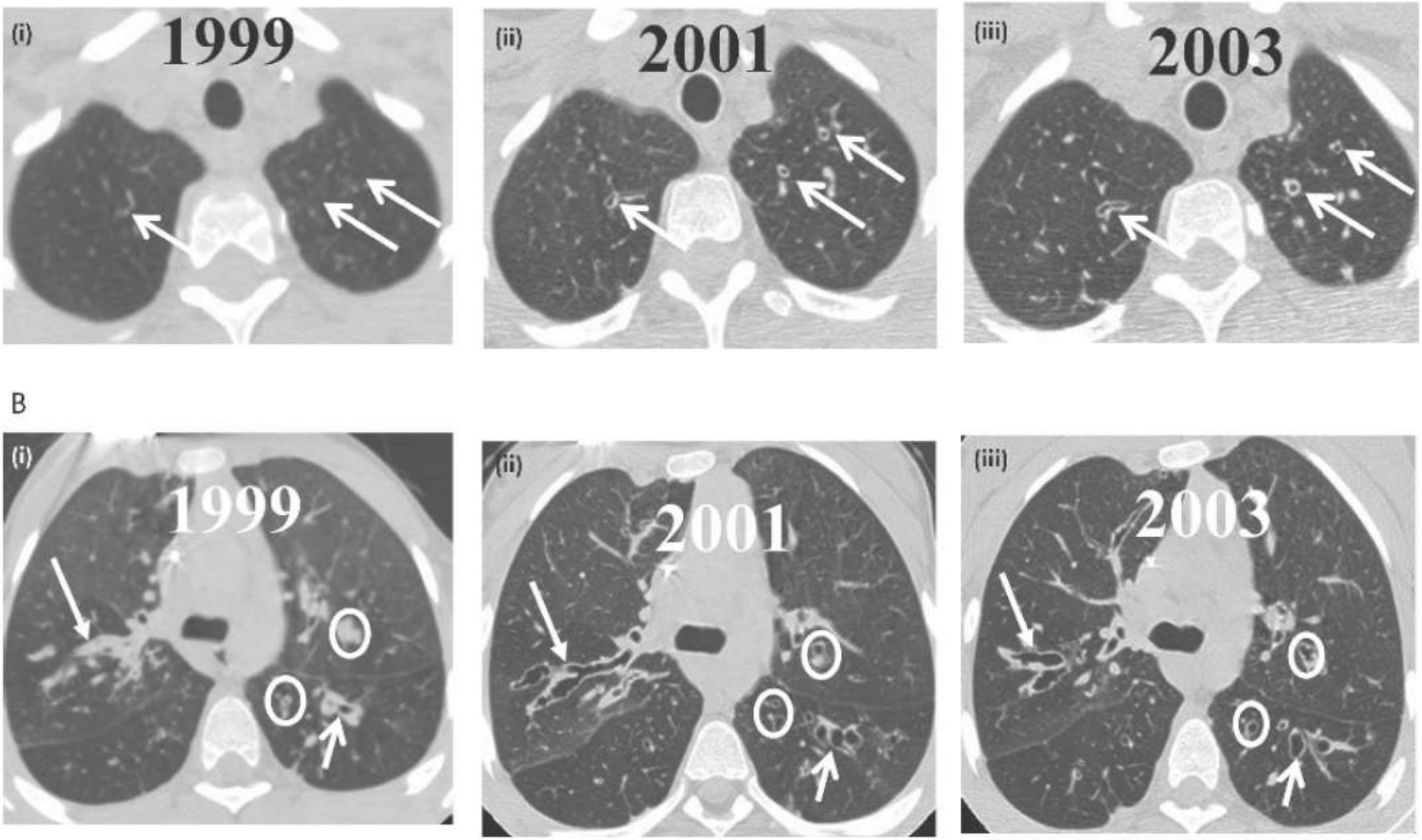

CFTR Gen Mutation
Abnormale CFTR Produktion
Kein CFTR
Nicht funktionstüchtiger CFTR
CFTR mit reduzierter Funktion
Reduzierte Cl^- Sekretion; Erhöhte Na^+/H_2O Absorption
Reduzierte Mukus-Clearance
Dicker, trockener Schleim
Bakterielle Infektion & Entzündung
Bronchialobstruktion
Atemwegsschädigung (Bronchiektasen)
Respiratorisches Versagen

Krankheitsverlauf am Beispiel der Lunge

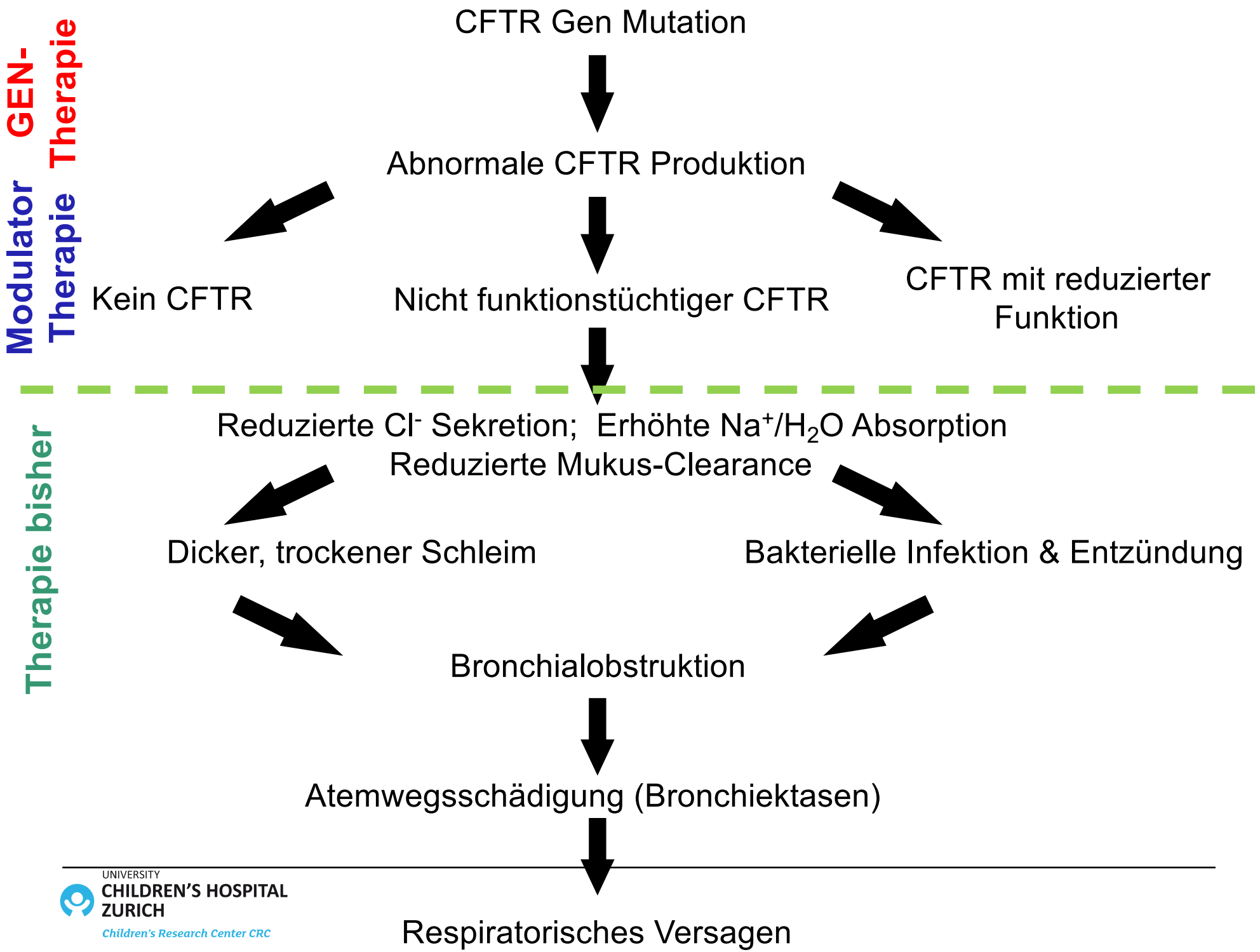


Mod nach Greally P. CMRO 2012:28;1059

Krankheitsverlauf am Beispiel der Lunge



De Jong PA Thorax 2006;61:80



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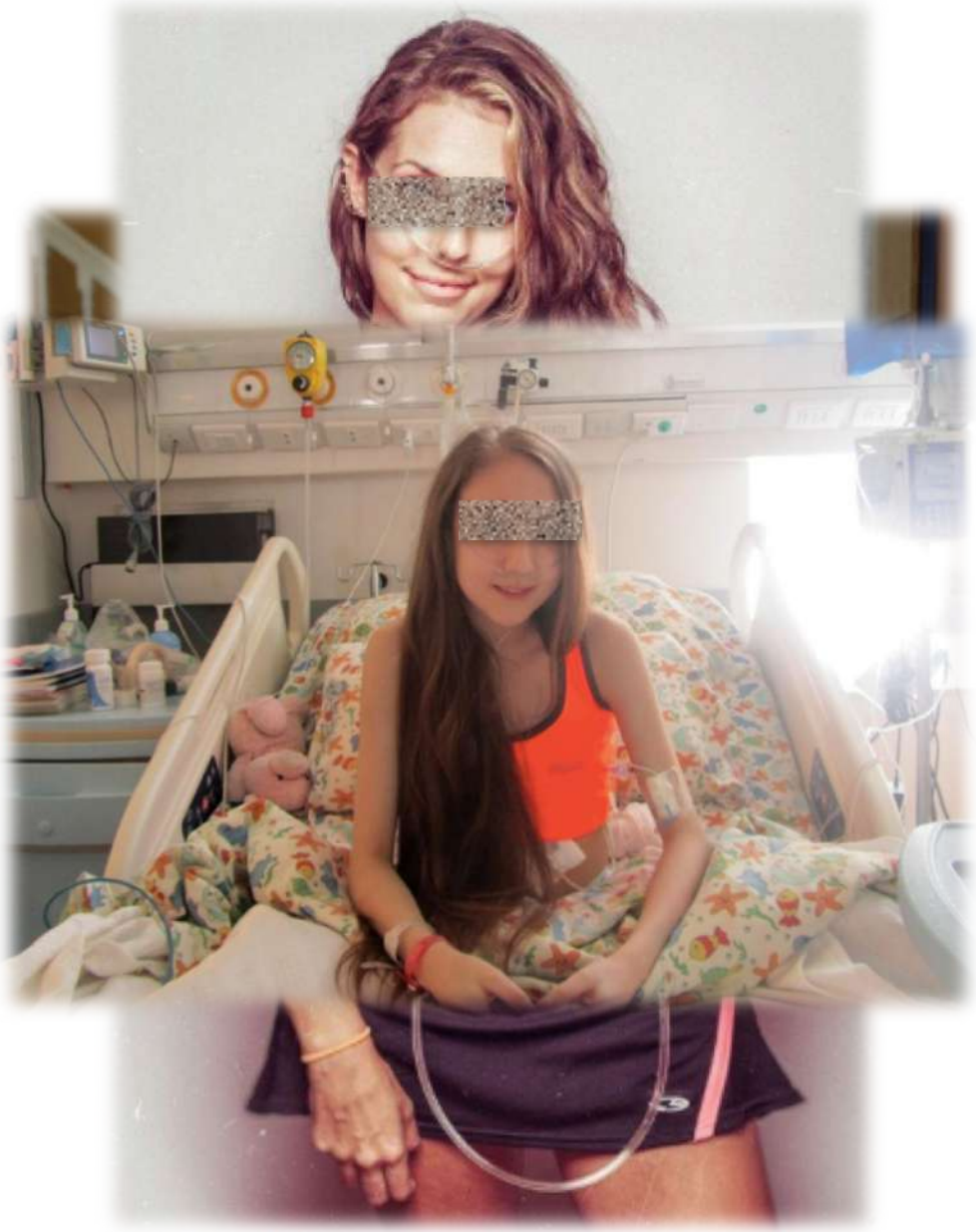
Children's Research Center CRC

CF Therapie heute

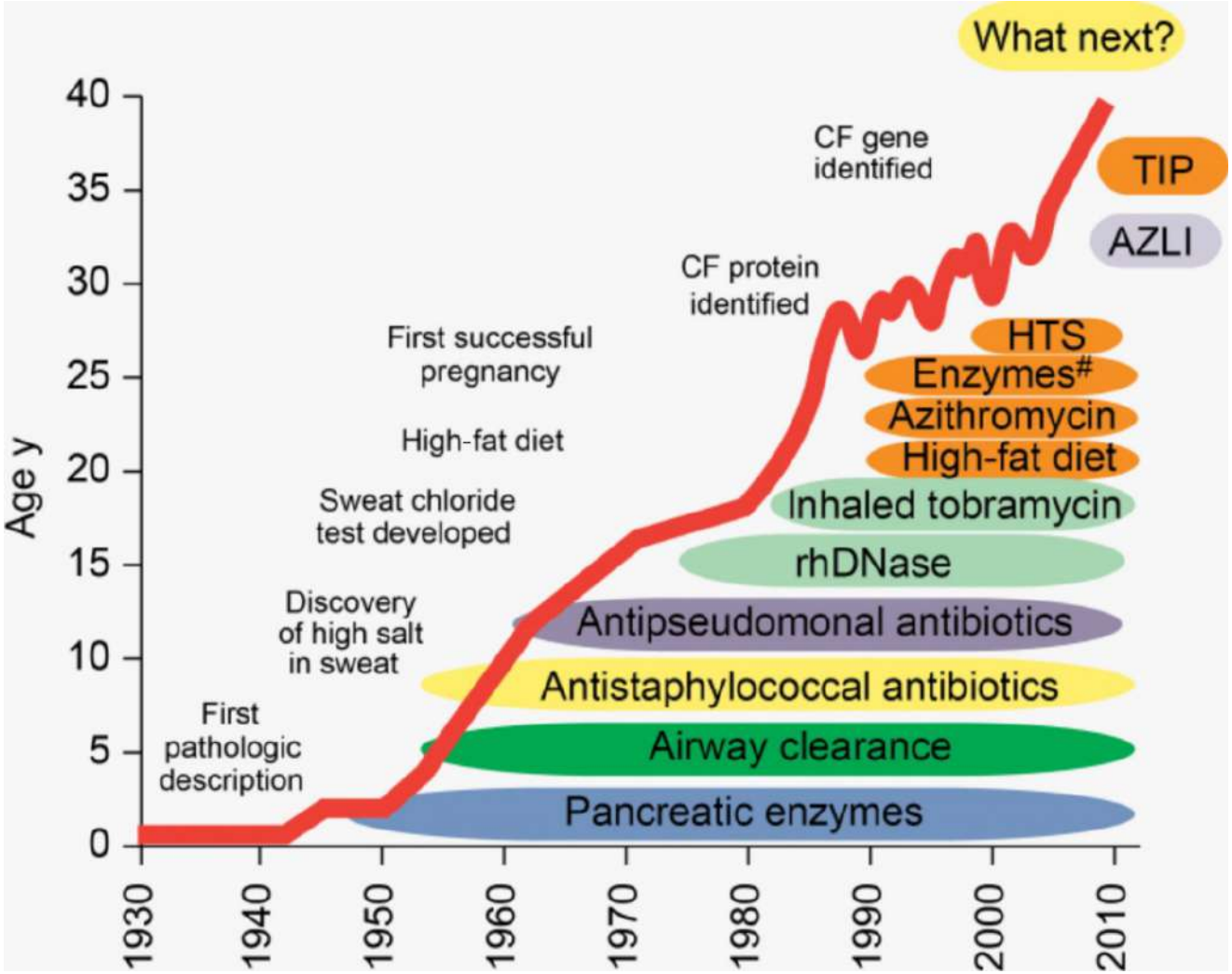
- Mucus Clearance
  - Atemphysiotherapie
    - Position
    - Ball / Trampolin
    - Stretching
    - Perzeption
  - PEP
  - Flutter
  - Autogene Drainage
    - “selective breathing”
  - Inhalation
  - Sport
  - Sauerstoff

CF Therapie heute

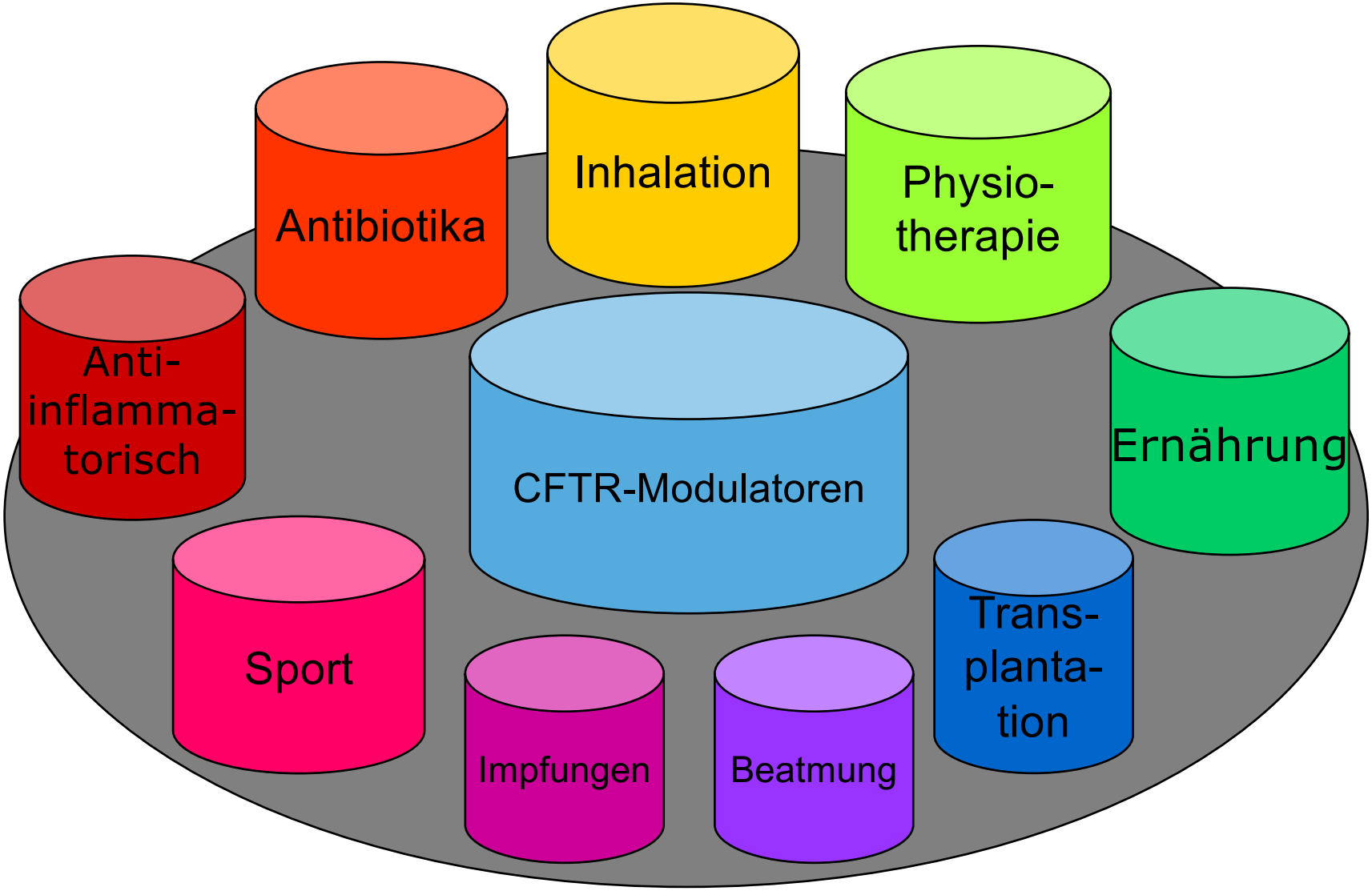
- Pancreas Enzyme
- Vitamin-Supplementation
  - AquADEK's usw
- Antibiotika
- Gallensäurebinder
- Kalcium Supplementation
- Bisphosphonate
- Systemische Steroide
- Anti-inflammatorische Therapie
- Antifungale Therapie
- Insulin
- Anti-IgE (Xolair®)
- Sauerstoff
- Künstliche Ernährung



