Avapritinib, Ripretinib & Co.:

Neue GIST-Therapien/Optionen bei Fortschreiten der GIST-Erkrankung (Progress)

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OFFENLEGUNG VON INDUSTRIEKOOPERATIONEN

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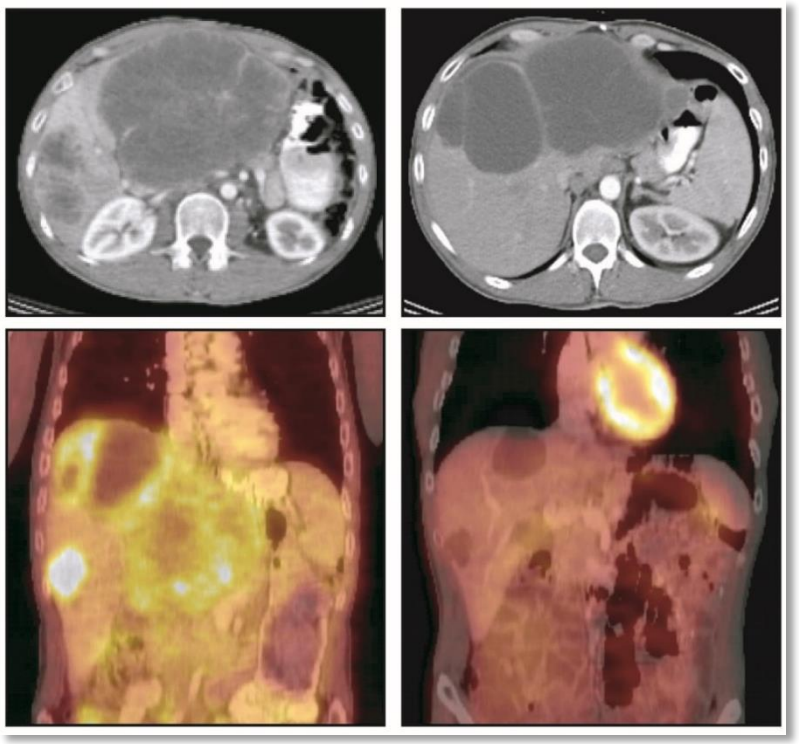
Studienarzt: Blueprint Medicines, Novartis, Daichii, Deciphera; Bayer, Incyte

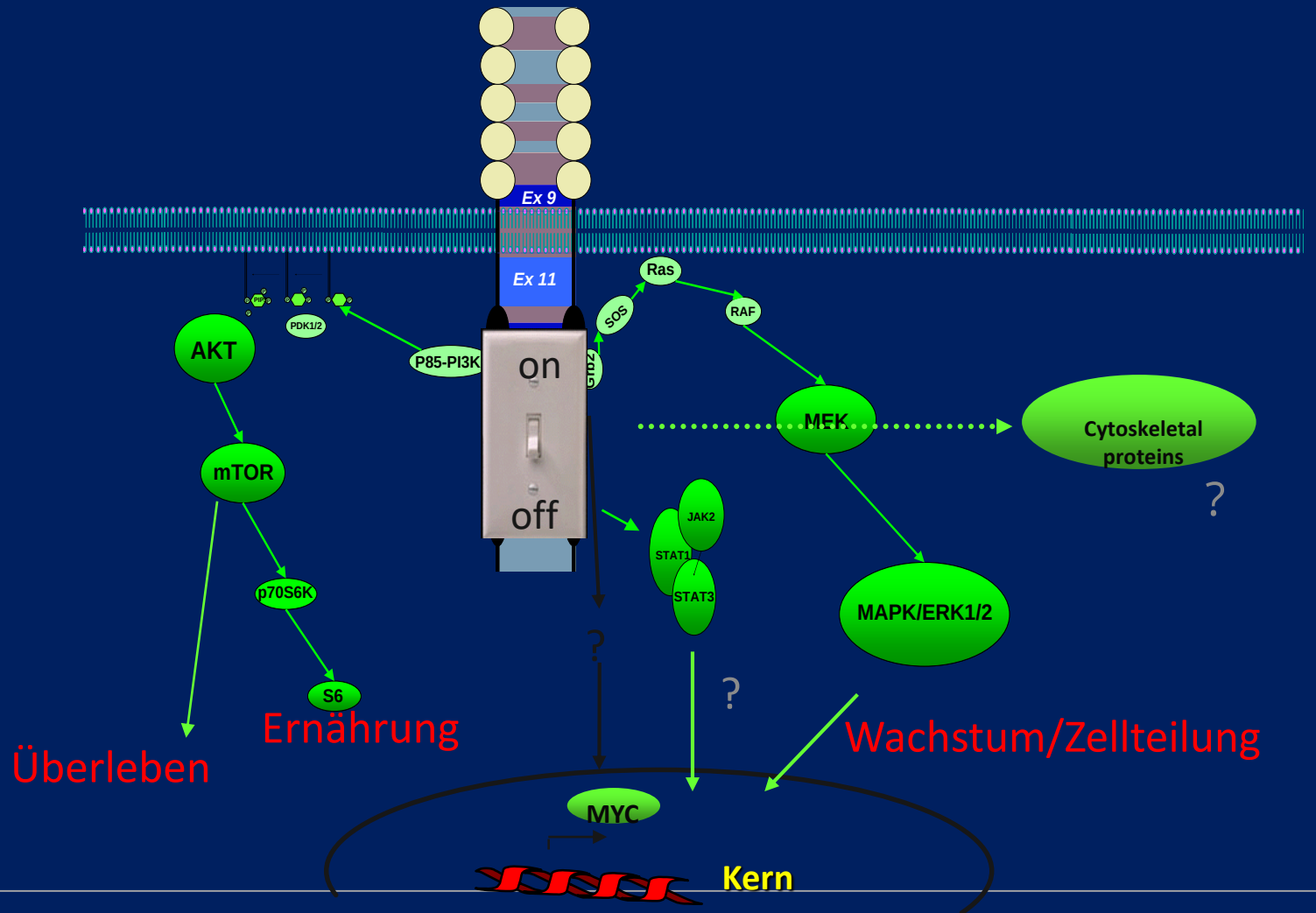
Beratung: Blueprint Medicines, Novartis, Daichii, Deciphera; Bayer, Incyte

Forschungsunterstützung: Novartis, Incyte, Blueprint Medicine

Resistenz erklärt – wichtig auch für Patienten



KIT und PDGFRA – welche Rolle für den Tumor?