CF Therapie heute

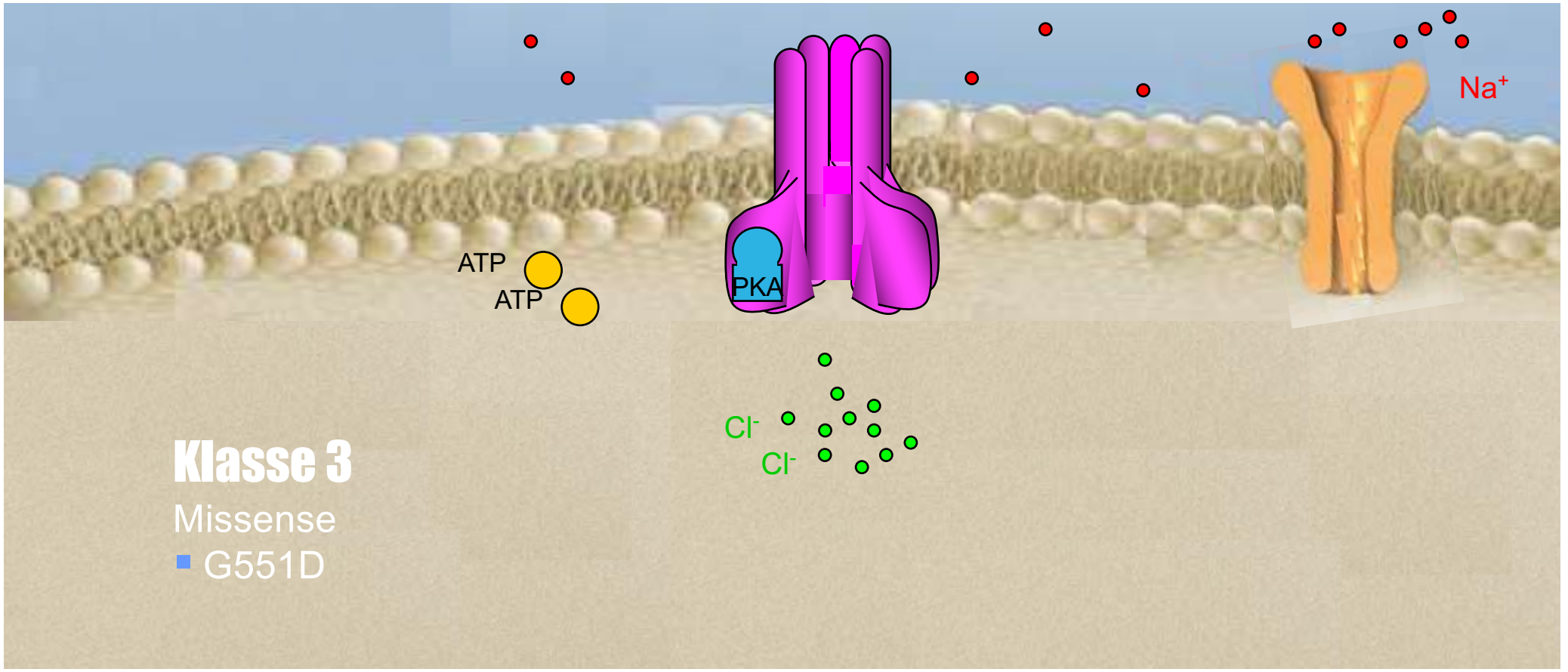


CF Therapie heute



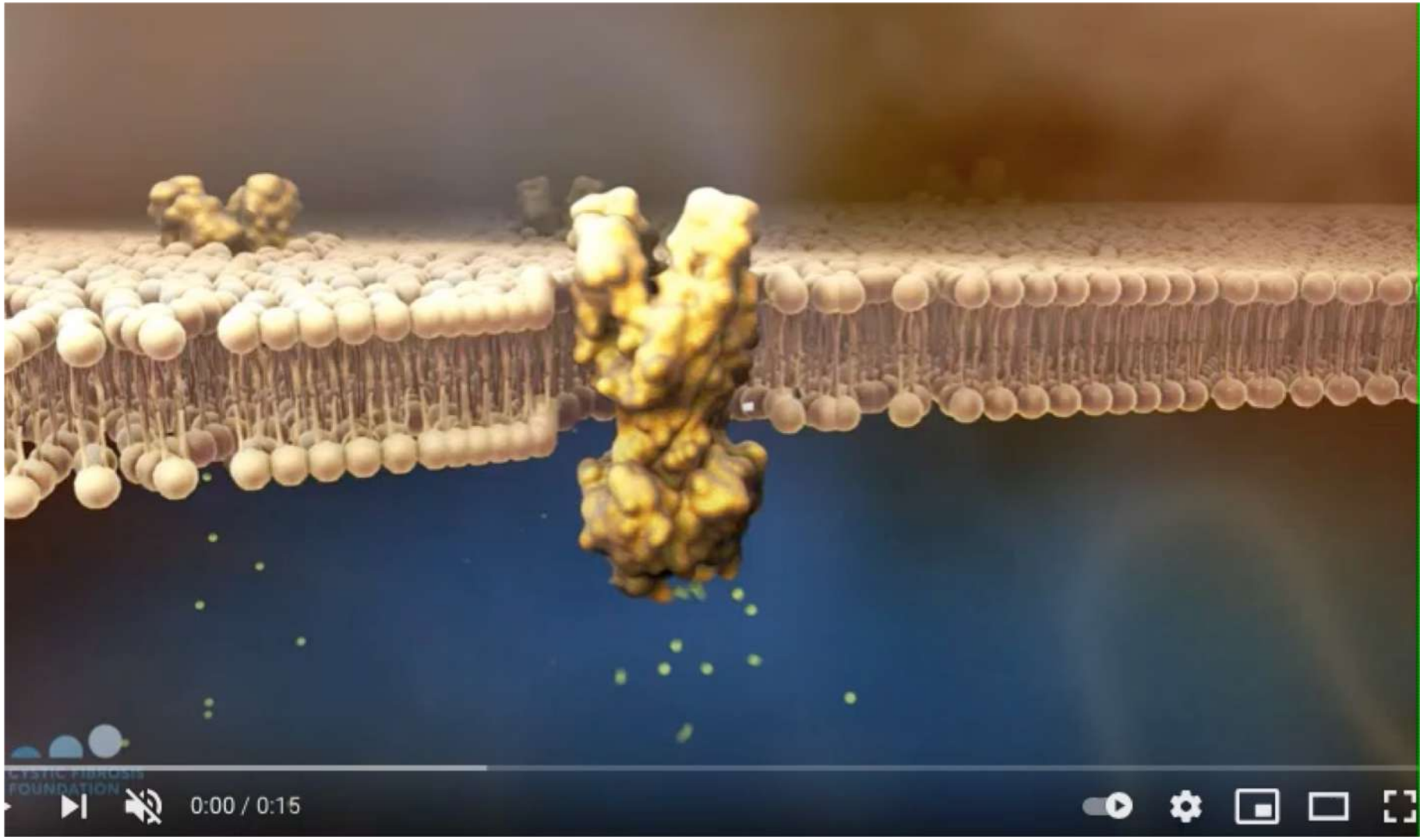
CFTR Modulatoren

Potentiator: Ivacaftor (Kalydeco®)



CFTR Modulatoren

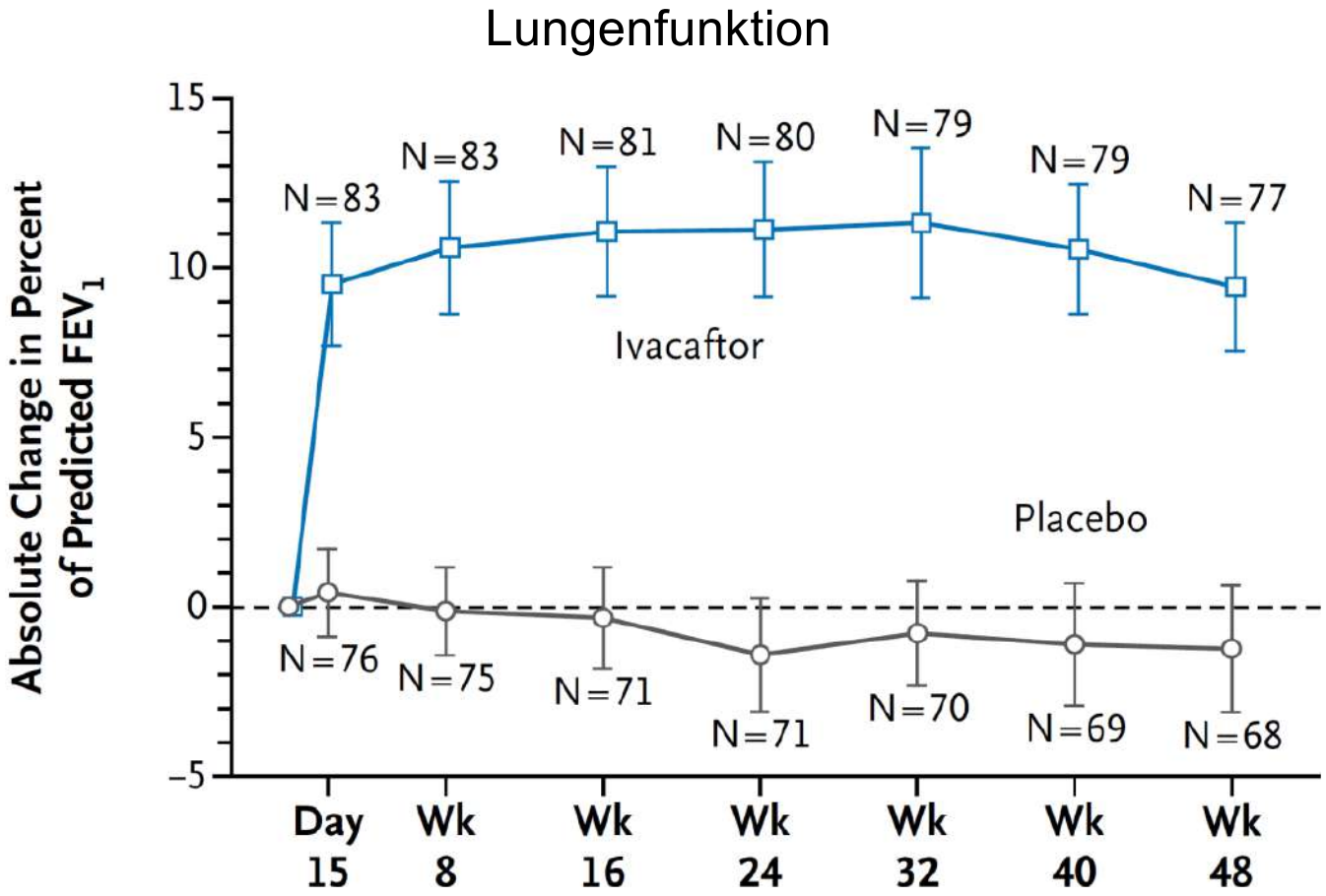
Potentiator: Ivacaftor (Kalydeco®)



CFTR Modulatoren

Potentiator: Ivacaftor (Kalydeco®)

STRIVE Studie: Patienten >12 Jahre mit der Gating Mutation G551D



Ramsey et al, NEJM 2011; Davies et al, Lancet Respir Med 2013 und 2016

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Potentiator: Ivacaftor (Kalydeco®)

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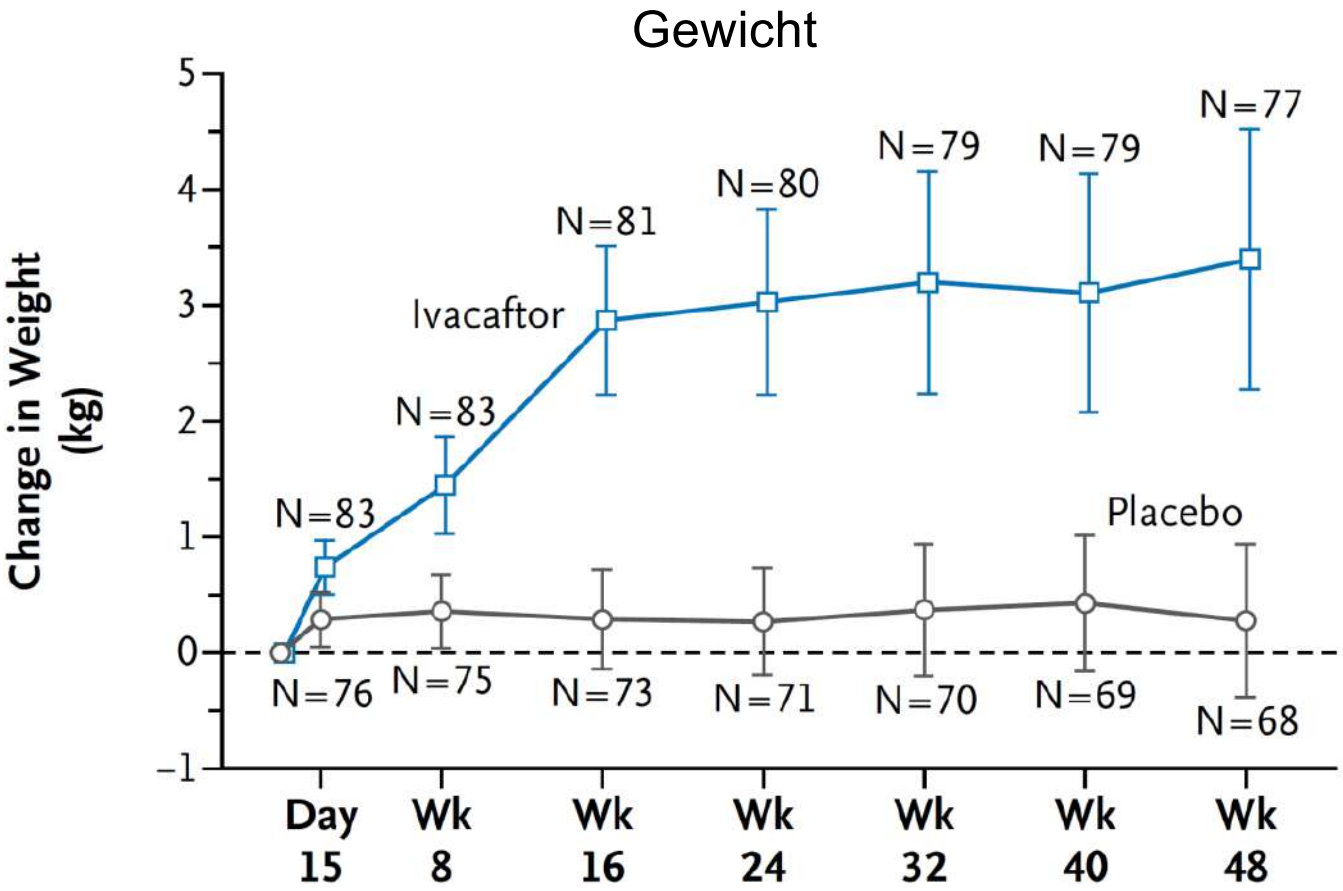

Ramsey et al, NEJM 2011; Davies et al, Lancet Respir Med 2013 und 2016

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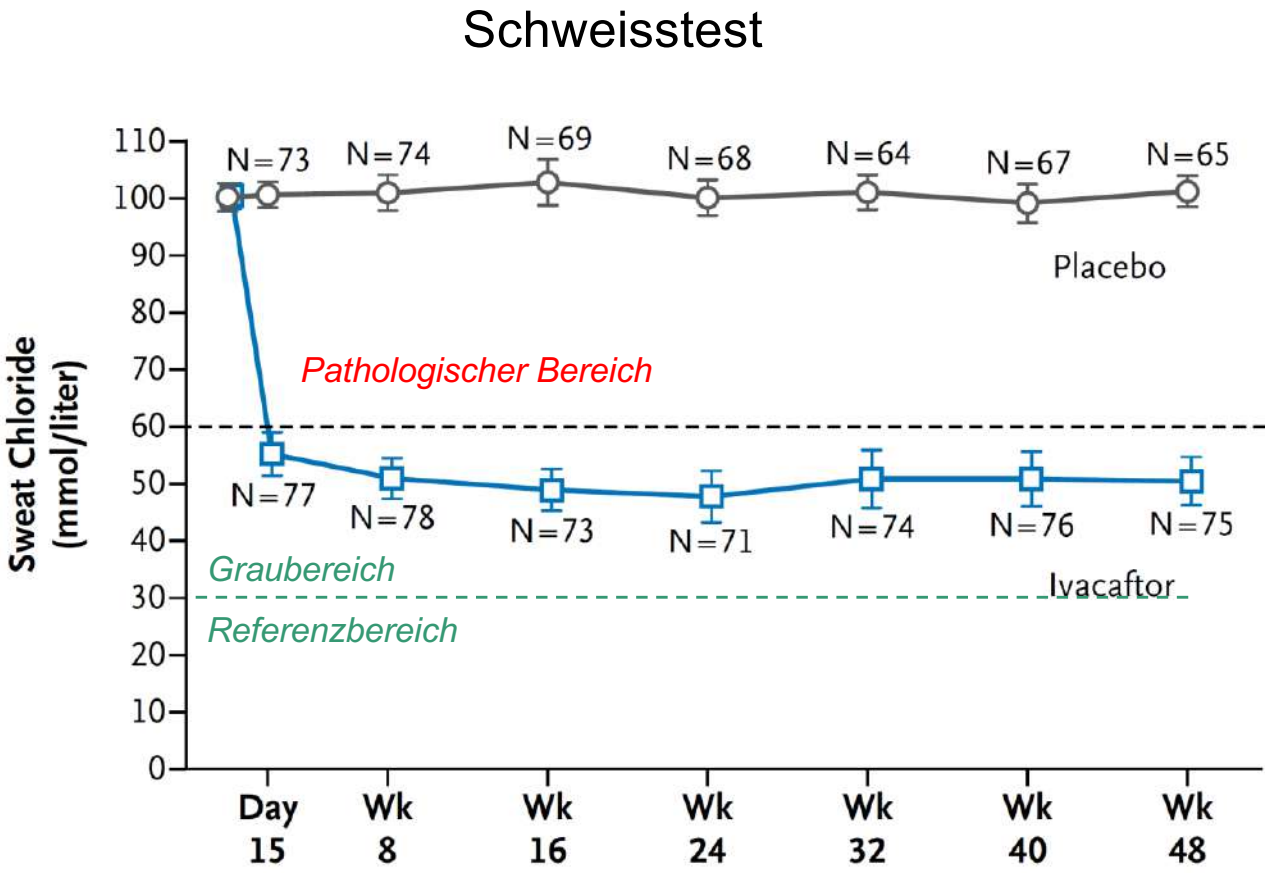
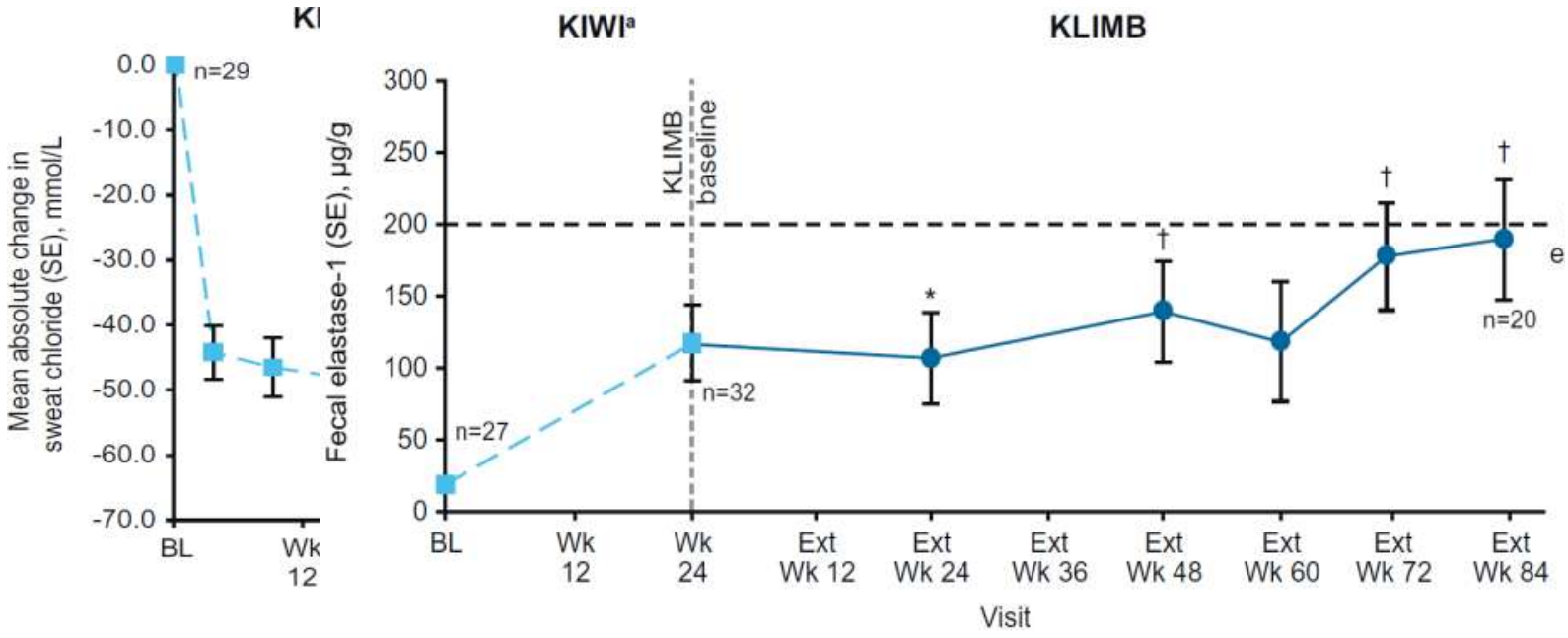


Ramsey et al, NEJM 2011; Davies et al, Lancet Respir Med 2013 und 2016

CFTR Modulatoren

Potentiator: Ivacaftor (Kalydeco®)

KIWI und KLIMB Studie Kinder 2-5 Jahre mit der Gating Mutation G551D



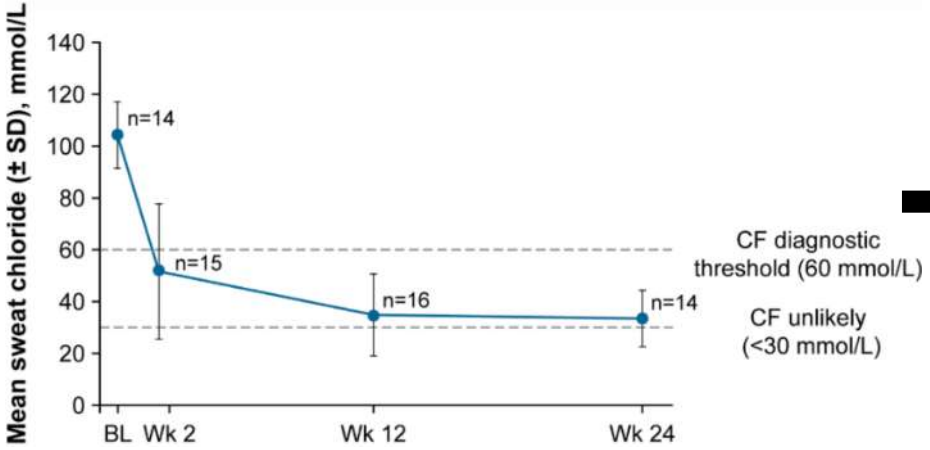
Werte >200ug/g = normale Pankreasfunktion

Rosenfeld et al., J Cyst Fibros 2019

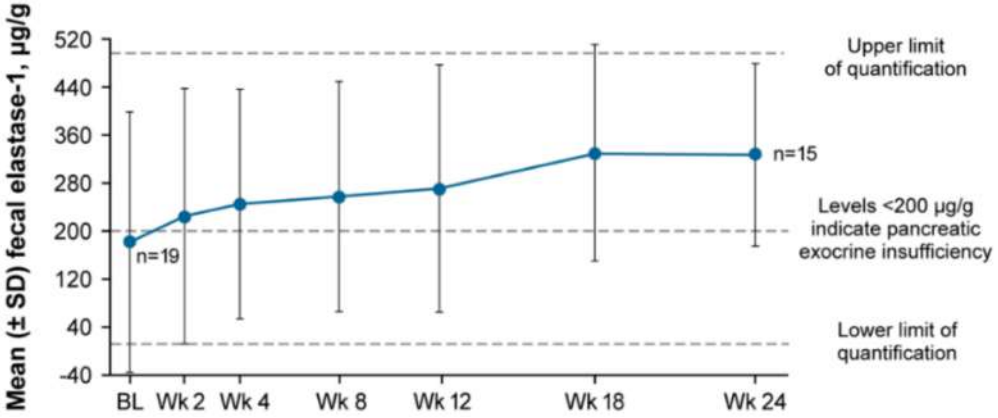
CFTR Modulatoren

Potentiator: Ivacaftor (Kalydeco®)

ARRIVAL Studie Kinder < 2 Jahre mit der Gating Mutation G551D



→ Stärkerer Effekt auf Schweiß-Chloridgehalt bei Kleinkindern



→ Wiederherstellung der Pankreasfunktion bei frühzeitiger Gabe?

Rosenfeld et al, Lancet Respir Med 2018

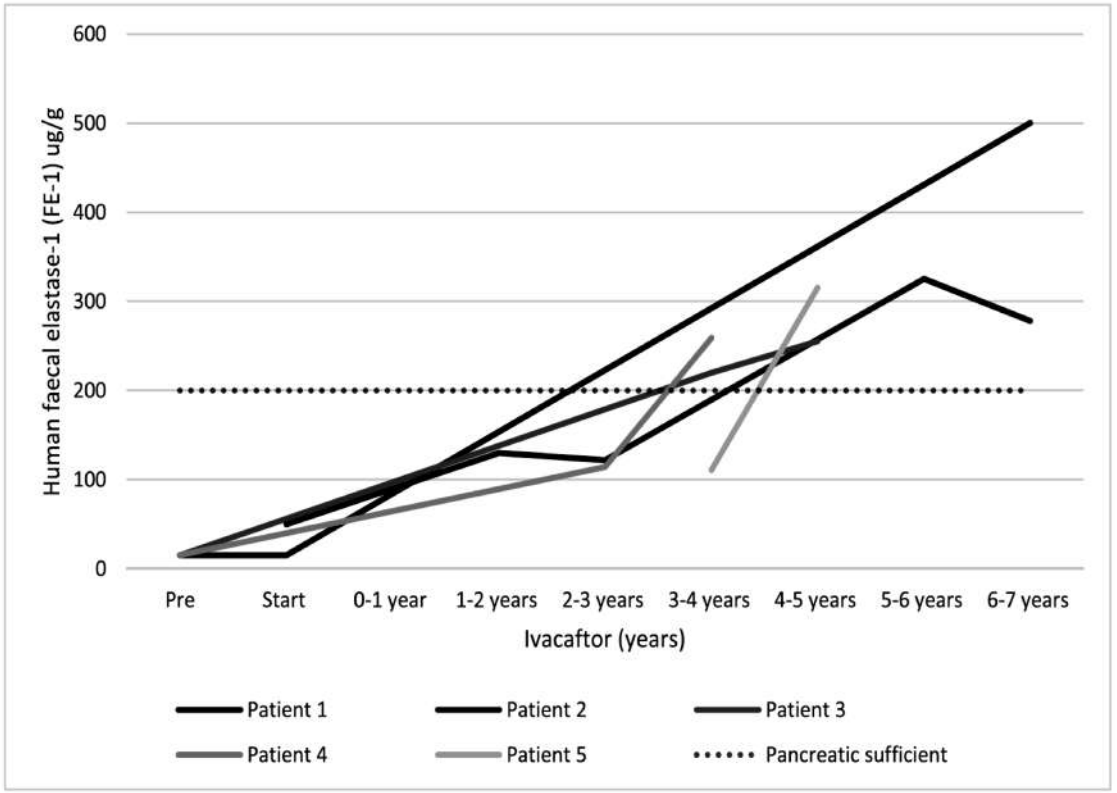
CFTR Modulatoren

Potentiator: Ivacaftor (Kalydeco®)

„Real-world evidence“

n=5 älter als 5 Jahre bei PS

- Alter MW 6 Jahre (4-7)
- Steigerung Stuhlelastase 299 mcg/g (197-485)
- Mittlere Therapiedauer bis zur PS 5 J. (3-7)
- 2 PERT gestoppt, 3 reduzierte Dosis

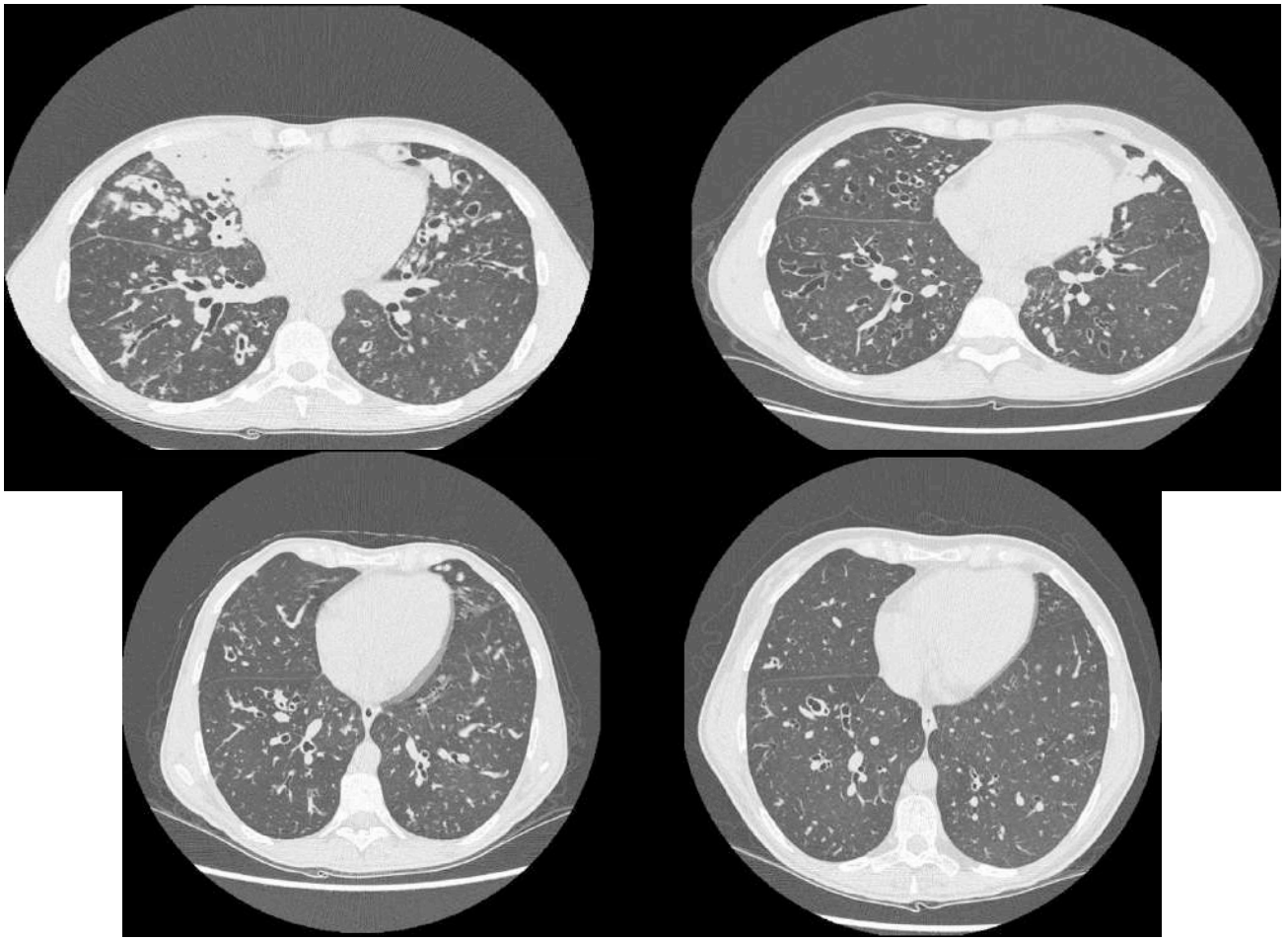


Nichols et al, Paediatr Respir Rev 2020

CFTR Modulatoren

Potentiator: Ivacaftor (Kalydeco®)

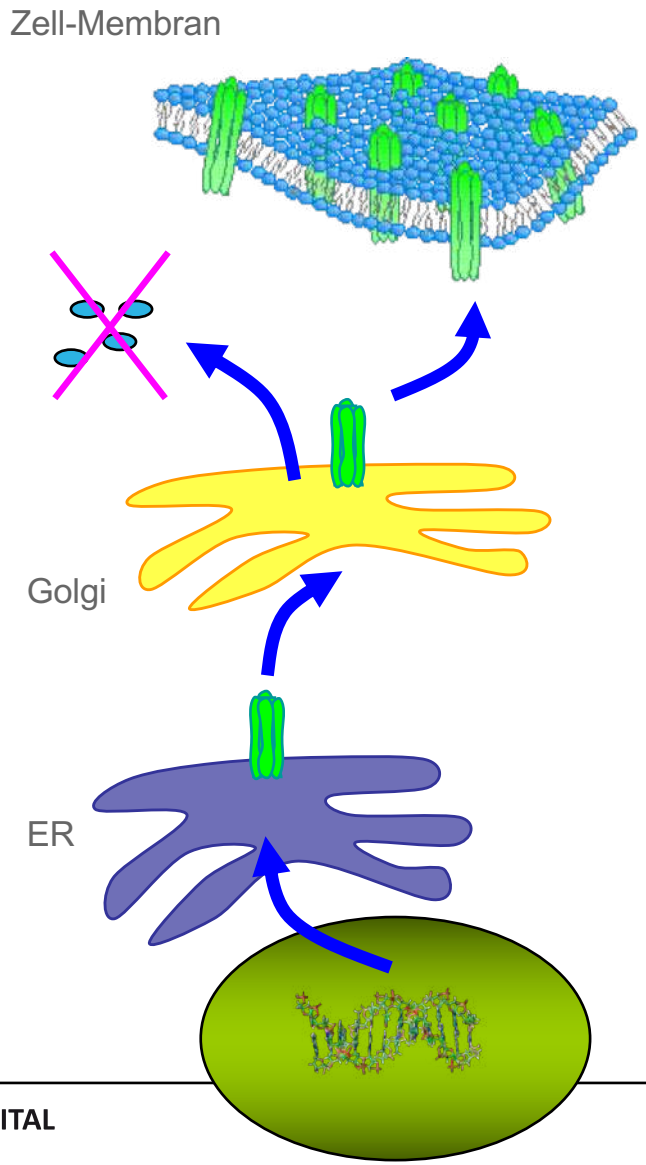
„Real-world evidence“



Ronan et al, Chest 2018

CFTR Modulatoren

Kombination von Potentiatoren (Ivacaftor) und Korrektor



Aktivierung der Öffnung des Kanals

Verminderung der Elimination des Proteins

Verbesserung der Ausreifung des Proteins

Verbesserung der Proteinfaltung

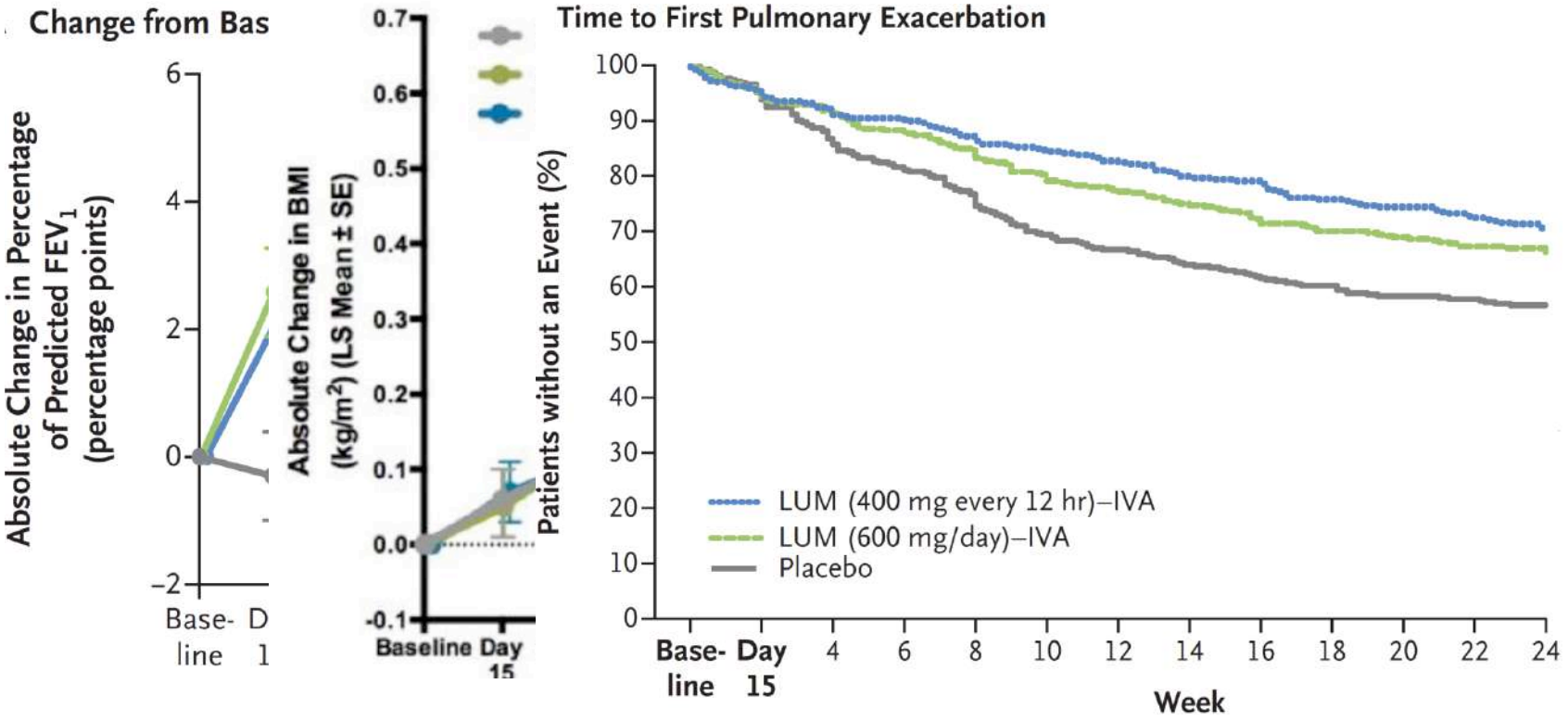
Potentiator

Korrektor

CFTR Modulatoren

Potentiator/Korrektor: Ivacaftor/Lumacaftor (Orkambi®)

TRAFFIC und TRANSPORT Studie Patienten > 12 Jahre F508del homozygot



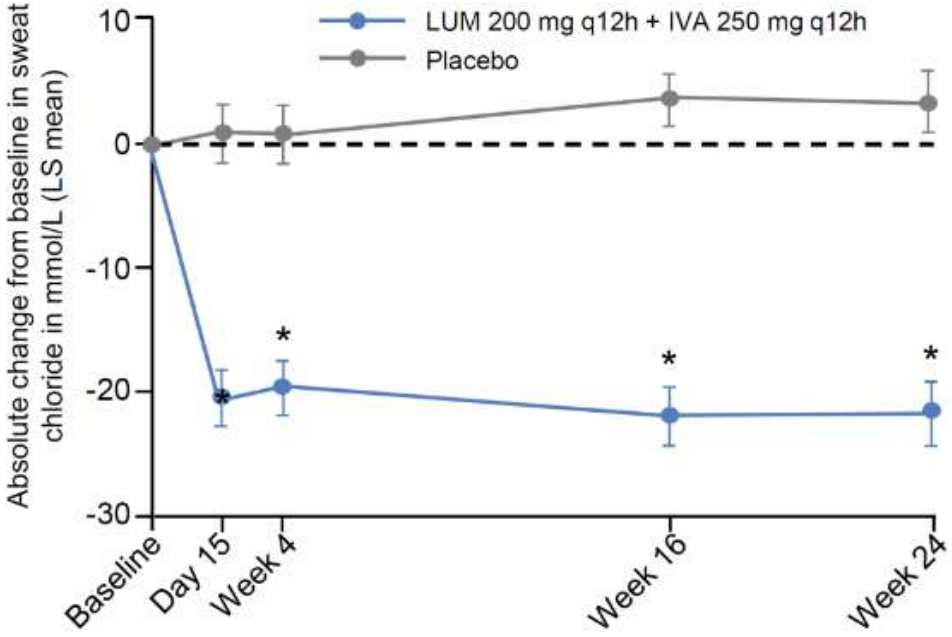
Wainwright et al, NEJM 2015

CFTR Modulatoren

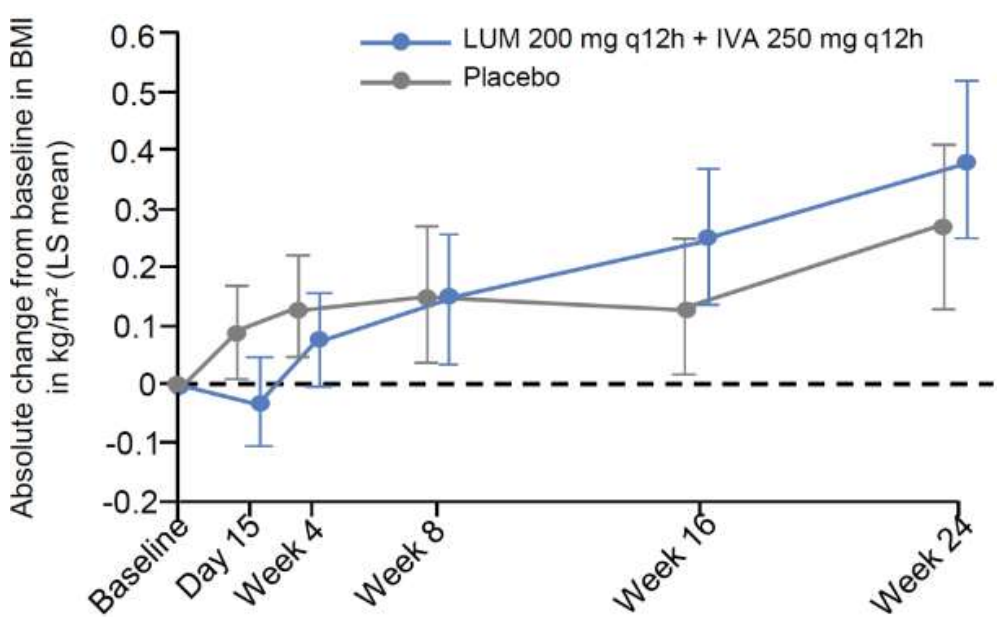
Potentiator/Korrektor: Ivacaftor/Lumacaftor (Orkambi®)