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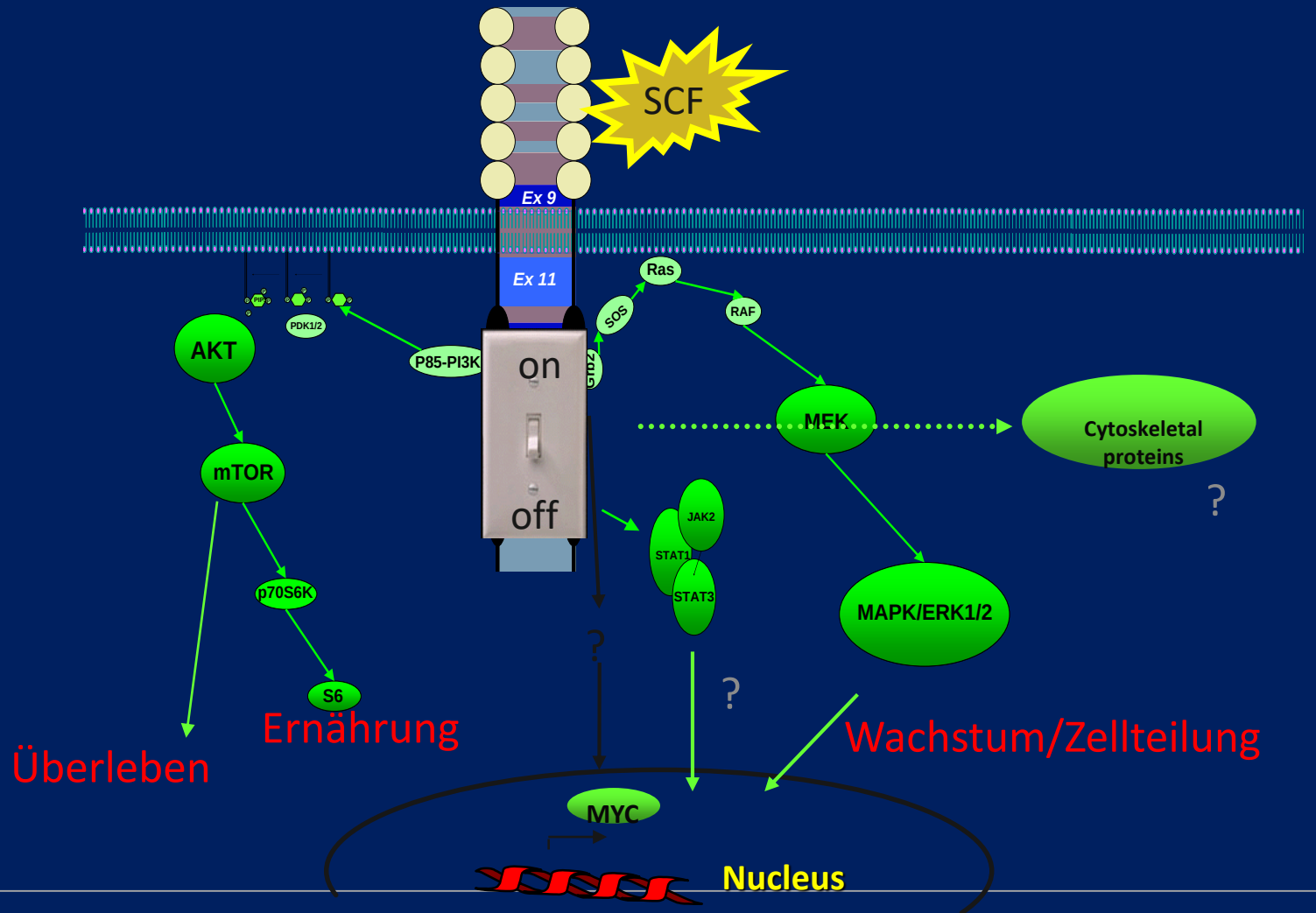
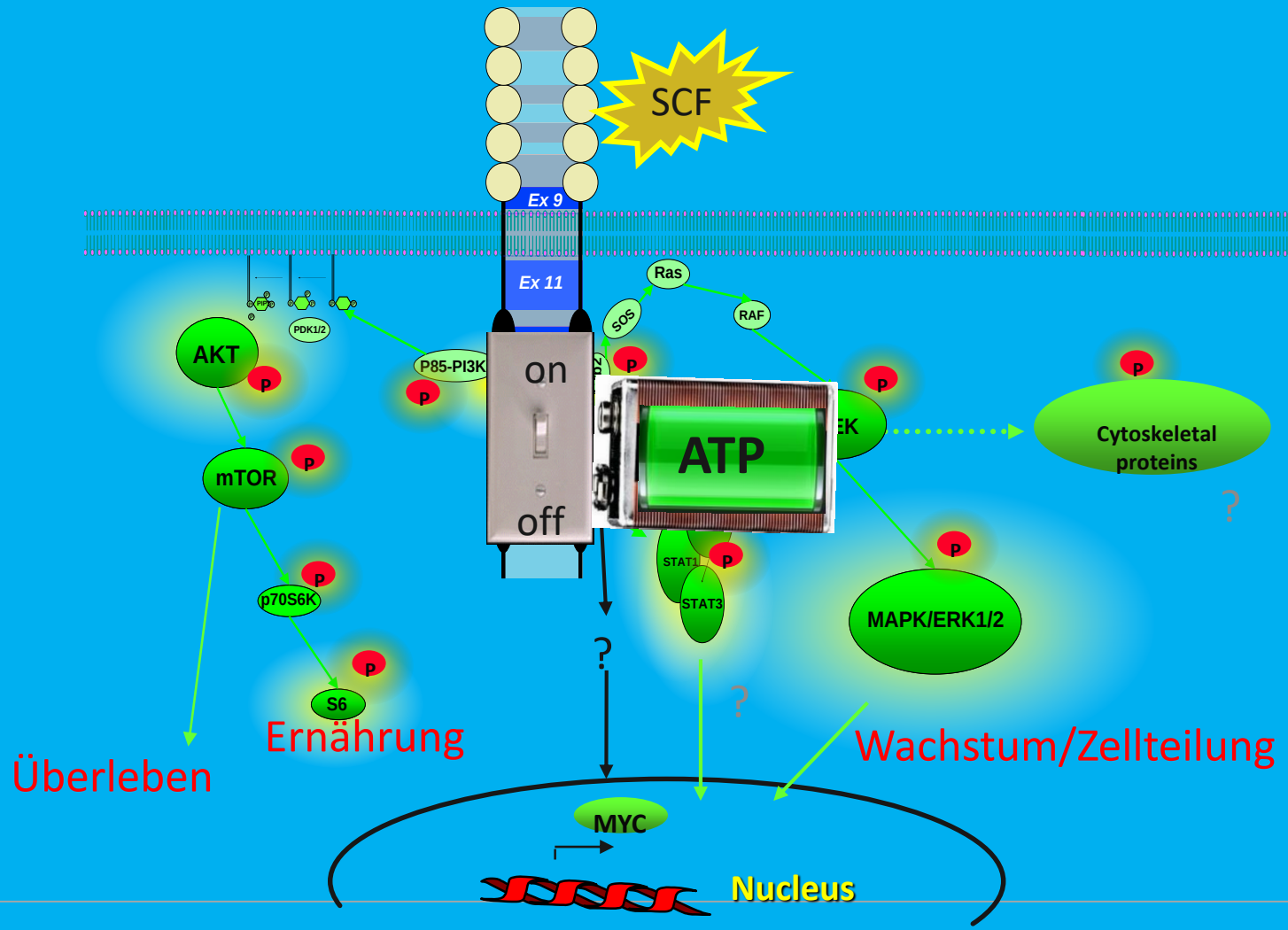
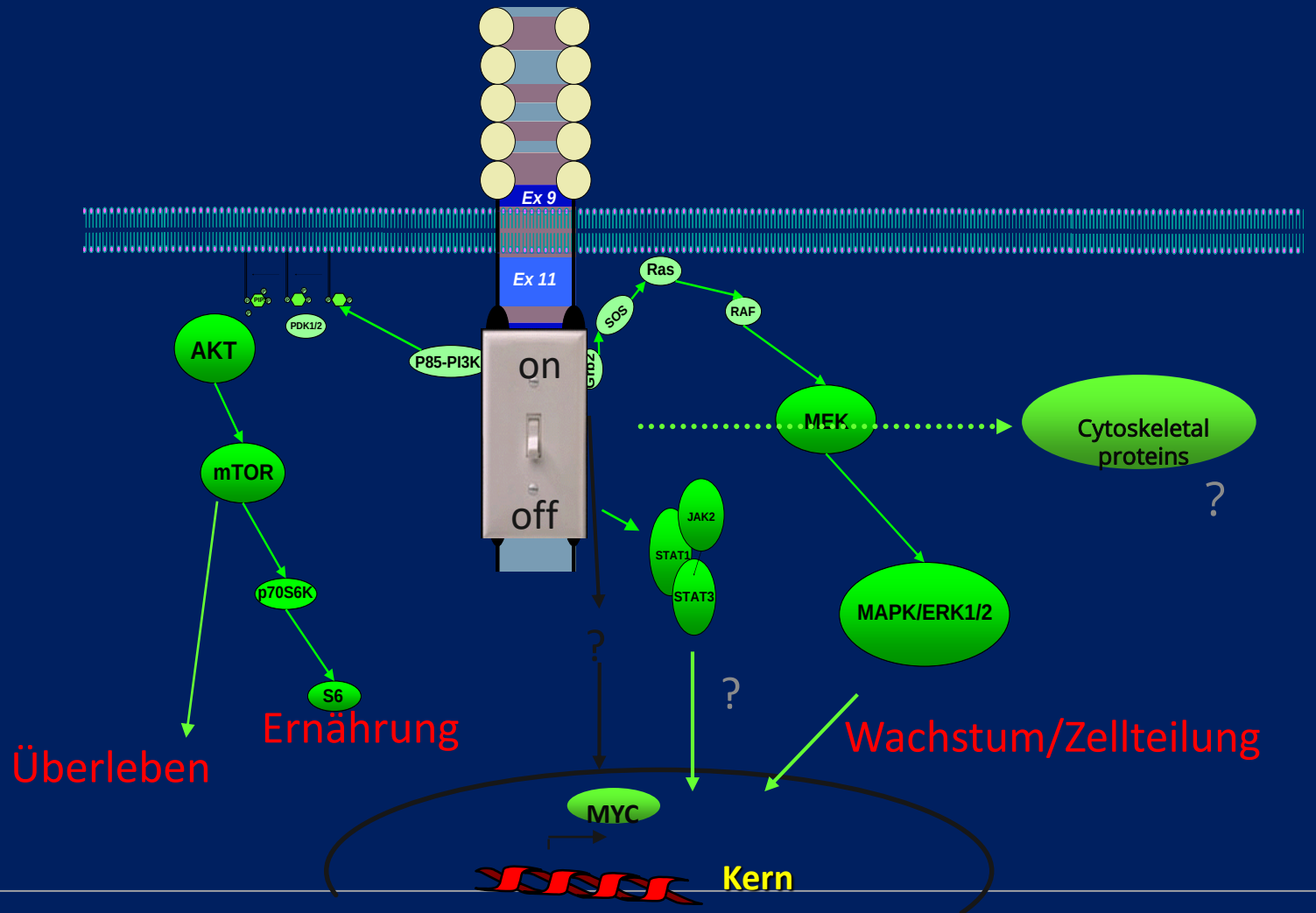


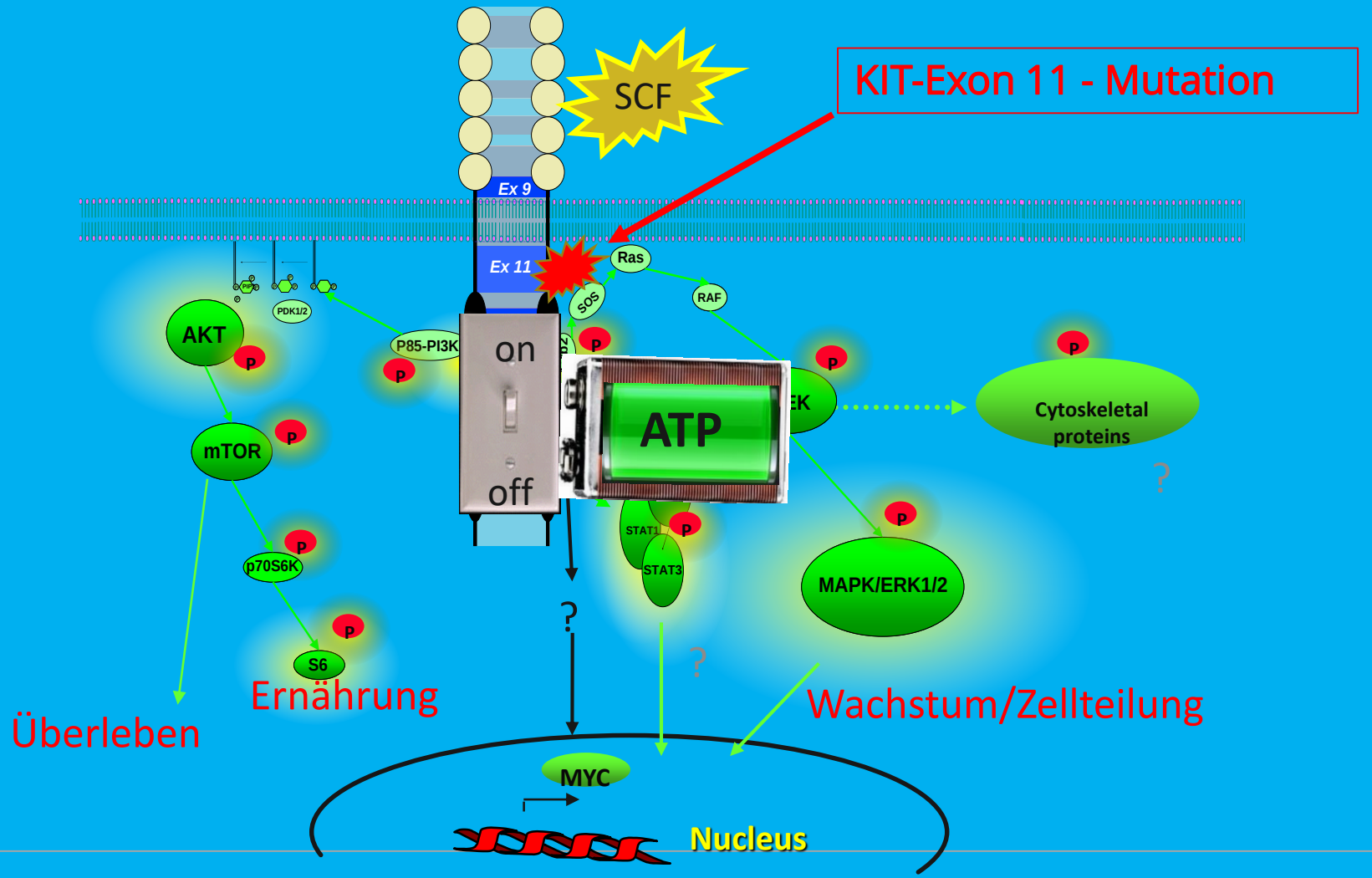
KIT und PDGFRA – welche Rolle für den Tumor?