6-11 Jahre F508del homozygot

Schweisstest



Gewicht

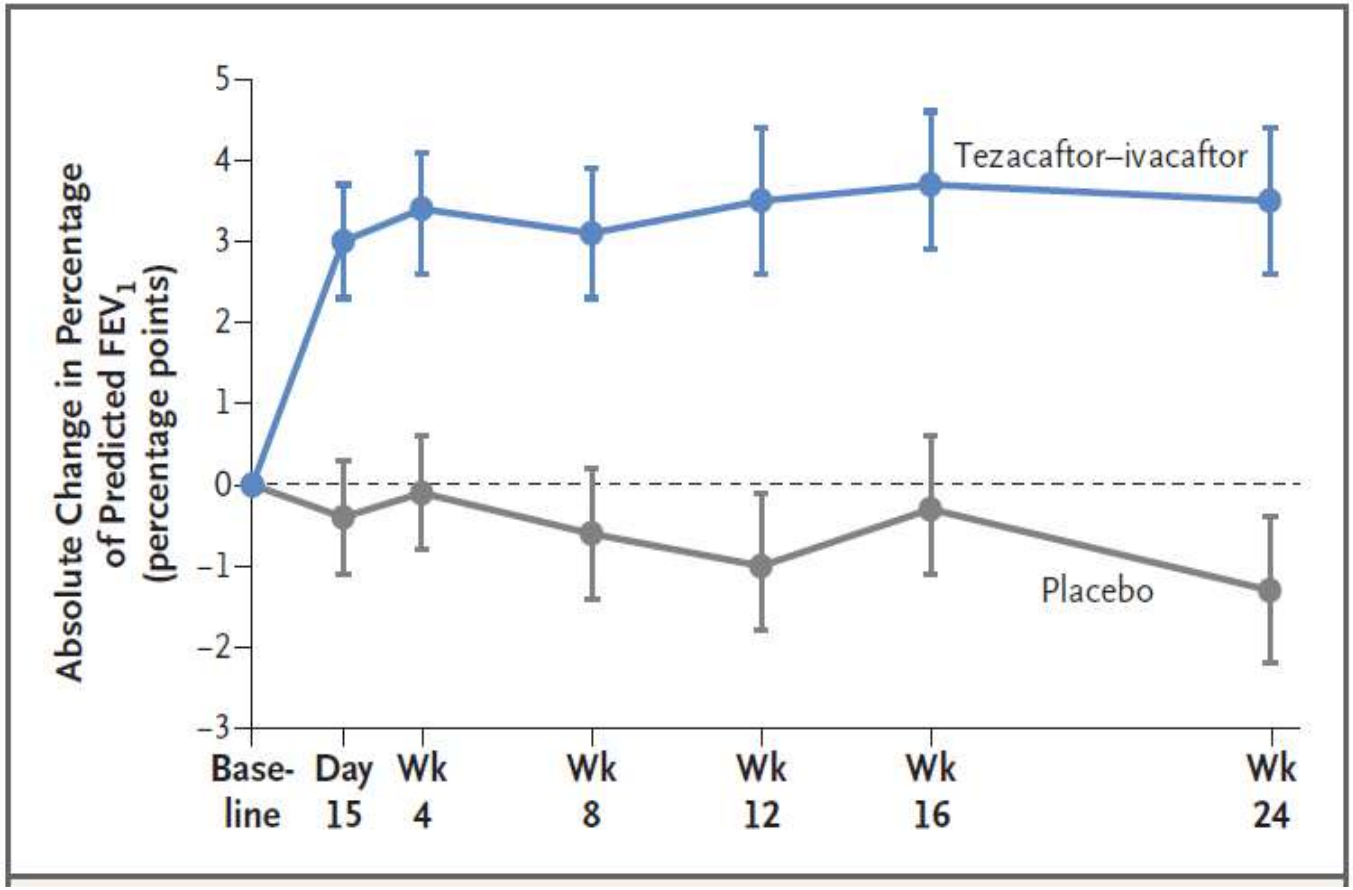


Ratjen et al, Lancet Respir Med 2017; McNamara et al., Lancet Respir Med 2019

CFTR Modulatoren

Potentiator/Korrektor: Ivacaftor/Tezacaftor (Symdeco®, Symkevi®)

EVOLVE und EXPAND Studien >12 Jahre F508del homozygot

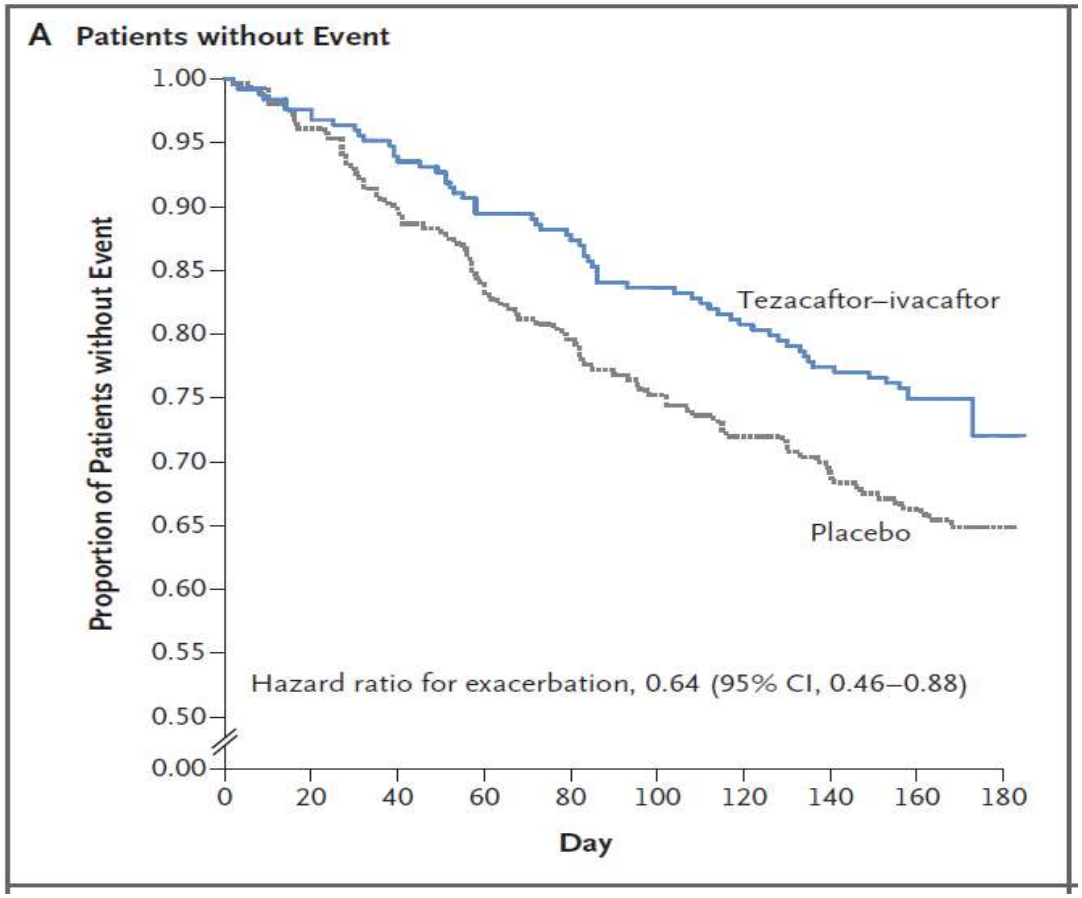


Taylor-Cousar, NEJM 2017

CFTR Modulatoren

Potentiator/Korrektor: Ivacaftor/Tezacaftor (Symdeco®, Symkevi®)

EVOLVE und EXPAND Studien >12 Jahre F508del homozygot

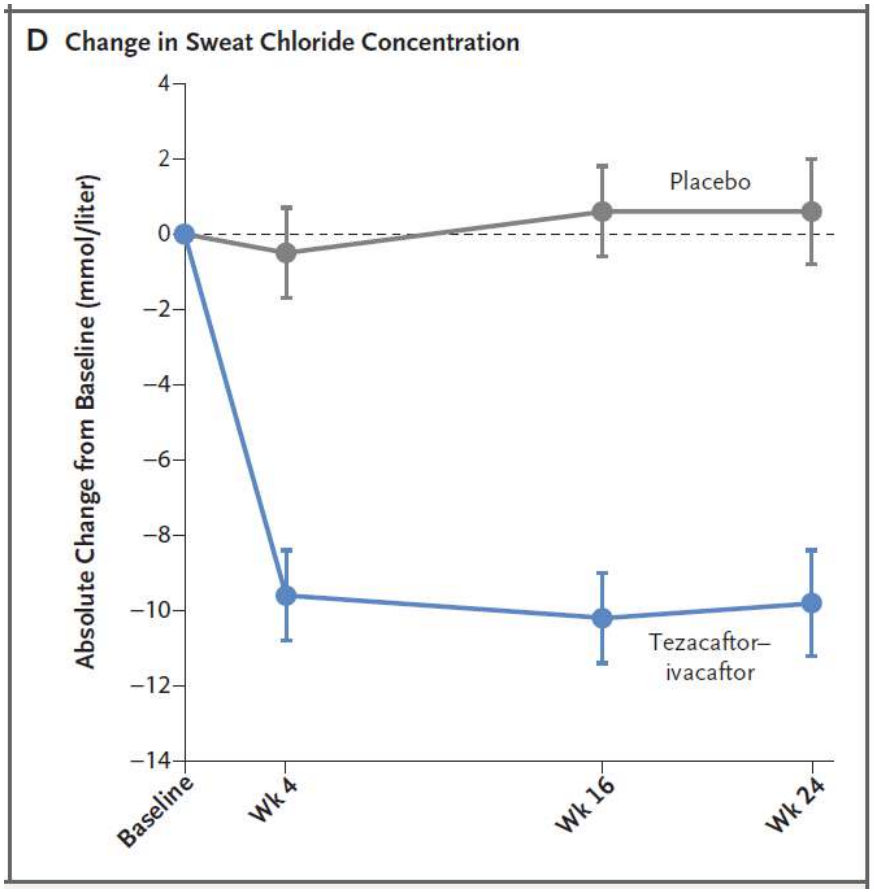


Taylor-Cousar, NEJM 2017

CFTR Modulatoren

Potentiator/Korrektor: Ivacaftor/Tezacaftor (Symdeco®, Symkevi®)

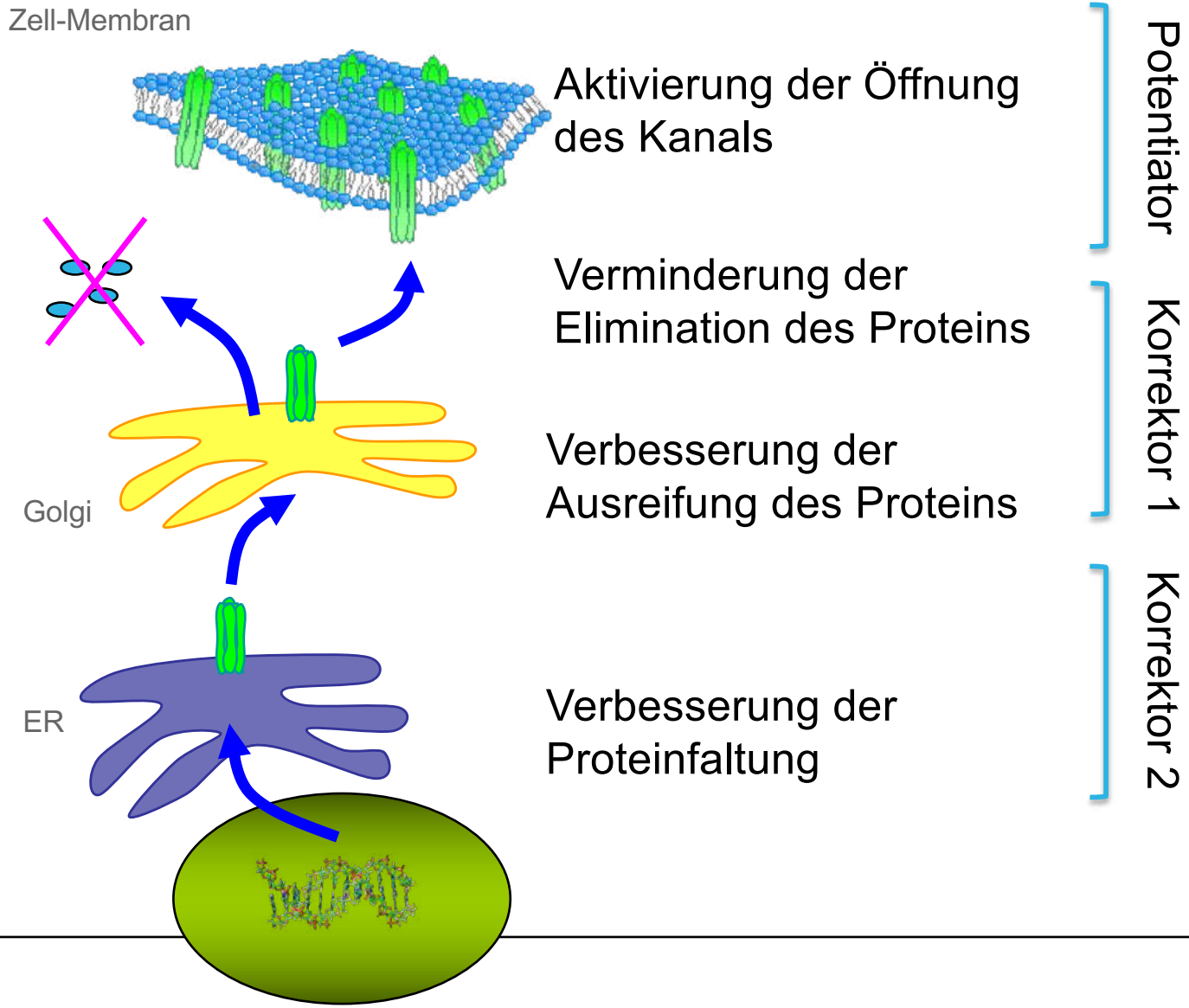
EVOLVE und EXPAND Studien >12 Jahre F508del homozygot



Taylor-Cousar, NEJM 2017

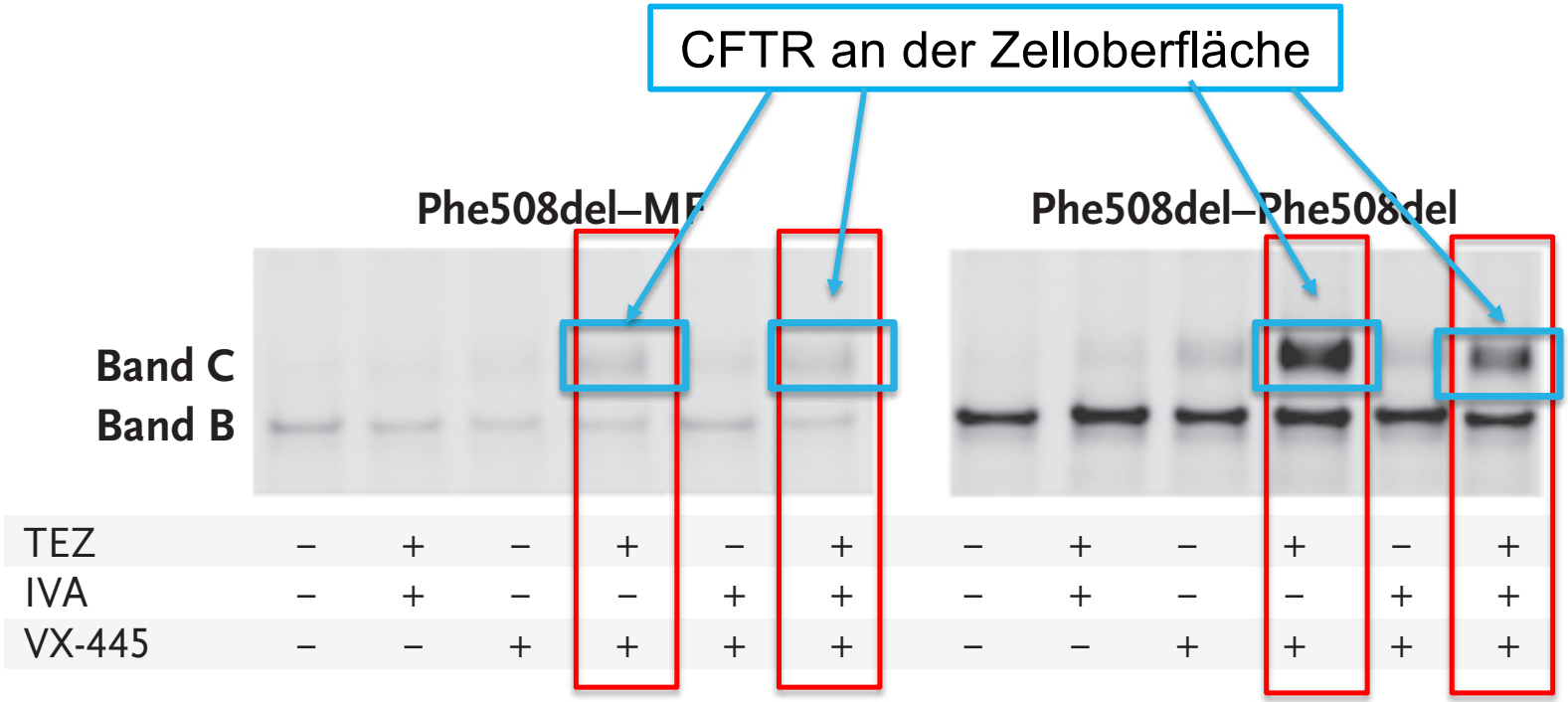
CFTR Modulatoren

3-fach Kombination von Potentiatoren (Ivacaftor) und 2 Korrektoren



CFTR Modulatoren

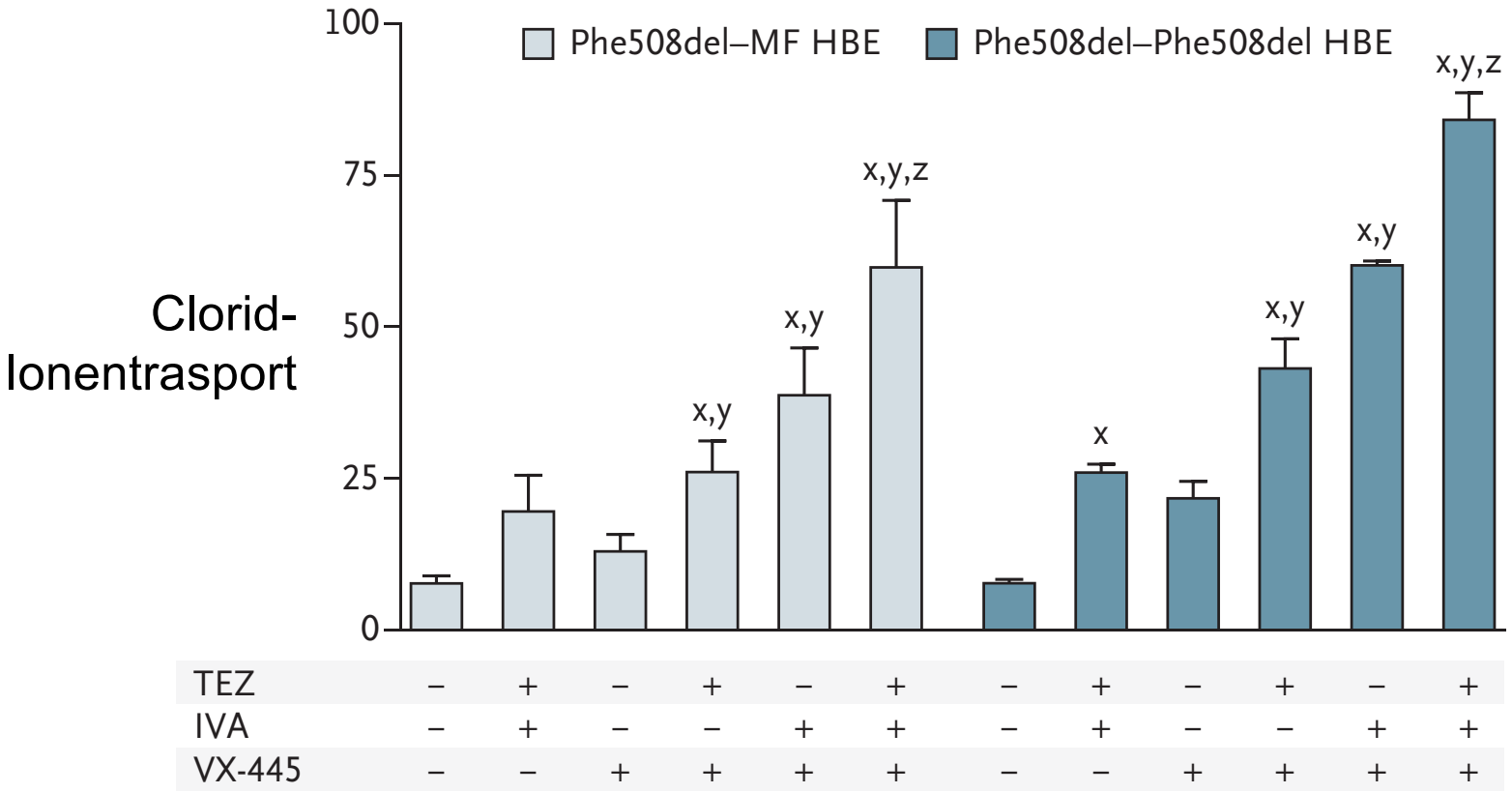
Elexacaftor–Tezacaftor–Ivacaftor: Effekte im Zell-Labor



Keating D. N Engl J Med 2018;379:1612-20

CFTR Modulatoren

Elexacaftor–Tezacaftor–Ivacaftor: Effekte im Zell-Labor

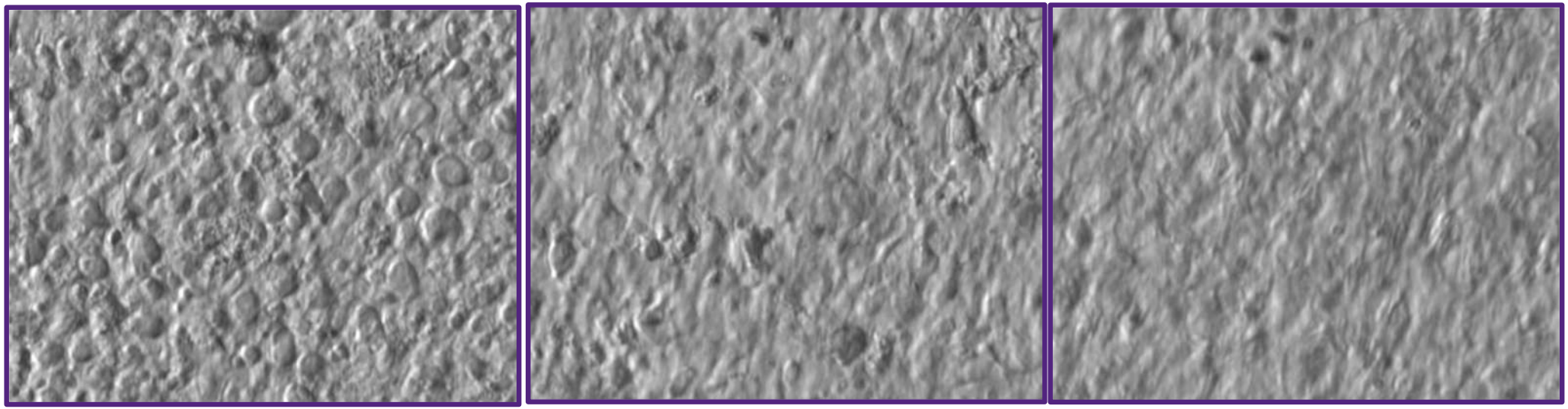


Keating D. N Engl J Med 2018;379:1612-20

CFTR Modulatoren

Elexacaftor–Tezacaftor–Ivacaftor: Effekte im Zell-Labor

Keine Behandlung | Behandlung mit Orkambi | Behandlung mit Trikafta



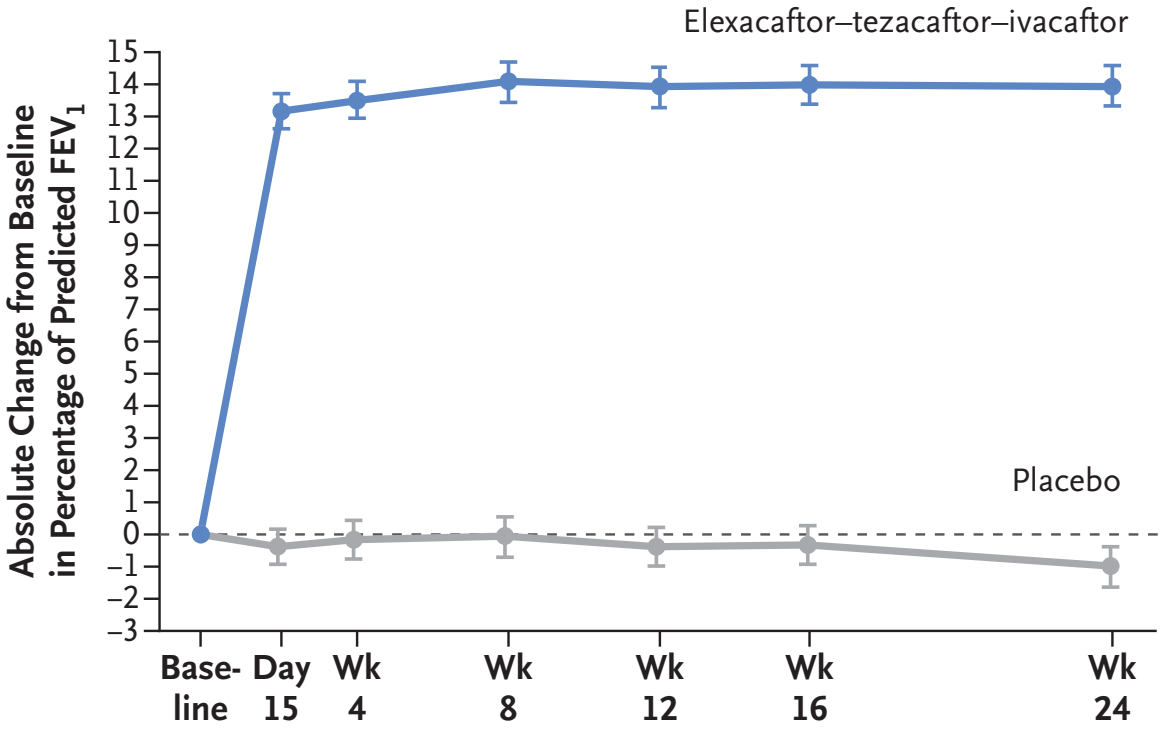
Kulturen von Zilientragenden Zellen

CFTR Modulatoren

Elexacaftor–Tezacaftor–Ivacaftor (Trikafta® / Kaftrio®)

AURORA Studie Patienten >12 Jahre mit F508del / Minimal Function Mutation

Lungenfunktion



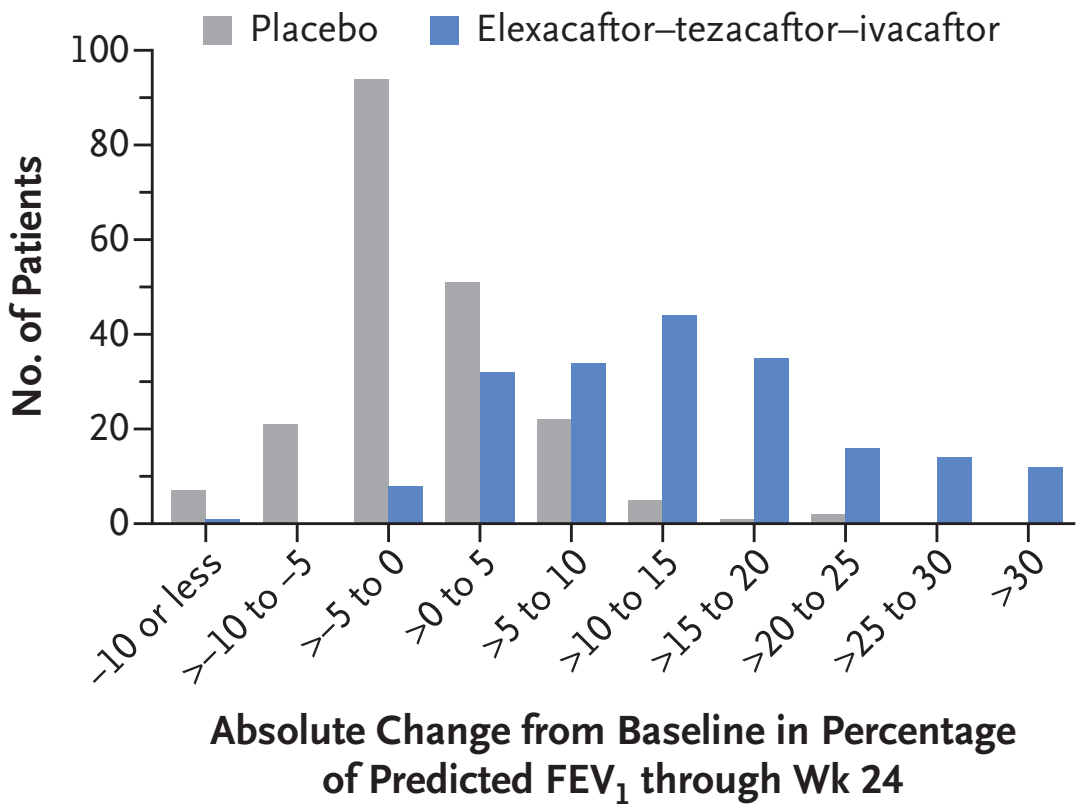
Middleton PG. N Engl J Med 2019;381:1809-19

CFTR Modulatoren

Elexacaftor–Tezacaftor–Ivacaftor (Trikafta® / Kaftrio®)

AURORA Studie Patienten >12 Jahre mit F508del / Minimal Function Mutation

Lungenfunktion



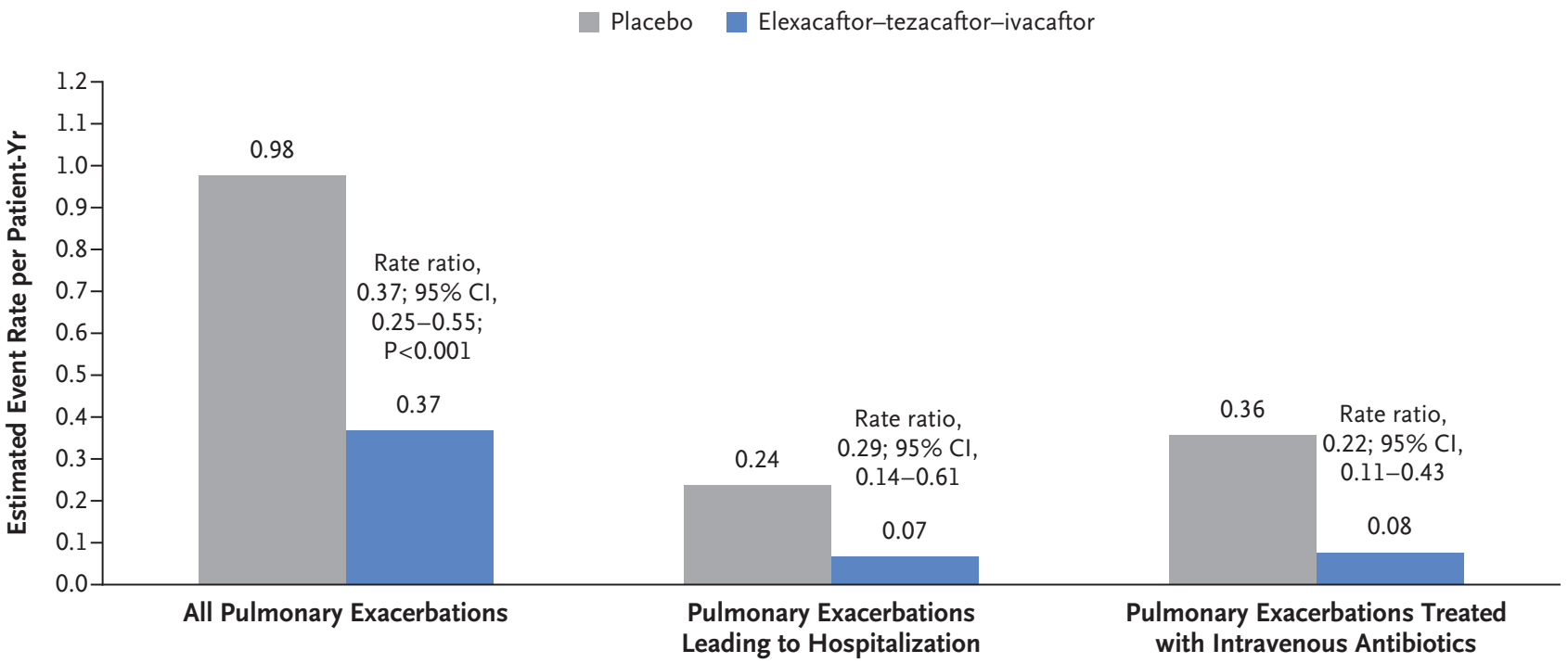
Middleton PG. N Engl J Med 2019;381:1809-19

CFTR Modulatoren

Elexacaftor–Tezacaftor–Ivacaftor (Trikafta® / Kaftrio®)

AURORA Studie Patienten >12 Jahre mit F508del / Minimal Function Mutation

Exacerbationen



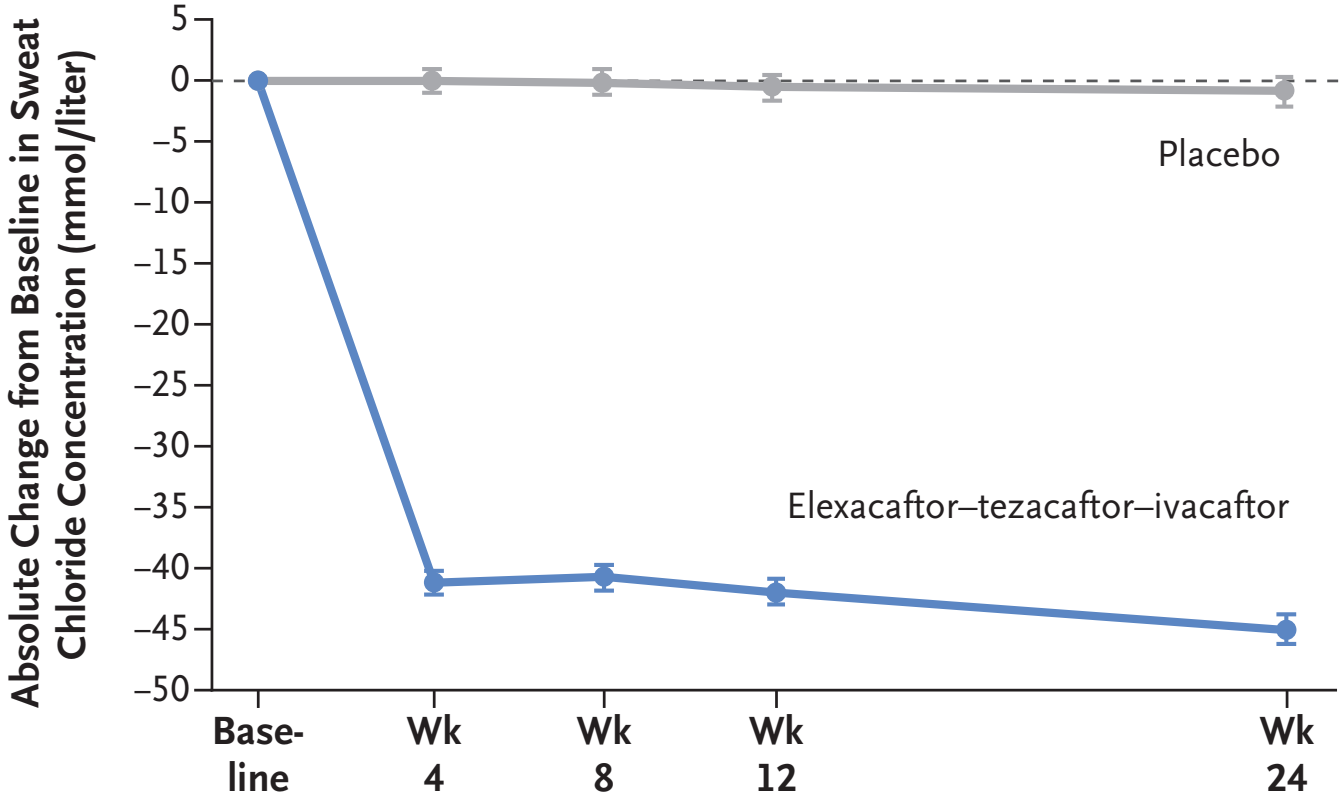
Middleton PG. N Engl J Med 2019;381:1809-19

CFTR Modulatoren

Elexacaftor–Tezacaftor–Ivacaftor (Trikafta® / Kaftrio®)

AURORA Studie Patienten >12 Jahre mit F508del / Minimal Function Mutation

Schweisstest



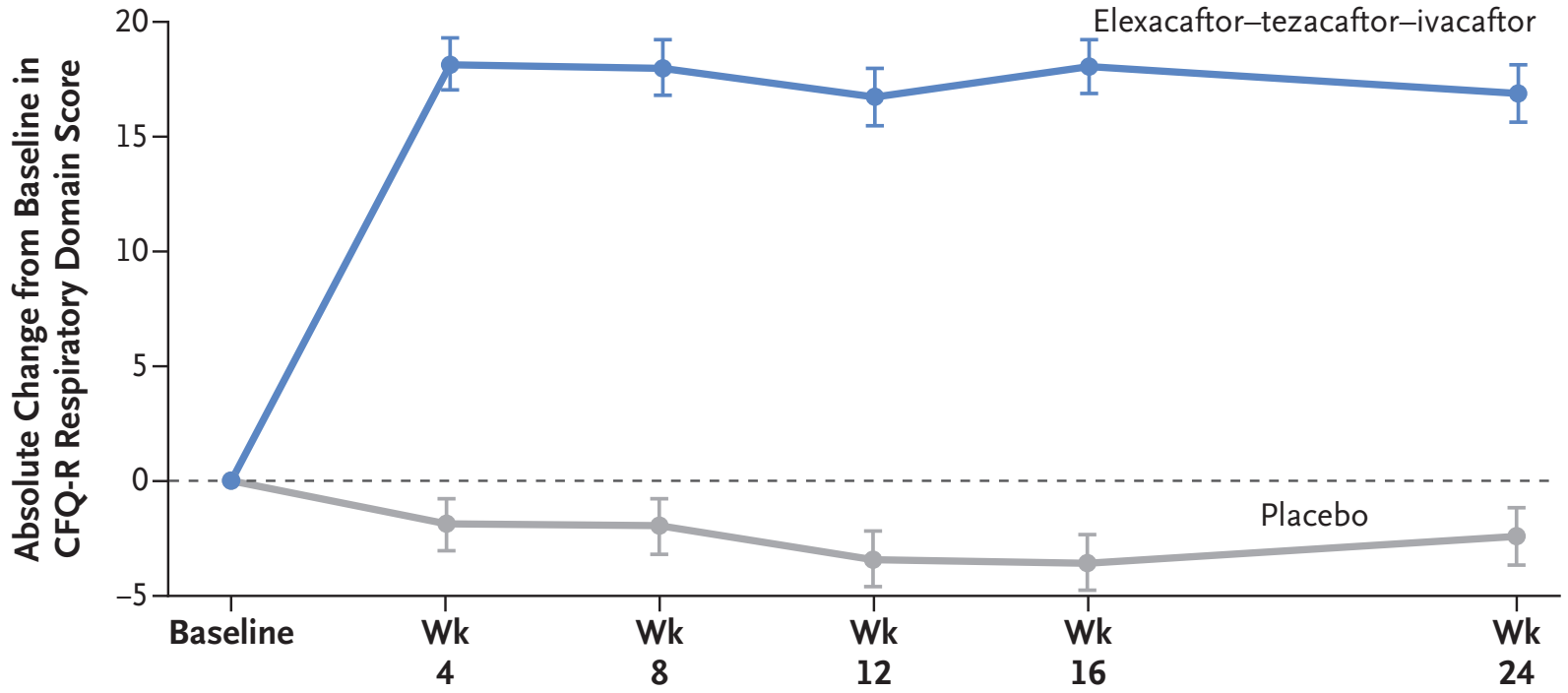
Middleton PG. N Engl J Med 2019;381:1809-19

CFTR Modulatoren

Elexacaftor–Tezacaftor–Ivacaftor (Trikafta® / Kaftrio®)

AURORA Studie Patienten >12 Jahre mit F508del / Minimal Function Mutation

Lebensqualität



Middleton PG. N Engl J Med 2019;381:1809-19

CFTR Modulatoren

Elexacaftor–Tezacaftor–Ivacaftor (Trikafta® / Kaftrio®)