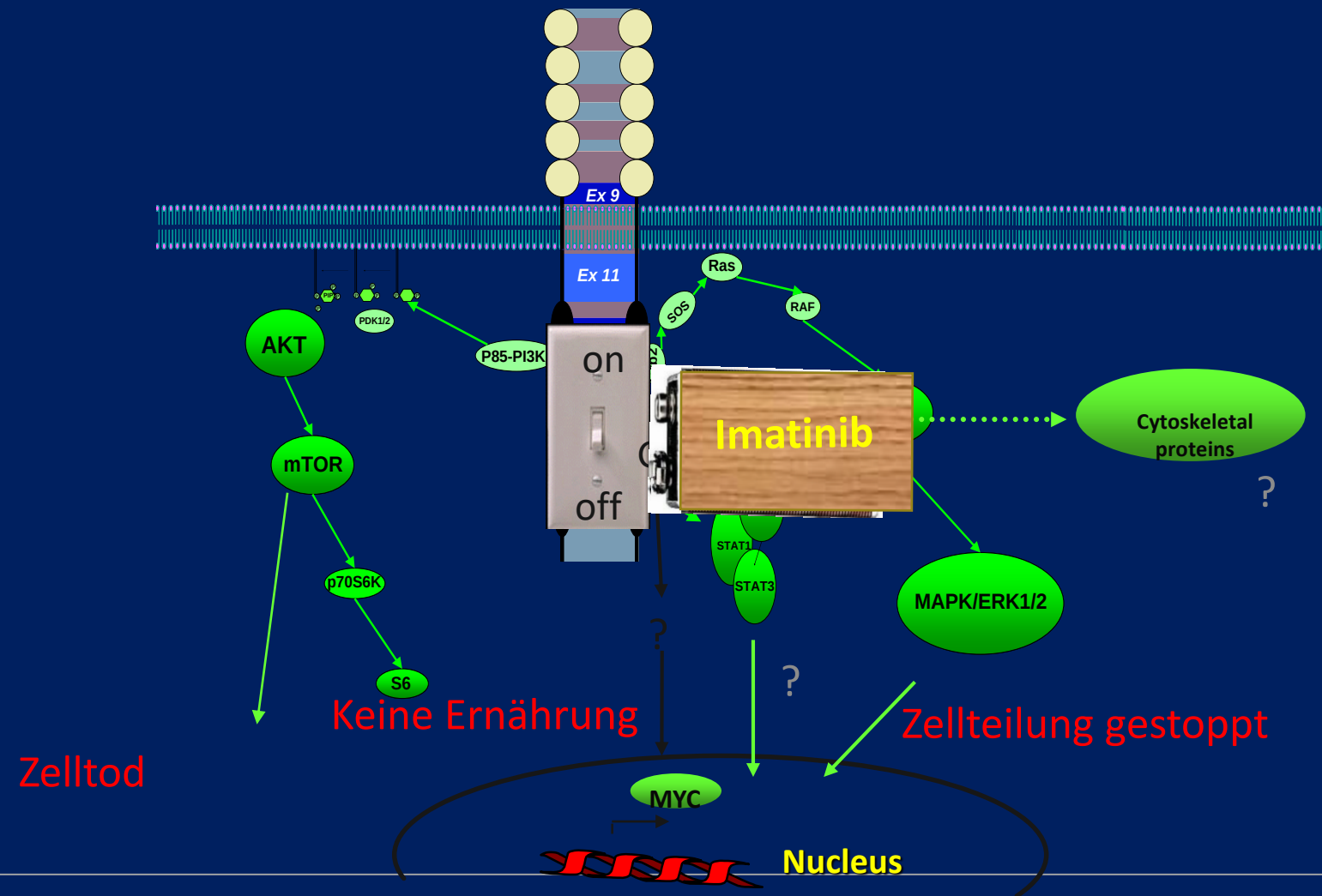
KIT und PDGFRA – welche Rolle für den Tumor?



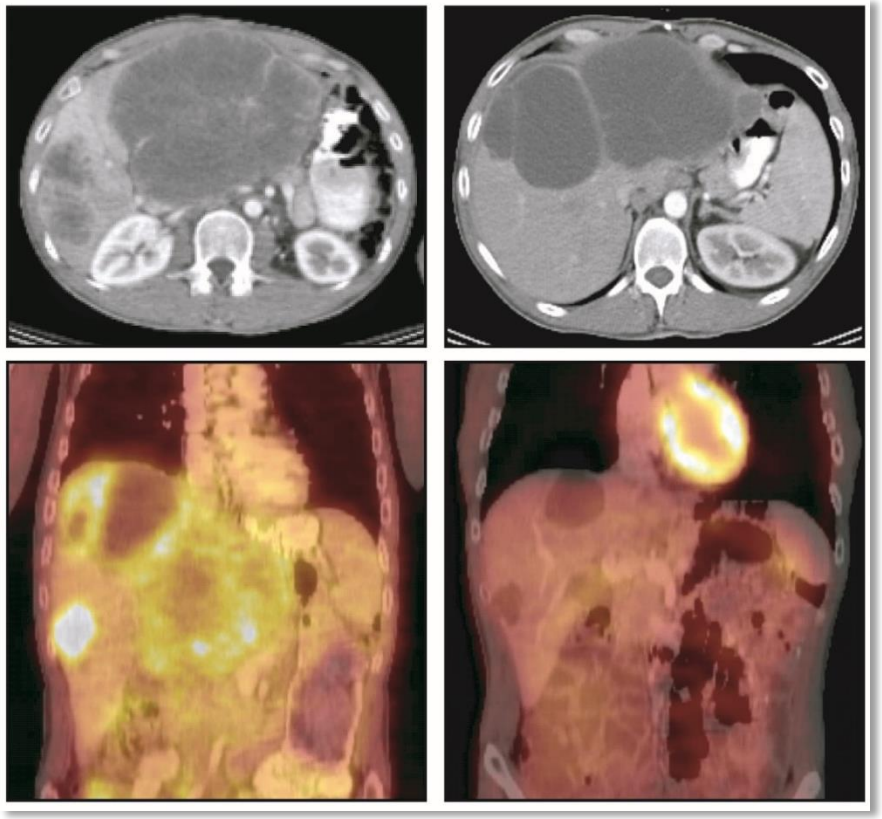
KIT und PDGFRA – welche Rolle für den Tumor?