AURORA Studie Patienten >12 Jahre mit F508del / Minimal Function Mutation

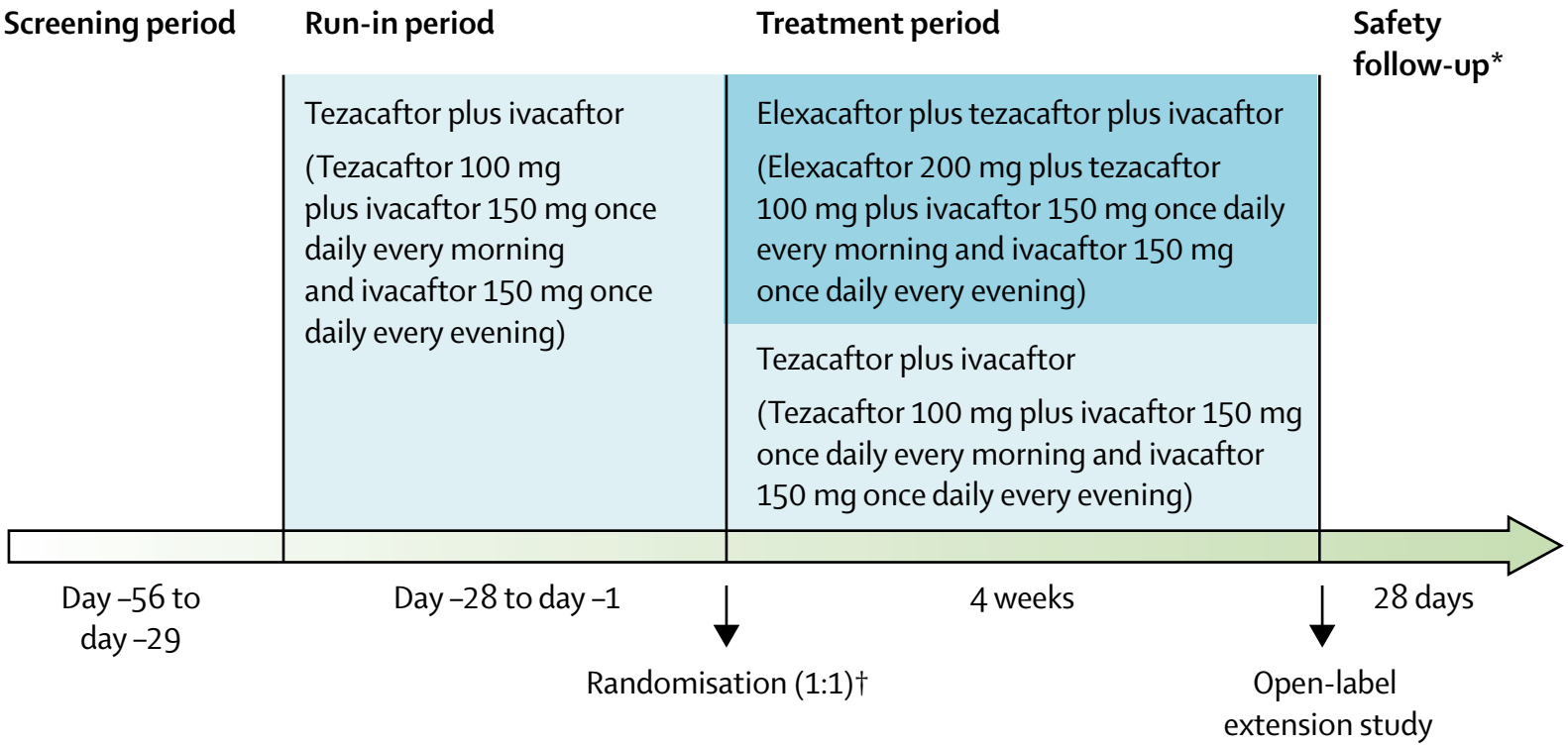
Nebenwirkung	Trikafta	Placebo
Jede Nebenwirkung	93%	96%
Exacerbation	21.8%	47.3%
Mehr Sputum	19.8%	19.4%
Kopfschmerzen	17.3%	14.9%
Husten	16.8%	38.3%
Durchfall	12.9%	7%
Müdigkeit	4.5%	10%
Ausschläge	10.9%	6.5%
Leberwert Erhöhung	10.9%	4.0%

Middleton PG. N Engl J Med 2019;381:1809-19

CFTR Modulatoren

Elexacaftor–Tezacaftor–Ivacaftor (Trikafta® / Kaftrio®)

Patienten >12 Jahre mit homozygoter F508del Mutation



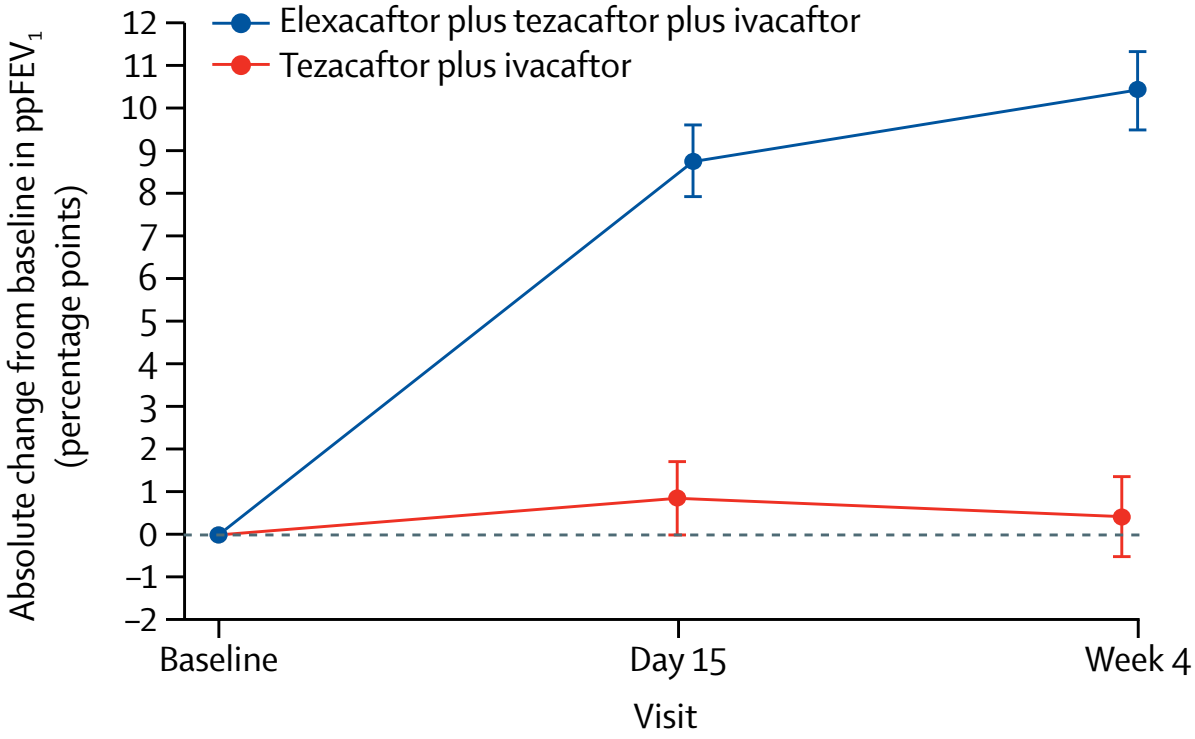
Hejiermann H. Lancet 2019; 394: 1940–48

CFTR Modulatoren

Elexacaftor–Tezacaftor–Ivacaftor (Trikafta® / Kaftrio®)

Patienten >12 Jahre mit homozygoter F508del Mutation

Lungenfunktion



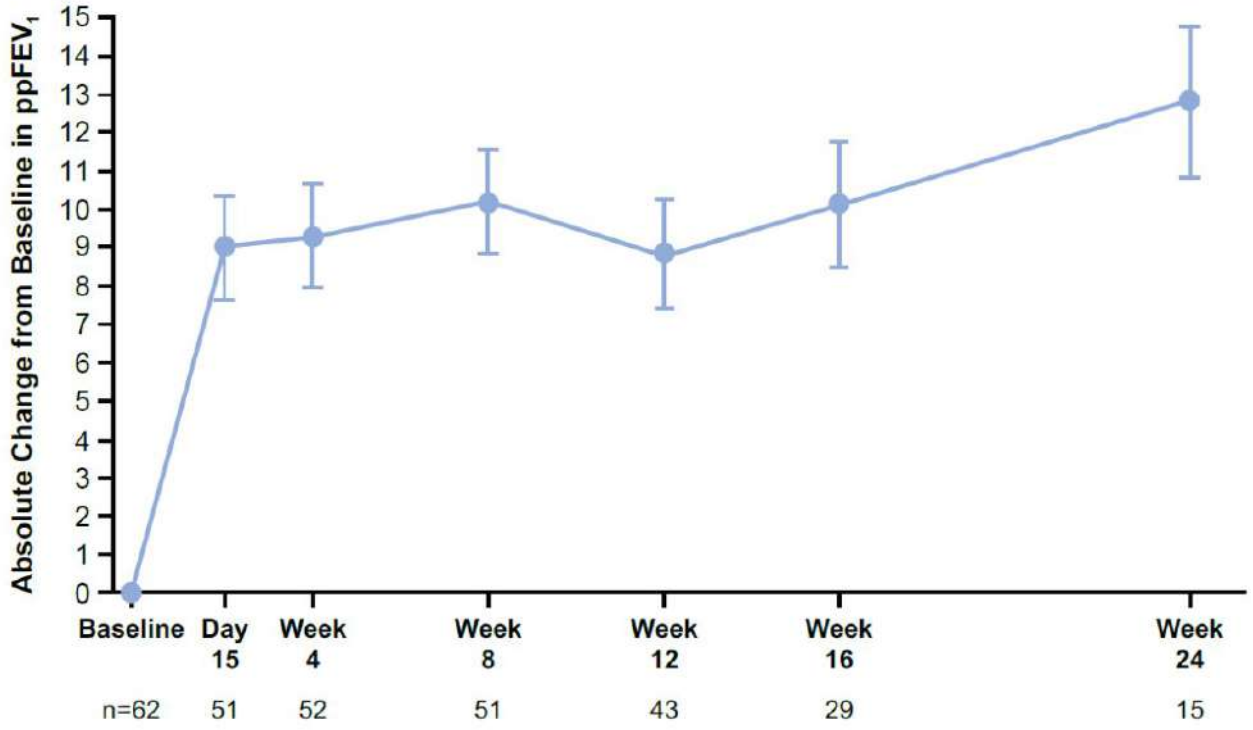
Hejiermann H. Lancet 2019; 394: 1940–48

CFTR Modulatoren

Elexacaftor–Tezacaftor–Ivacaftor (Trikafta® / Kaftrio®)

Patienten 6-11 Jahre mit F508del / MF Mutation oder Homozygot F508del

Lungenfunktion: FEV1 und Lung Clearance Index



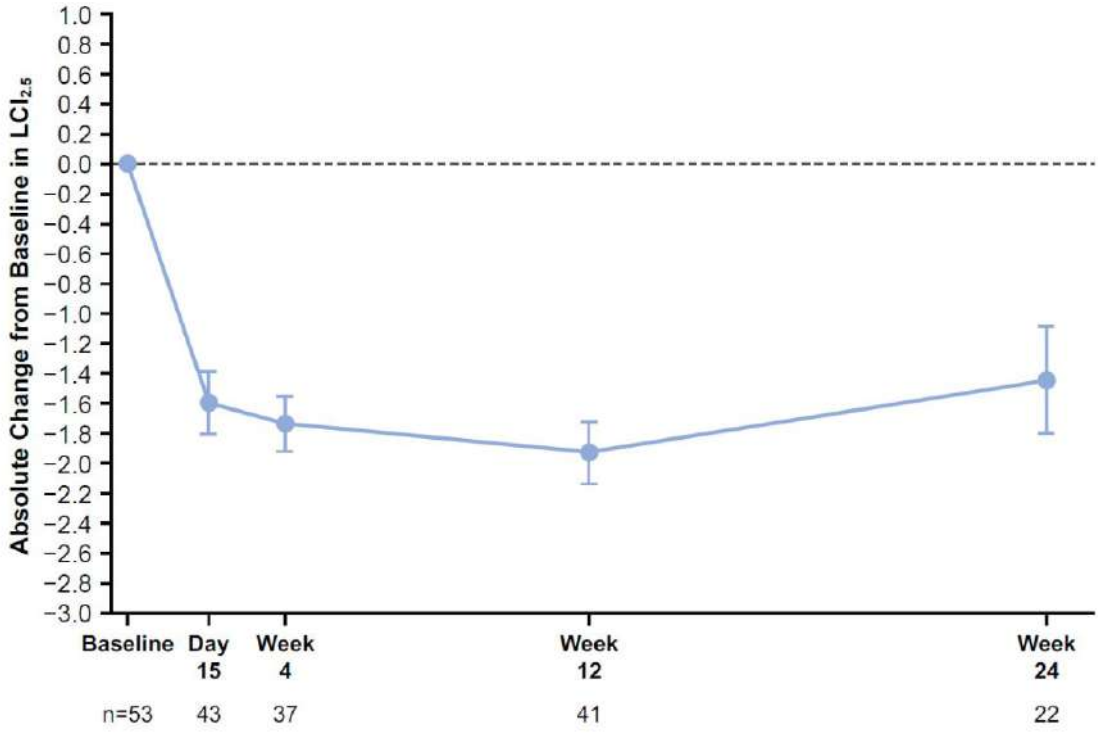
Zemanik ET. Am J Respir Crit Care Med. 2021 Mar 18

CFTR Modulatoren

Elexacaftor–Tezacaftor–Ivacaftor (Trikafta® / Kaftrio®)

Patienten 6-11 Jahre mit F508del / MF Mutation oder Homozygot F508del

Lungenfunktion: FEV1 und Lung Clearance Index



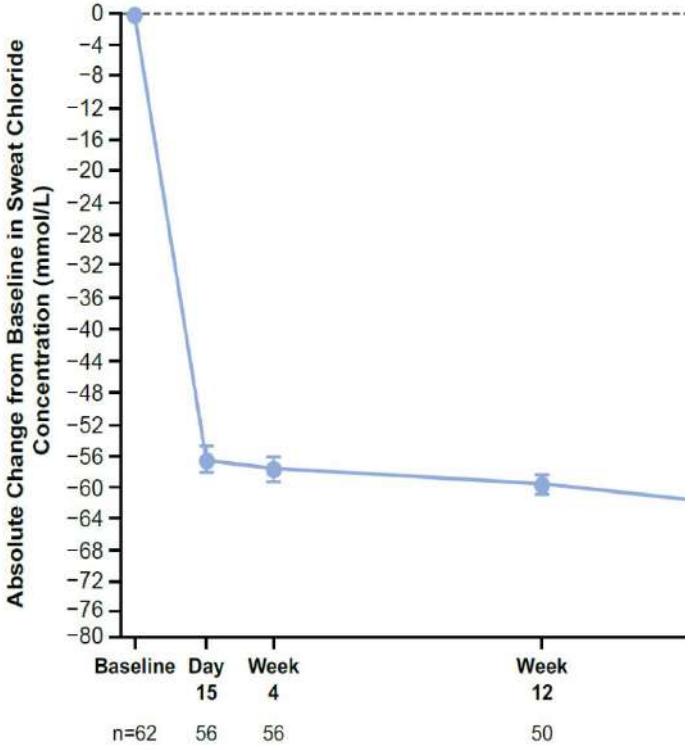
Zemanik ET. Am J Respir Crit Care Med. 2021 Mar 18

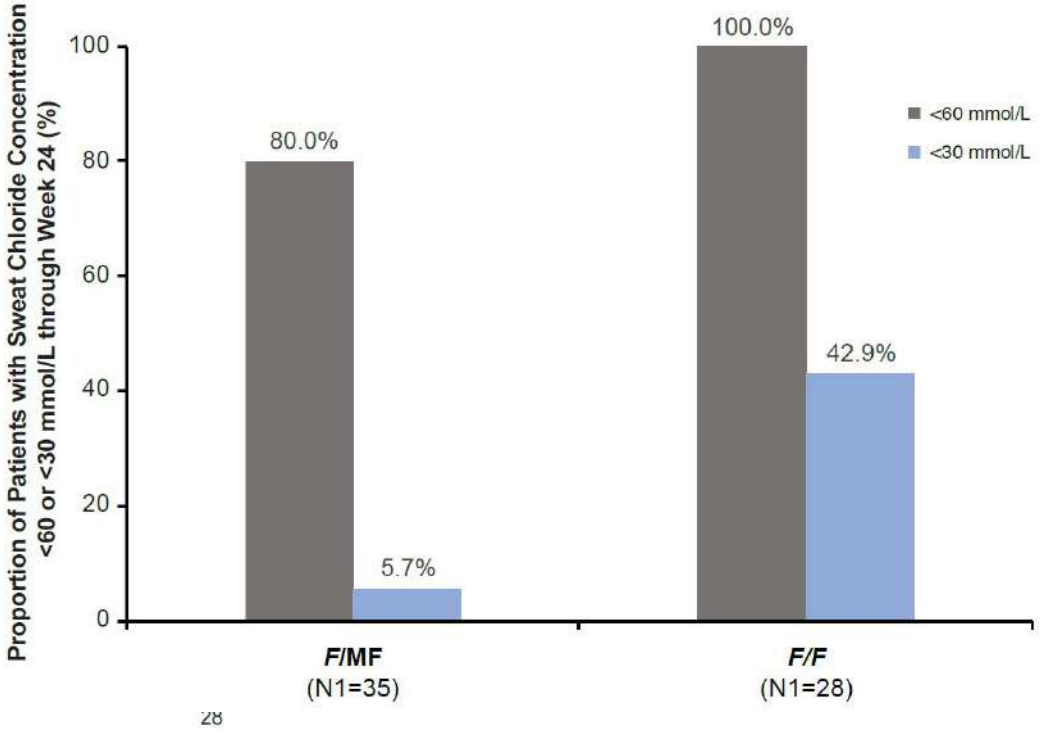
CFTR Modulatoren

Elexacaftor–Tezacaftor–Ivacaftor (Trikafta® / Kaftrio®)

Patienten 6-11 Jahre mit F508del / MF Mutation oder Homozygot F508del

Schweisstest



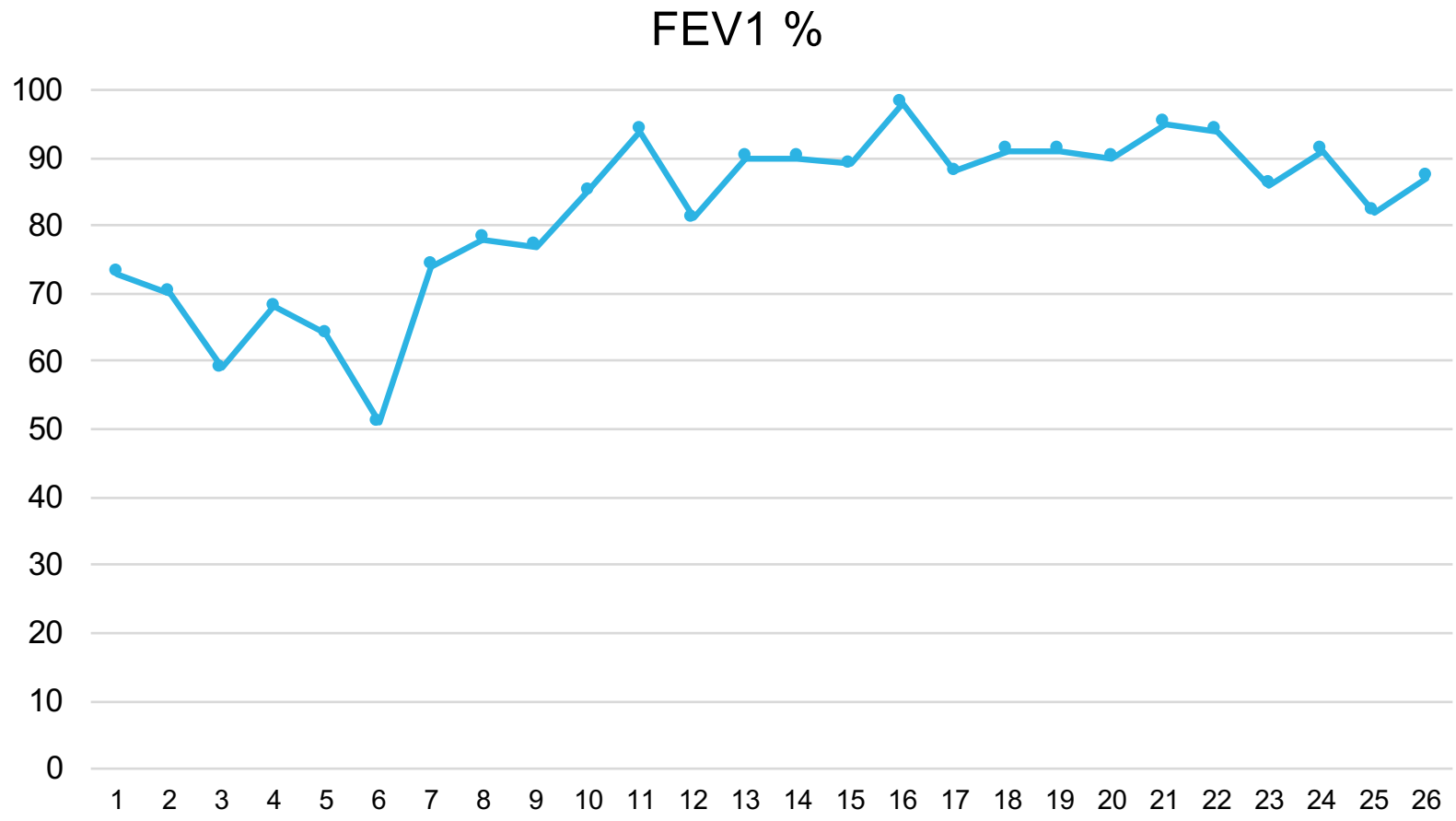


Zemanik ET. Am J Respir Crit Care Med. 2021 Mar 18

Eigene Erfahrungen und persönliche Beurteilung

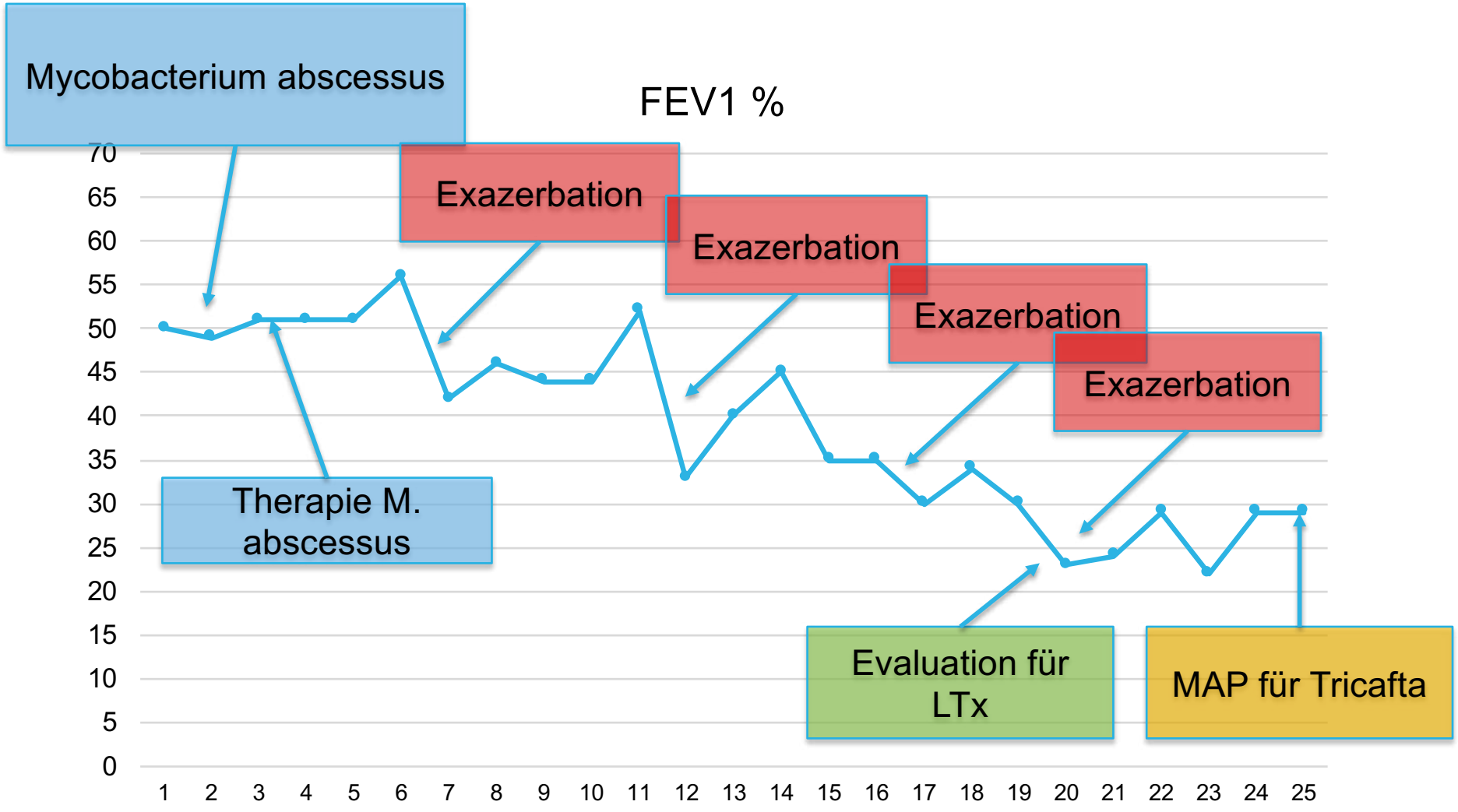
Ivacaftor/Tezacaftor (Symdeco®, Symkevi®)

Marko 20jährig



Eigene Erfahrungen und persönliche Beurteilung

Ivacaftor/Tezacaftor (Symdeco®, Symkevi®)



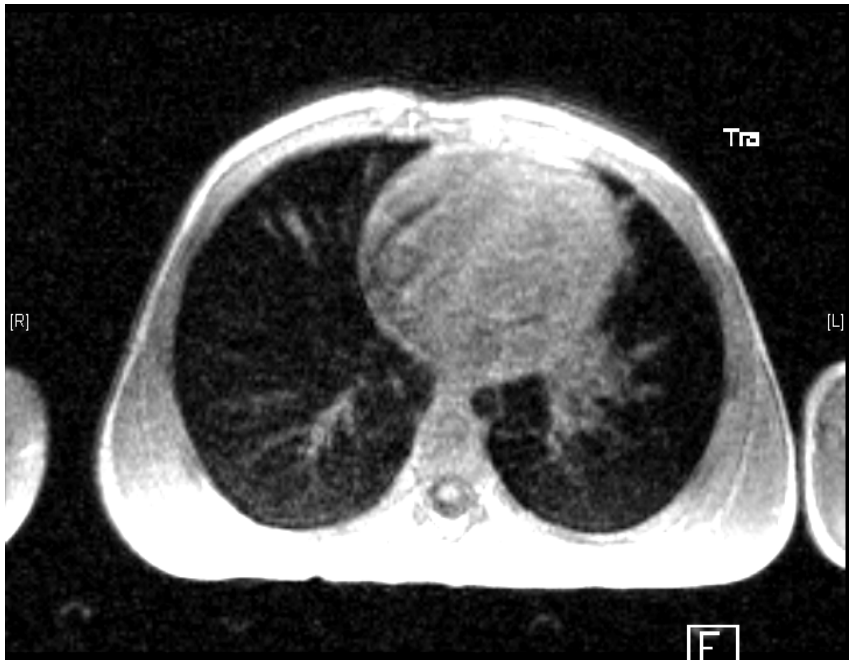
Eigene Erfahrungen und persönliche Beurteilung

Ivacaftor (Kalydeco®)

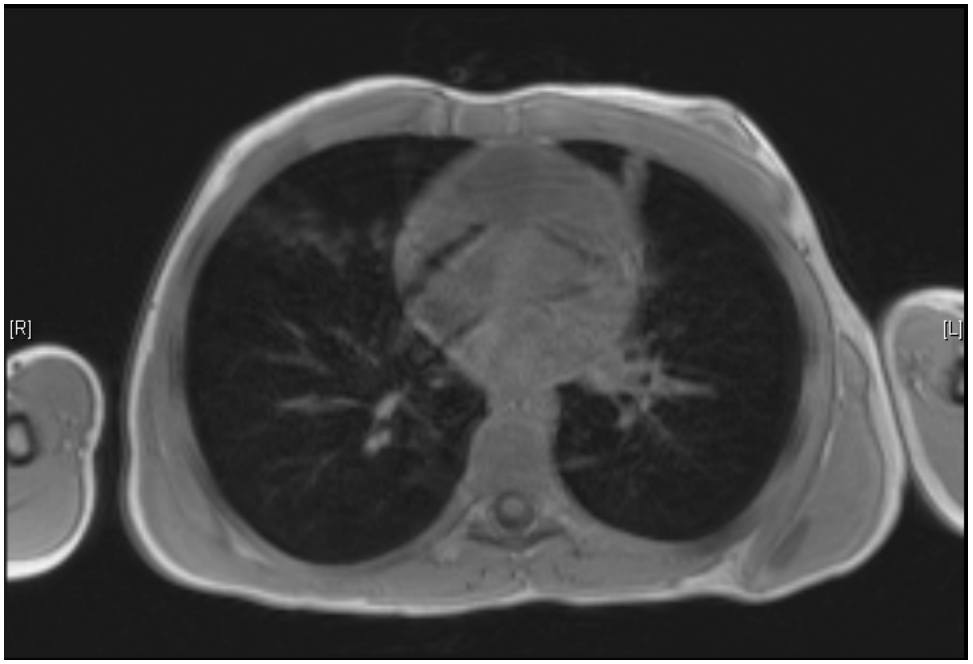
Geschwisterkinder, beide heterozygot für F508del und G551D

- Mädchen, 11 J.

11/2015



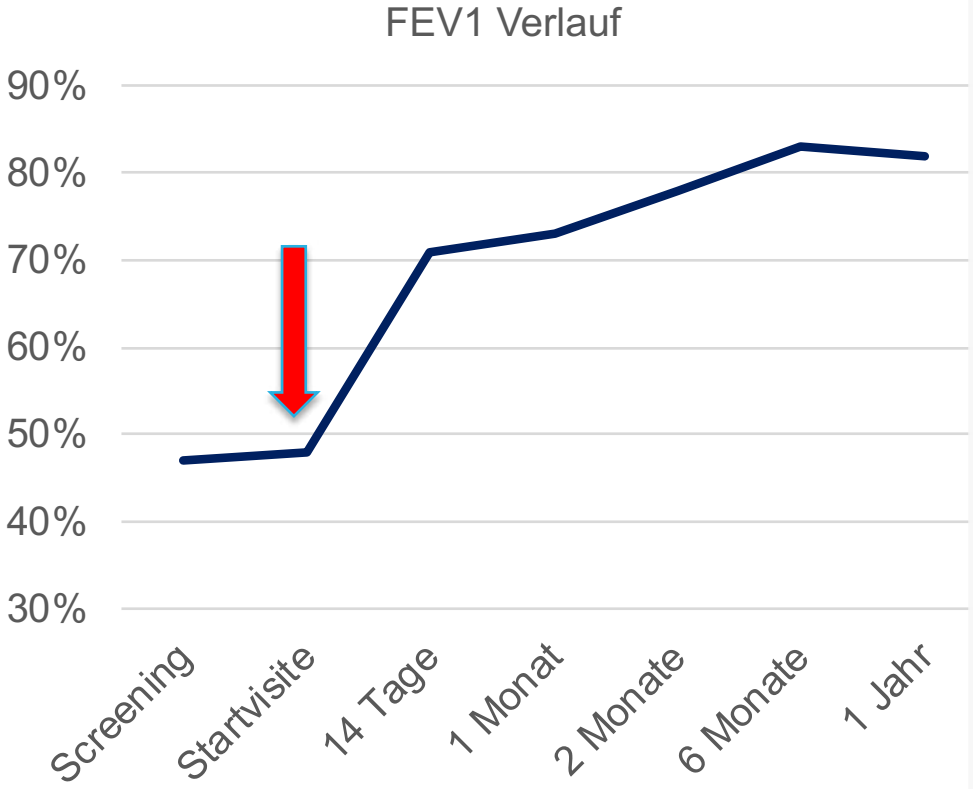
02/2018

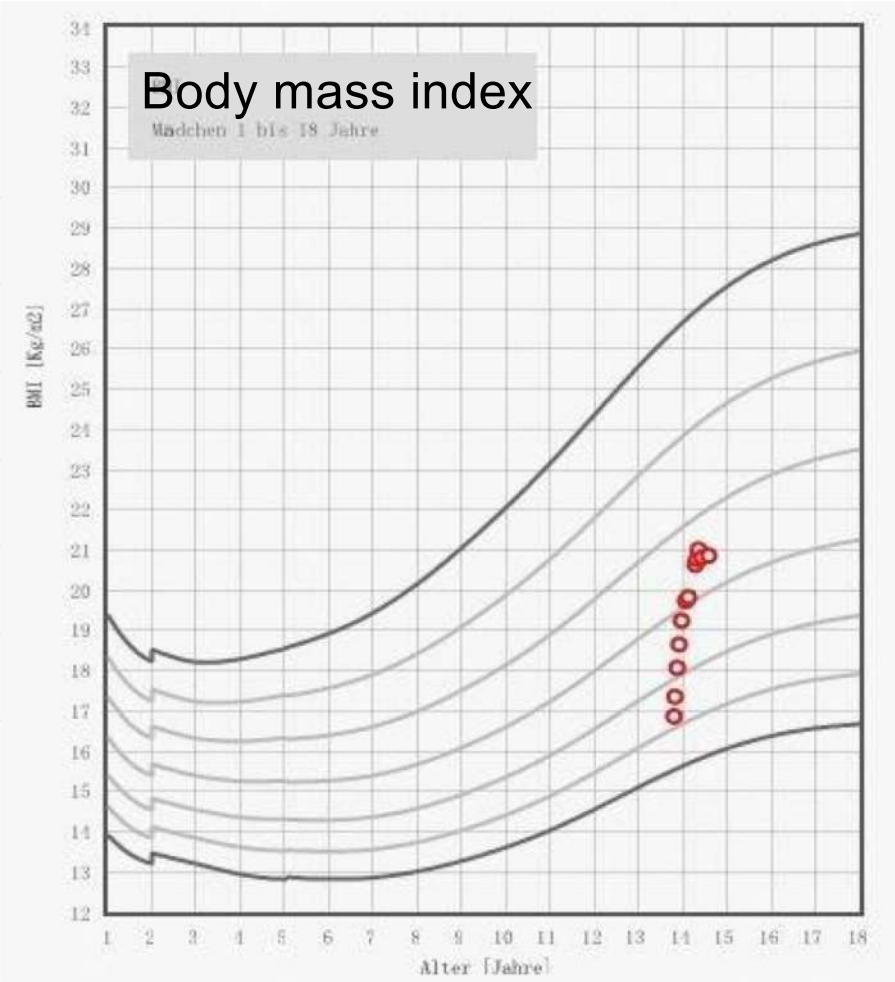


Eigene Erfahrungen und persönliche Beurteilung

Elexacaftor–Tezacaftor–Ivacaftor (Trikafta® / Kaftrio®)

Vanessa, 13 jährig F508del/MF, schwer krank

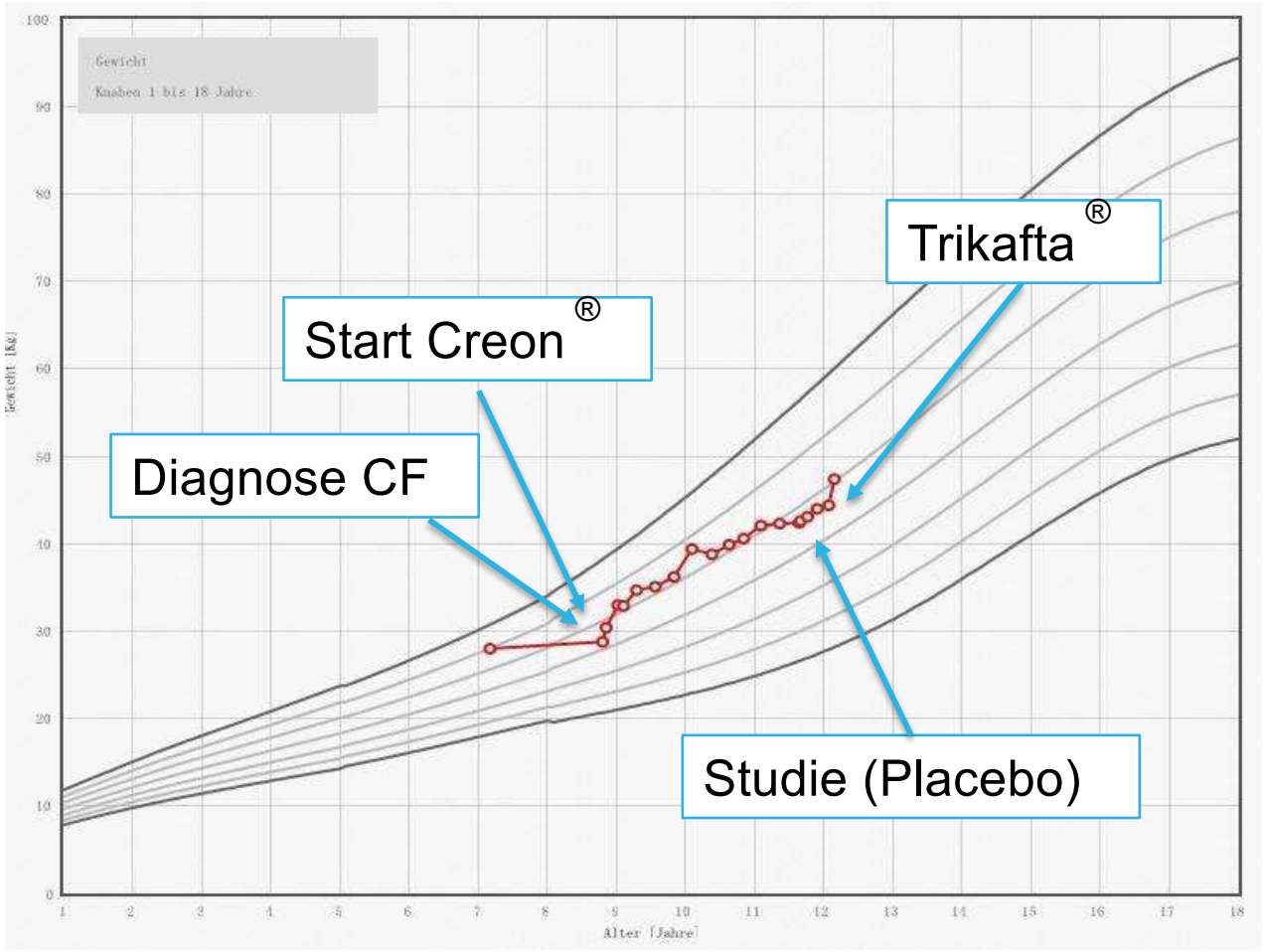




Eigene Erfahrungen und persönliche Beurteilung

Elexacaftor–Tezacaftor–Ivacaftor (Trikafta® / Kaftrio®)

Paul 11 Jahre, späte Diagnose, F508del / MF



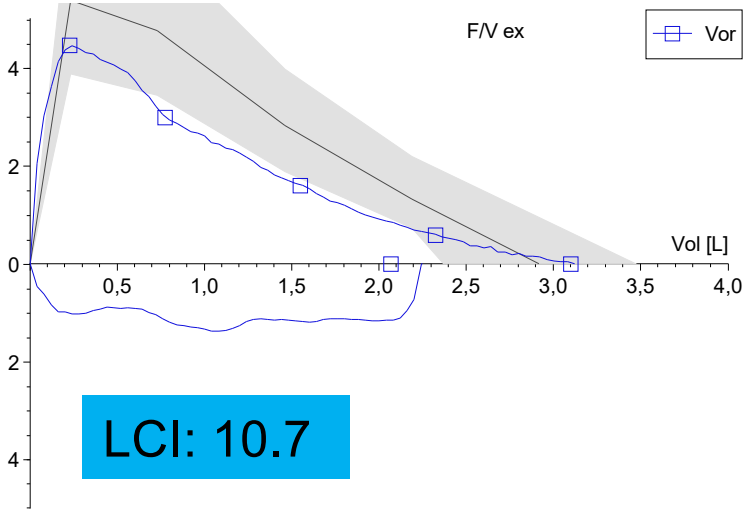
Eigene Erfahrungen und persönliche Beurteilung

Elexacaftor–Tezacaftor–Ivacaftor (Trikafta® / Kaftrio®)

Paul 11 Jahre, späte Diagnose, F508del / MF

Vor Studienstart

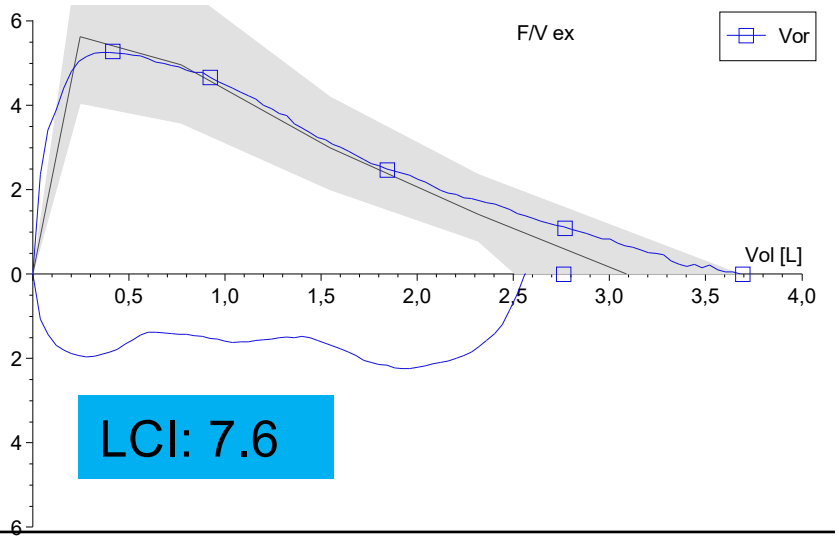
FVC	**[L]**	2.92	3.10	106		0.55
FEV1	**[L]**	2.48	2.07	83		-1.45
FEV 0.75	**[L]**		1.82			
FEV1%F	**[%]**	85.60	66.72	78		-2.66
PEF	**[L/s]**	5.39	4.46	83		-1.22
MEF75	**[L/s]**	4.76	3.00	63		-2.67
MEF50	**[L/s]**	2.83	1.61	57		-2.19
MEF 25	**[L/s]**	1.32	0.60	45		-2.13
MMEF	**[L/s]**	2.83	1.32	47		-2.81
FET	**[s]**		6.37			