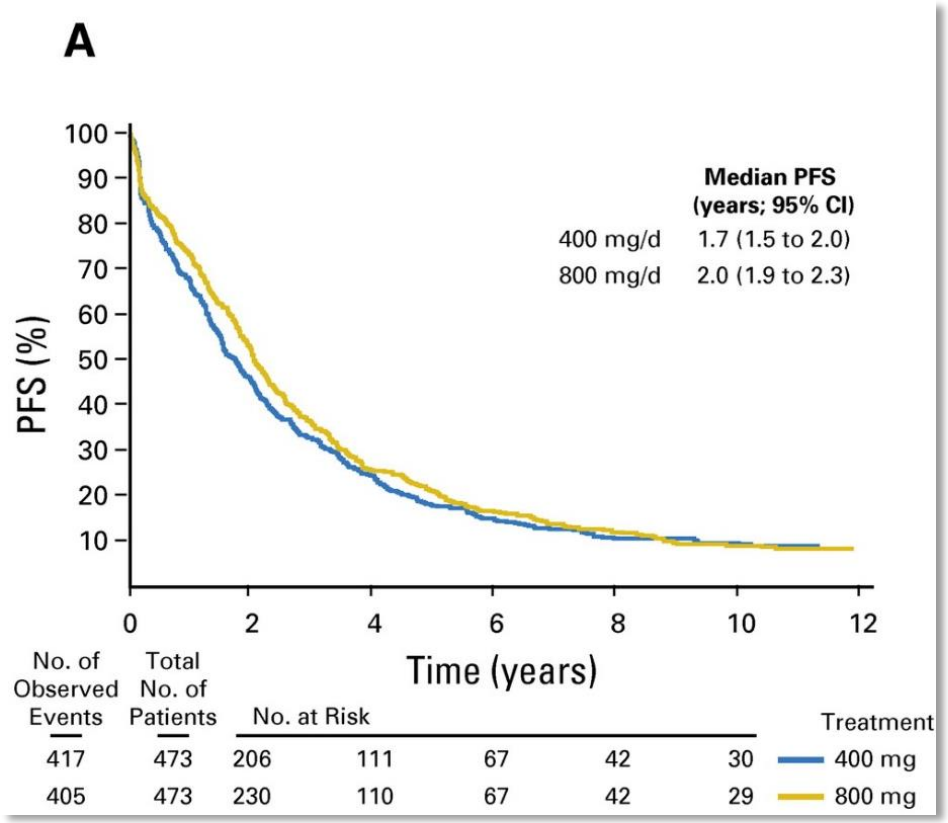


KIT und PDGFRA – welche Rolle für den Tumor?



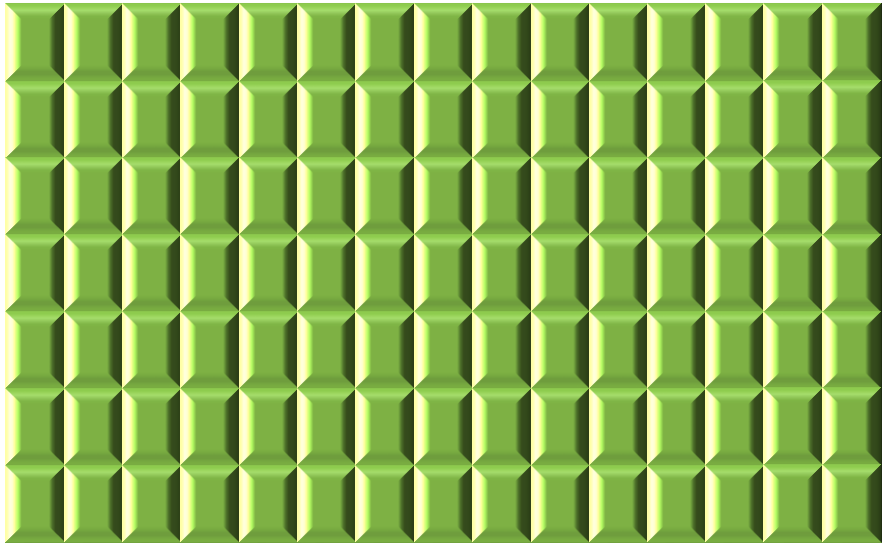
Resistenz kommt – bei den meisten Patienten…



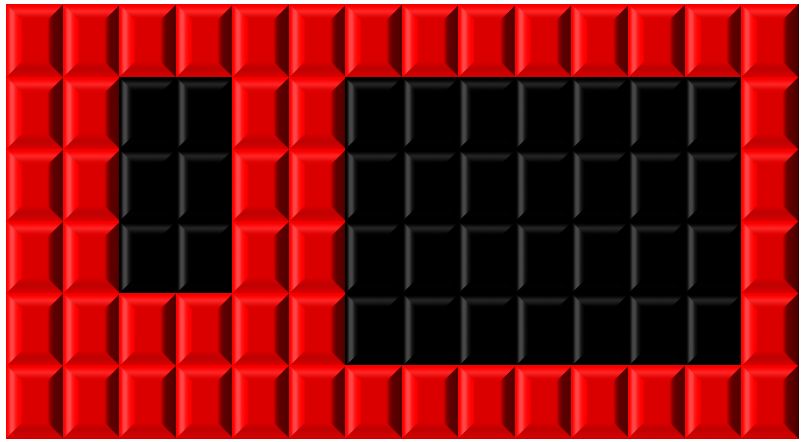


Casali et al, J Clin Oncol 2017 35:1713-1720

Entwicklung von Resistenz – wie entsteht das?



vor Therapie



Nach Therapie mit Imatinib

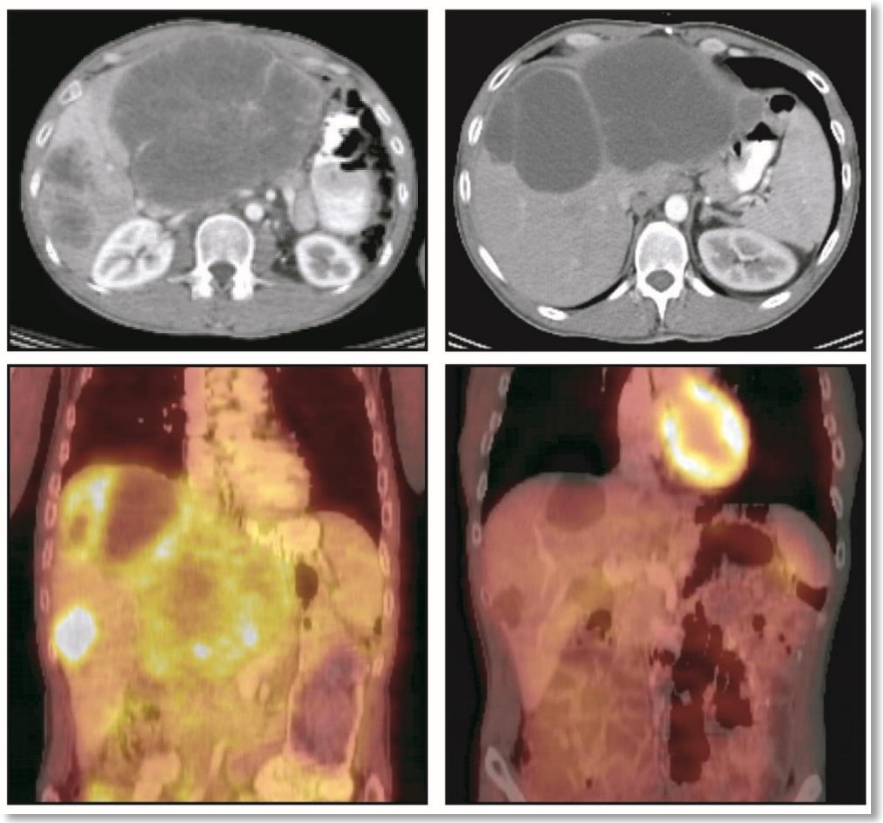
= wächst

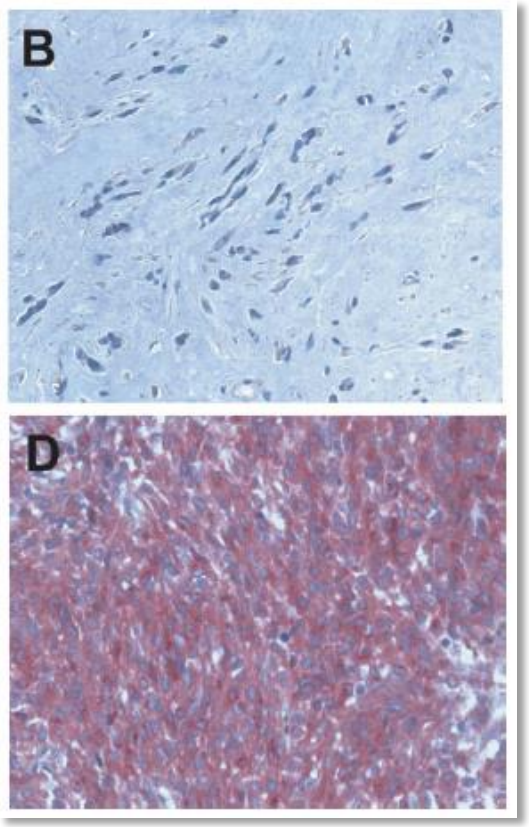
= wächst nicht

= abgestorben

Entwicklung von Resistenz – klinische Beobachtungen

Komplette Remissionen (Absterben aller Tumorzellen) sind sehr selten!