LCI: 10.7

1 Monat nach Trikafta® Verum

FVC	**[L]**	3.09	3.69	120	1.70
FEV1	**[L]**	2.63	2.76	105	0.44
FEV.75	**[L]**		2.43		
FEV1%FVC	**[%]**	85.65	74.80	87	-1.67
PEF	**[L/s]**	5.63	5.28	94	-0.44
MEF 75	**[L/s]**	4.96	4.66	94	-0.42
MEF50	**[L/s]**	2.99	2.48	83	-0.81
MEF25	**[L/s]**	1.42	1.10	77	-0.75
MMEF	**[L/s]**	2.99	2.24	75	-1.20
FET	**[s]**		5.50		



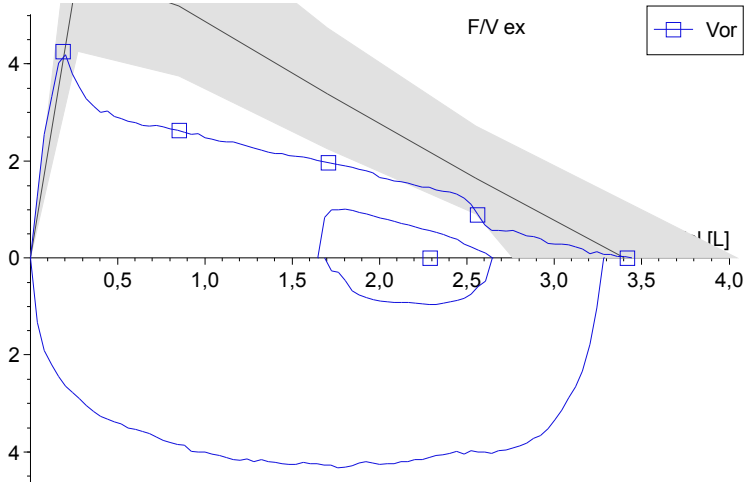
LCI: 7.6

Eigene Erfahrungen und persönliche Beurteilung

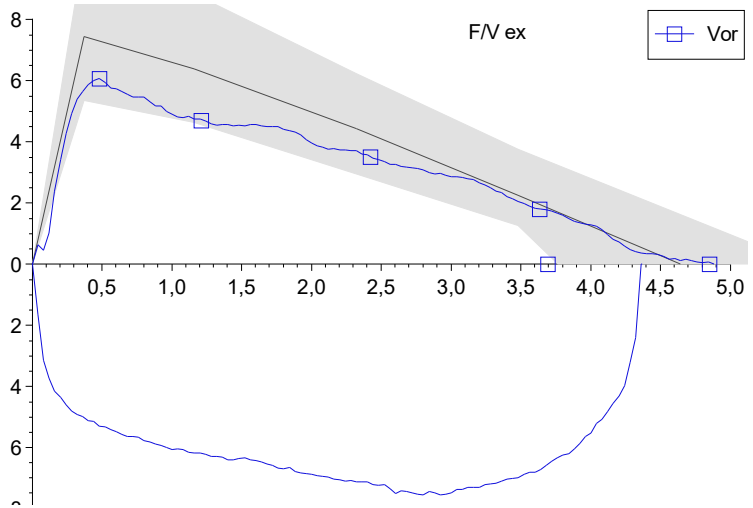
Elexacaftor–Tezacaftor–Ivacaftor (Trikafta® / Kaftrio®)

Julian 16 jährig:

FVC	[L]	3.40	3.42	100	0.13	0.04
FEV1	[L]	2.93	2.29	78	0.07	-1.82
FEV.5	[L]		1.39		0.01	
FEV 0.75	[L]		1.90		0.04	
FEV 1 % VC IN	[%]	84.16	67.67	80	2.07	-3.63
FEV1%F	[%]	86.50	66.98	77	0.60	-2.67
PEF	[L/s]	5.91	4.25	72	0.23	-2.00
MEF75	[L/s]	5.18	2.62	51	0.13	-3.57
MEF50	[L/s]	3.37	1.96	58	0.23	-2.13
MEF 25	[L/s]	1.63	0.88	54	0.17	-1.71
MMEF	[L/s]	3.37	1.81	54	0.24	-2.40



FVC	[L]	4.64	4.85	105	2	0.39
FEV1	[L]	3.99	3.69	93	5	-0.61
FEV.5	[L]		2.39		4	
FEV 0.75	[L]		3.15		5	
FEV1%F	[%]	86.34	76.15	88	3	-1.49
PEF	[L/s]	7.43	6.06	82	0	-1.31
MEF75	[L/s]	6.39	4.70	74	5	-1.91
MEF50	[L/s]	4.43	3.50	79	7	-0.99
MEF 25	[L/s]	2.25	1.79	80	21	-0.67
MMEF	[L/s]	4.43	3.22	73	13	-1.30

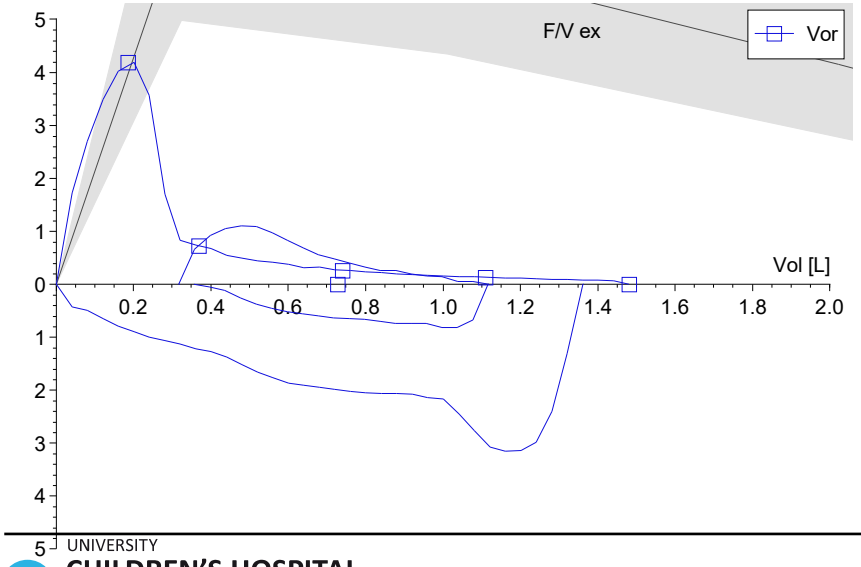


Eigene Erfahrungen und persönliche Beurteilung

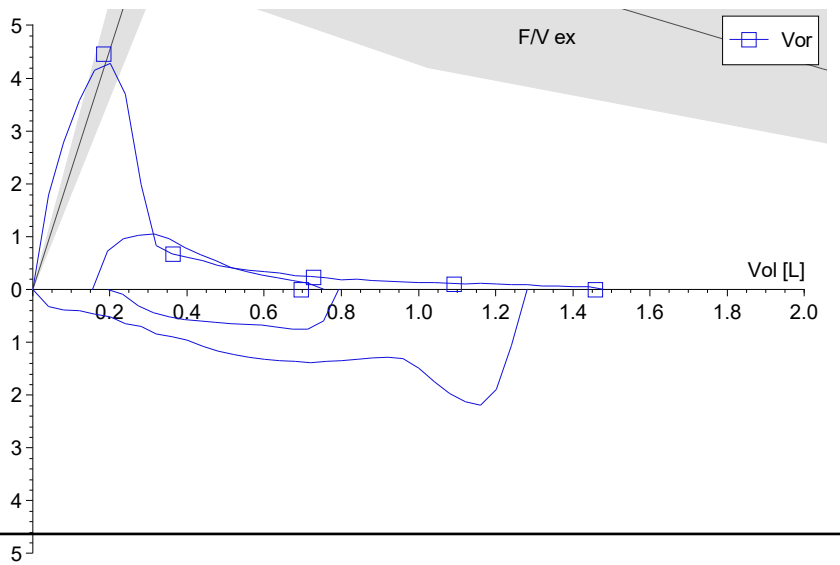
Elexacaftor–Tezacaftor–Ivacaftor (Trikafta® / Kaftrio®)

Ana 19 jährig:

	Soll	Vor	Vor%	CV %	Z-score	Z-Score
Testdatum		18.09.19				
Testzeit		11:28				
FVC [L]	4.04	1.48	37	1	-5.56	
FEV 1 [L]	3.56	0.73	20	1	-6.25	
FEV.75 [L]		0.64		2		
FEV.5 [L]		0.54		2		
FEV1%M [%]	88.91	49.14	55	1	-3.75	
PEF [L/s]	6.93	4.19	60	2	-2.81	
MEF75 [L/s]	5.99	0.72	12	6	-6.36	
MEF50 [L/s]	4.14	0.25	6	4	-5.74	
MEF25 [L/s]	2.18	0.12	5	7	-5.60	
MMEF [L/s]	4.14	0.25	6	3	-5.74	



	Soll	Vor	Vor%	CV %	Z-score	Z-Score
Testdatum		18.12.19				
Testzeit		11:21				
FVC [L]	4.10	1.46	36	4	-5.66	
FEV 1 [L]	3.60	0.70	19	1	-6.32	
FEV.75 [L]		0.62		0		
FEV.5 [L]		0.54		0		
FEV1%M [%]	88.79	47.82	54	1	-3.79	
PEF [L/s]	7.43	4.46	60	3	-3.30	
MEF75 [L/s]	6.41	0.67	10	3	-4.25	
MEF50 [L/s]	4.17	0.23	6	4	-5.81	
MEF25 [L/s]	2.20	0.10	5	9	-5.81	
MMEF [L/s]	4.17	0.23	5	7	-5.81	



UNIVERSITY CHILDREN'S HOSPITAL ZURICH

Children's Research Center CRC

Persönliche Beurteilung
Wem was geben?

Patienten mit Gating Mutation ab 6 Monaten

Patienten mit F508del 2-12a

Patienten mit F508del/ Residual function Mutation > 12 Jahre

Patienten mit F508del/ Minimal function und homozygote > 12 Jahre

https://www.cfsource.ch/gsw-berne/hcp/treatment-finder?dc=oe1ui4fzY0iSKHS2Zq

Persönliche Beurteilung
Wann starten?

kalydeco
(Ivacaftor)

trikafta
(Elexacaftor/Tezacaftor/Ivacaftor
und Ivacaftor)

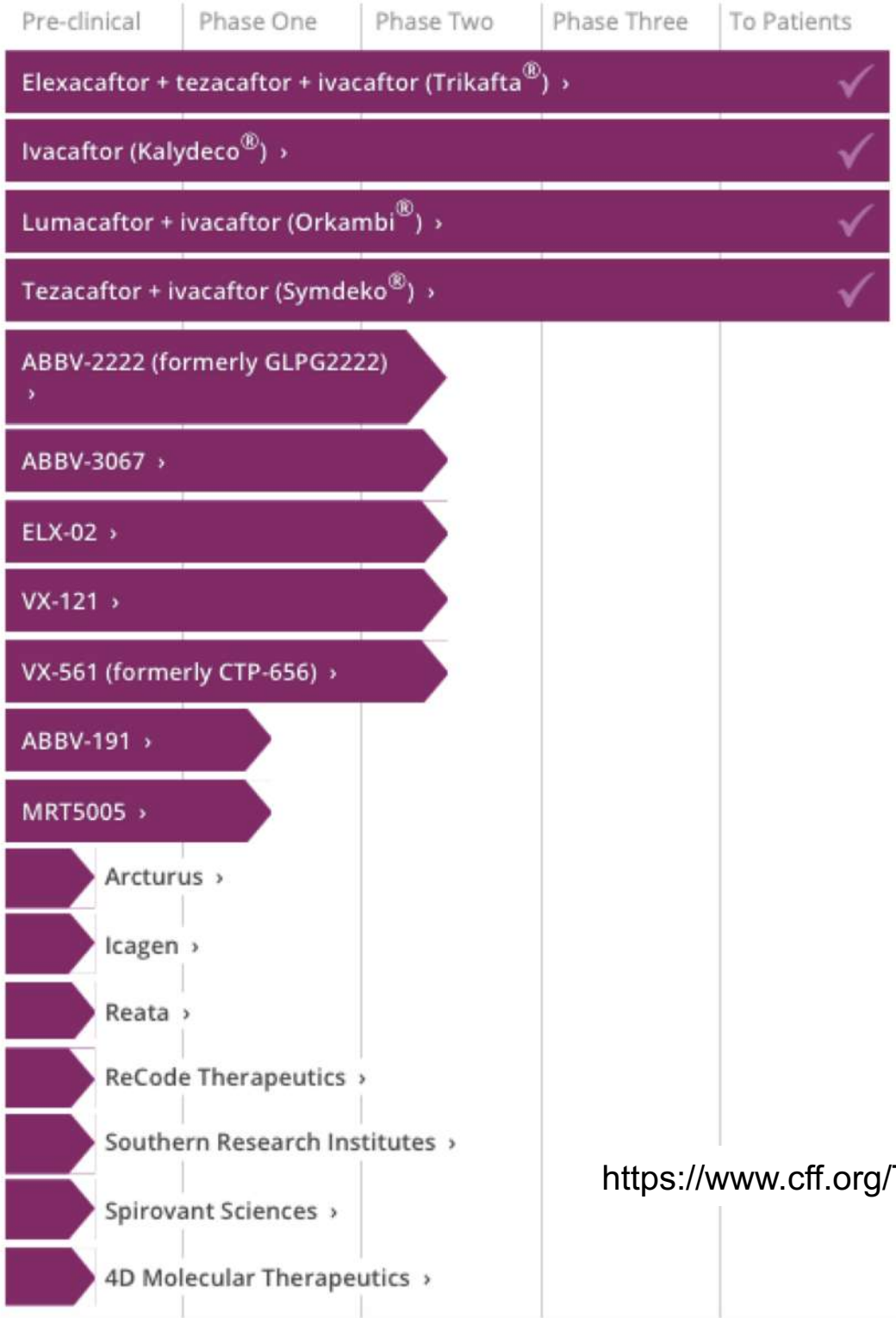
ORKAMBI
(Lumacaftor/Ivacaftor)

symdeko
(Tezacaftor/Ivacaftor
und Ivacaftor)

Persönliche Beurteilung
Überwachung der Nebenwirkungen

- Leberwerte
- Kreatinkinase
- Augenarzt*in
- Sonnenschutz
- Antikonzeptiva

CFTR Modulatoren
Aktuelle Pipeline



https://www.cff.org/Trials/Pipeline

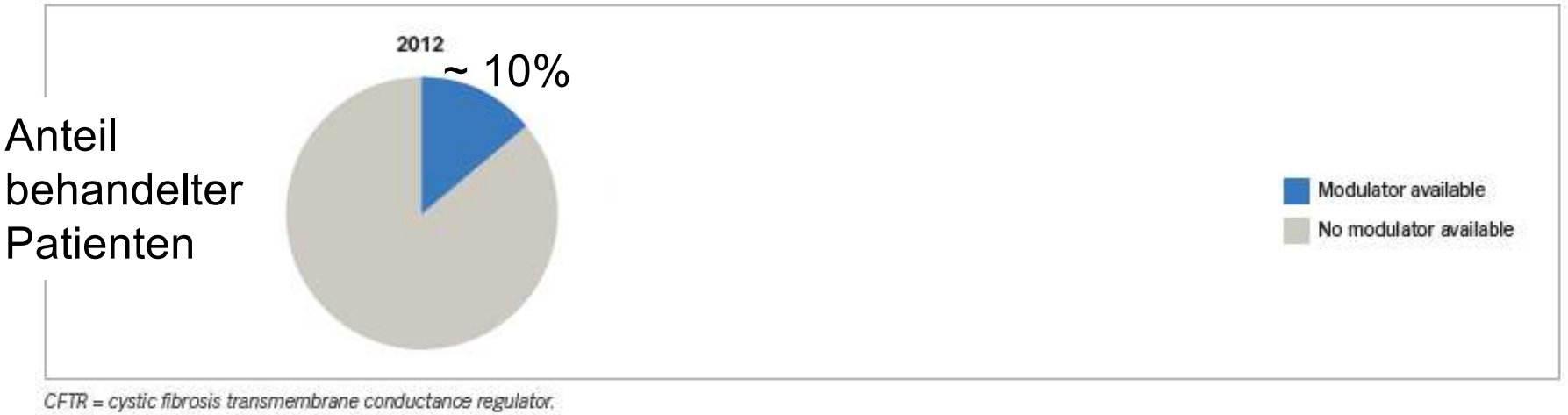
Konklusionen

- CFTR-spezifische Therapien zunehmend als wesentliche Therapiesäule bei CF
- Hochpotente Therapien aktuell aber nur bei seltenen Mutationen (Gating-Mutationen) oder erst ab 12 Jahren
- Langzeit-Wirkung / -Nebenwirkungen unbekannt, auch späte Komplikationen der CF bisher kaum untersucht
- Weitere vielversprechende CFTR-Modulatoren und CFTR-spezifische Therapieansätze in der Pipeline
- Basistherapie (Creon, Inhalation, Physiotherapie…) gelten weiterhin (noch) als Grundpfeiler der CF-Therapie

Now, this is not the end…
…it is not even the beginning of the end
But it is, perhaps, the end of the beginning.

CFTR Modulatoren

Wo stehen wir heute mit den CFTR Modulatoren



CFTR = cystic fibrosis transmembrane conductance regulator.

- Trikafta / Kaftrio sehr wirksam, aber zunächst erst ab 12 Jahren.
- Kalydeco ebenfalls sehr wirksam, ab 1 Jahr (4 LM USA), aber nur bei seltenen Gating-Mutationen.
- Orkambi bereits ab 2 Jahren zugelassen, bei ca. 45-50% der Patienten, aber nicht so wirksam.
- Symdeko / Symkevi ab 12 / 6 Jahren zugelassen, bei etwas mehr Patienten als Orkambi, aber ebenfalls nicht so wirksam.
- 10% noch keine Therapieoption

Jia et al, US Respiratory & Pulmonary Diseases. 2019

HIT-CF Europe

WWW.HITCF.ORG

- Zugang zu CFTR-Modulatoren für Patienten mit seltenen Mutationen

- Personalisierte CF-Therapie anhand Organoide

- Biobank für künftige Forschungsprojekte

- Einschluss: Erwachsene CF-Patienten mit einer Kombination von Mutationen, die nicht ultra-selten sind:

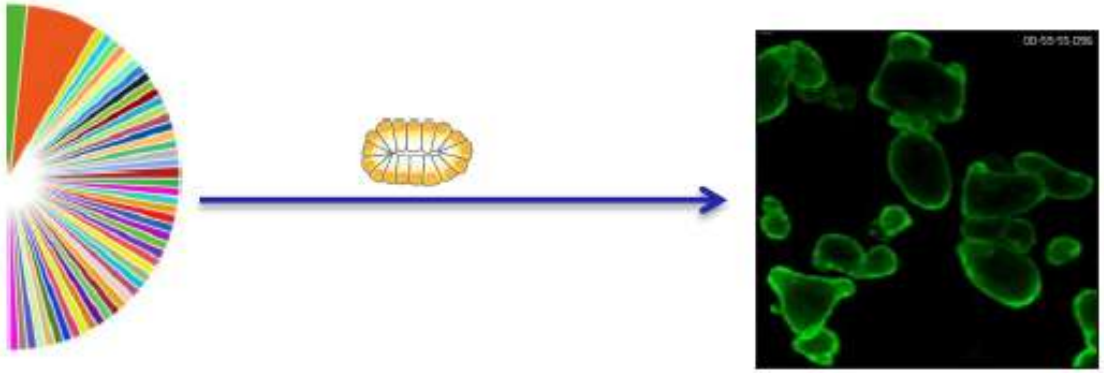
G542X, R553X, W1282X, R1162X, E60X, Q493X, 1717-1G>A, 621+1G>T, 3120+1G>A, 1898+1G->A, CFTRdele2,3 and 2183AA->G

Two clinical stages

1.

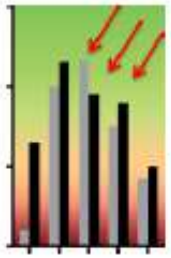
Collect 500 biopsies from European CF-patients

Test drugs of three pharmaceutical companies on these organoids



2.

Select the best responders per drug



Execute 3 double-blinded, placebo-controlled cross-over clinical trials