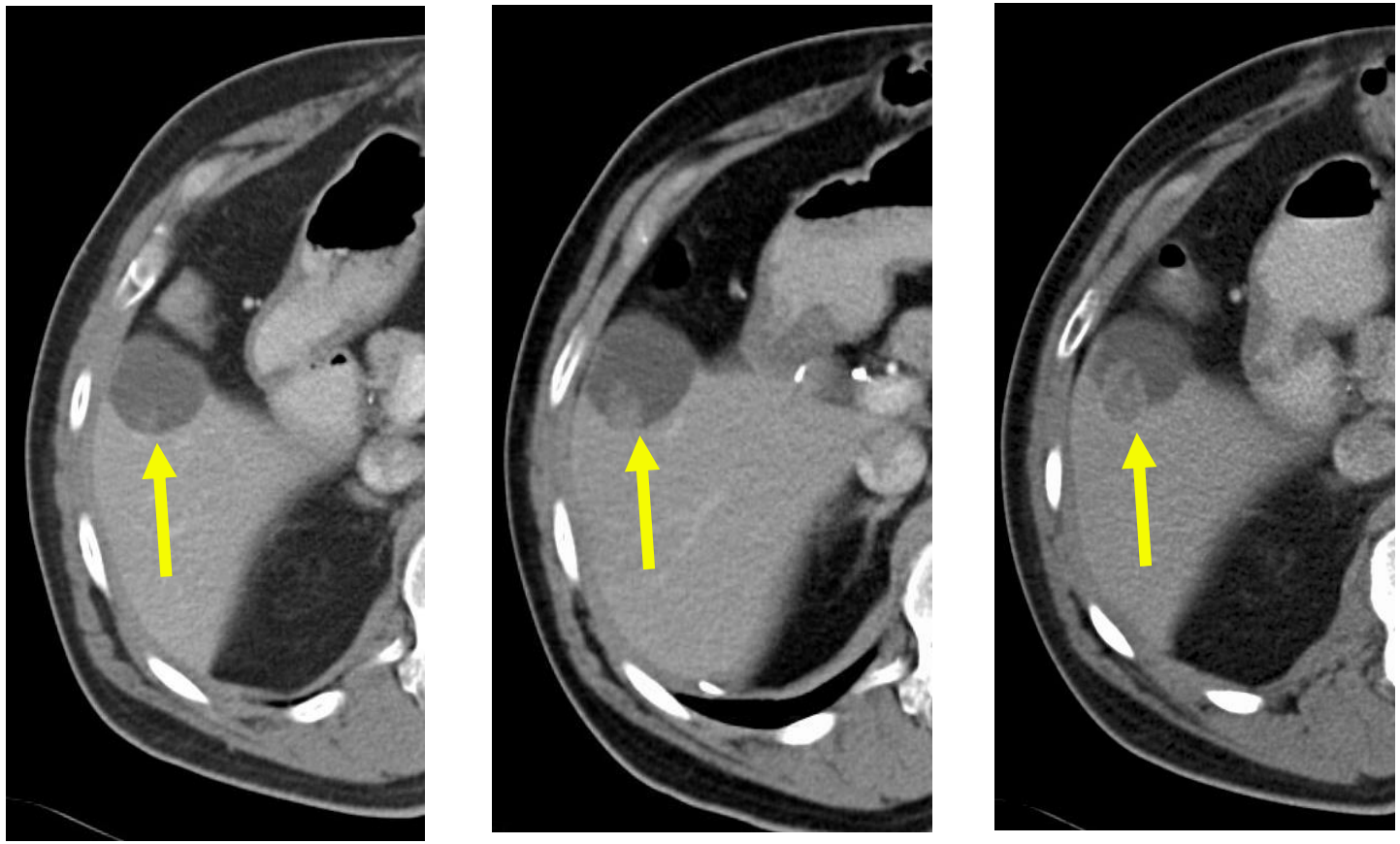




Bauer et al, Int J Cancer 2005;117:316–25

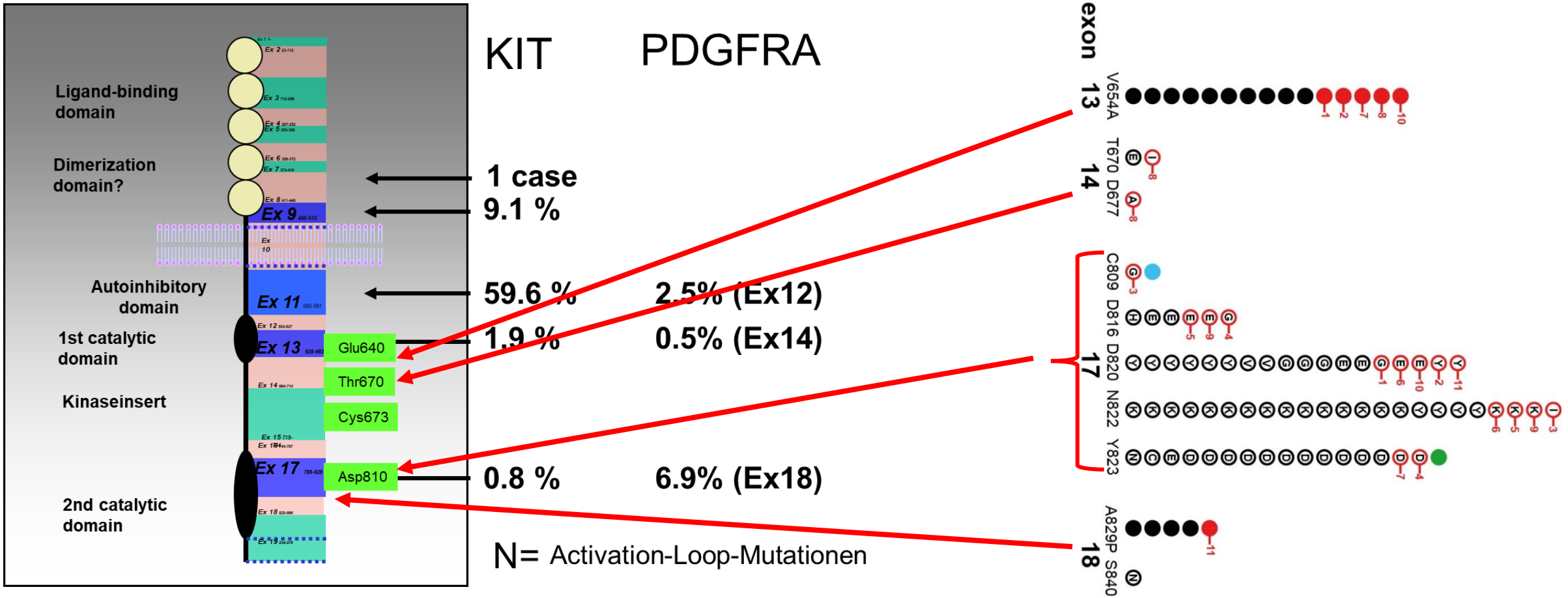
Entwicklung von Resistenz – klinische Beobachtungen

Resistenz entsteht häufig dort, wo schon vorher Metastasen waren



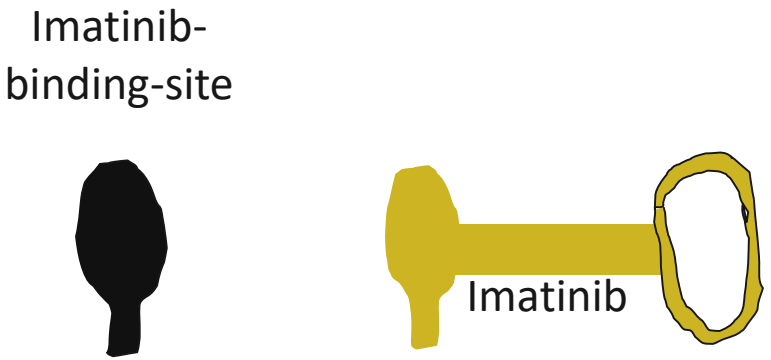
Mit freundl. Genehmigung G. Demetri

Was findet der Pathologe, wenn der Tumor resistent ist?



Heinrich MC, *ASCO* 2010: educational session, Hornick,J.L. et al. HumPathol 2007,38(5),679–687, Mühlenberg, Mol Cancer Ther. 2019 Jul 15 epub ahead

Resistenzmechanismen



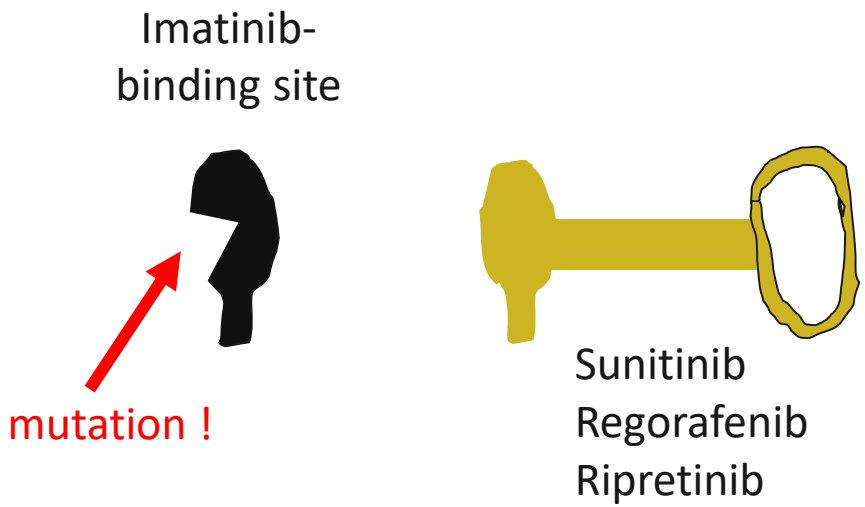
Resistenzmechanismen

Imatinib

Imatinib-
binding site

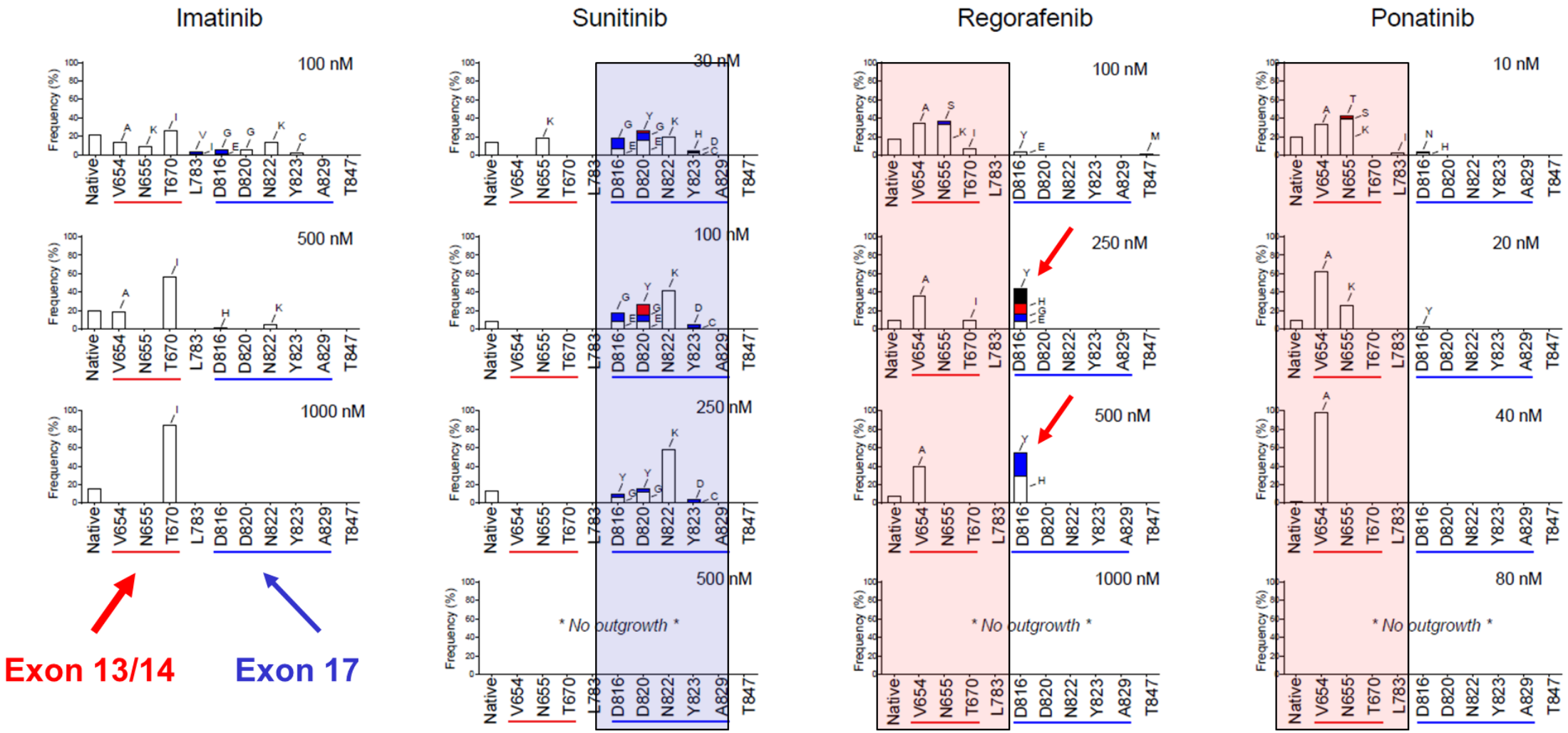
Mutation !

GIST – alternative Therapiestrategien

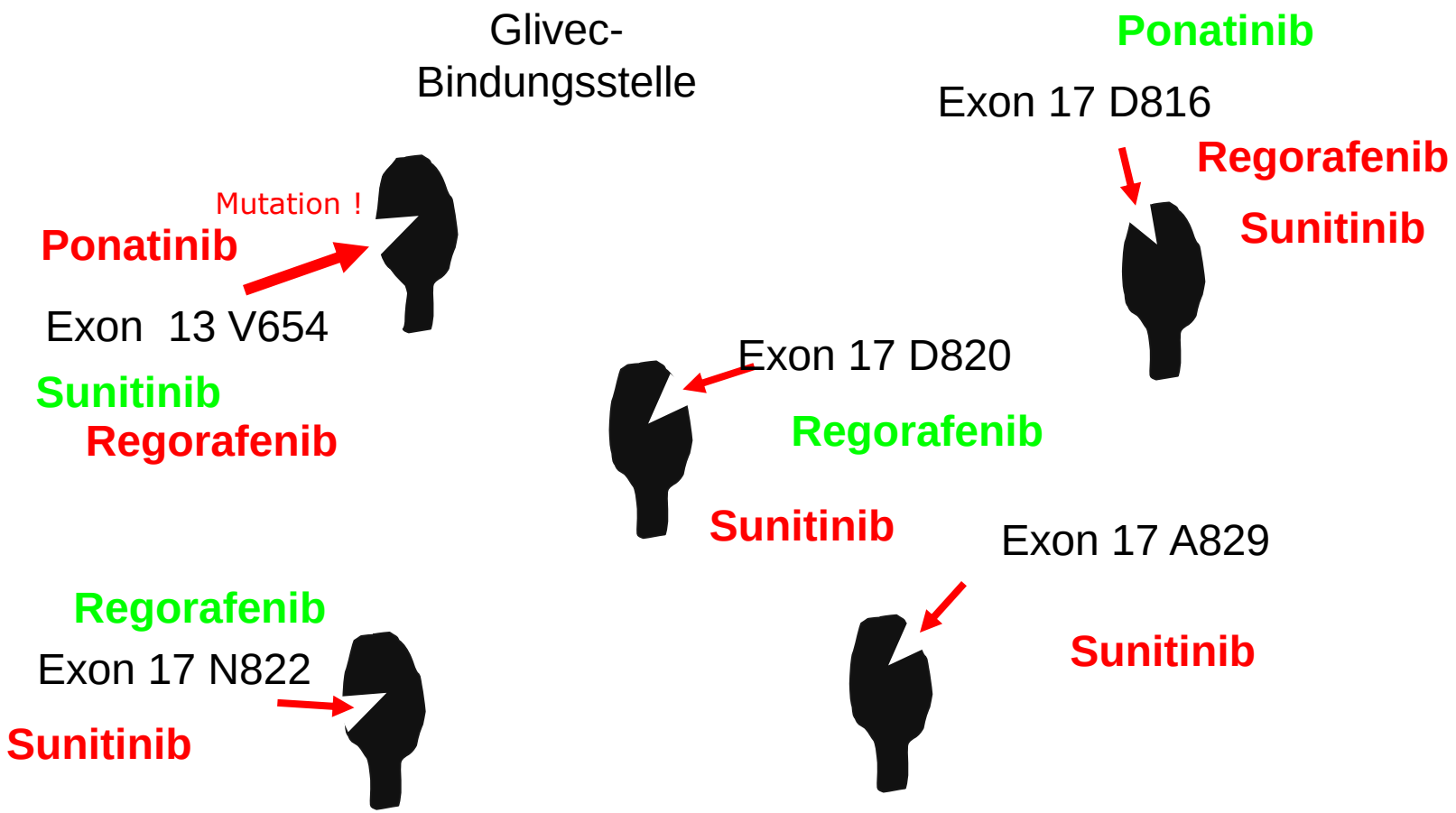


GIST – alternative Therapiestrategien

Mutagenese-Screen – Resistenz im Reagenzglas nachgestellt

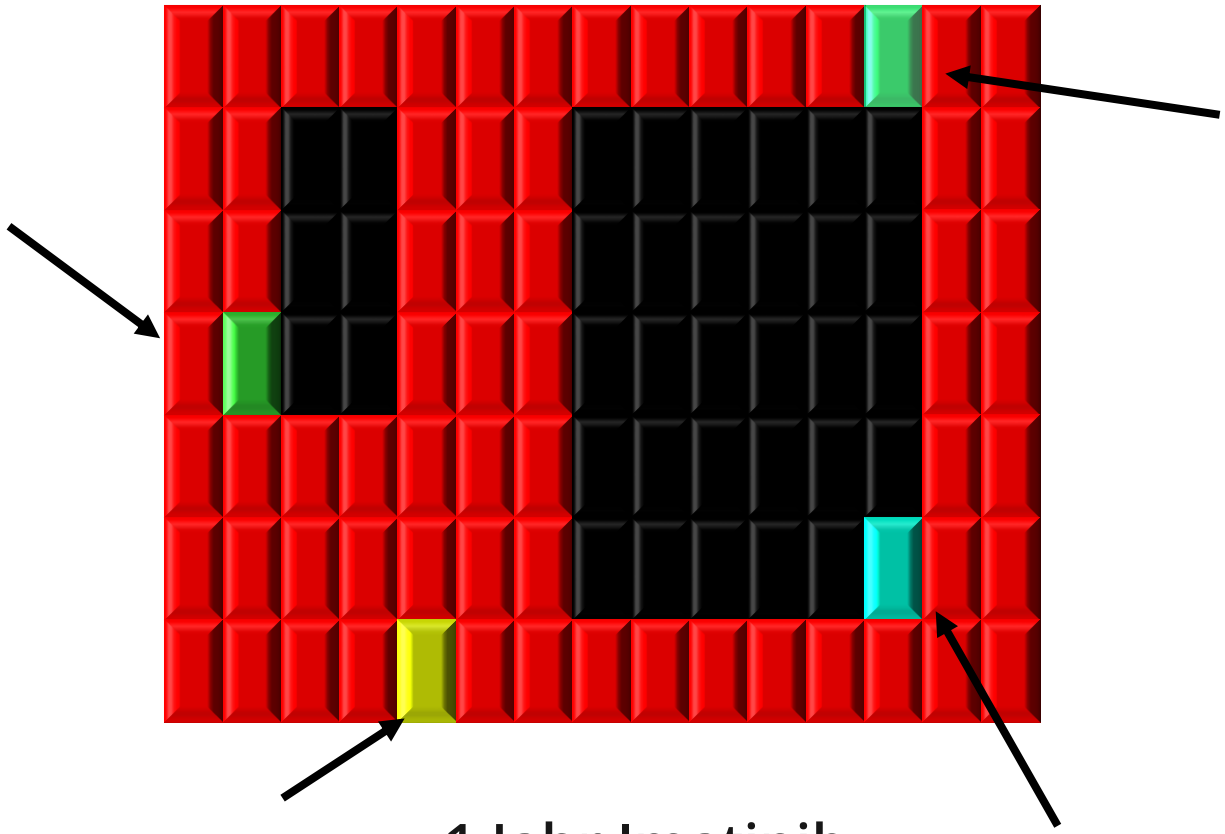


Mutagenese-Screen – Resistenz im Reagenzglas nachgestellt

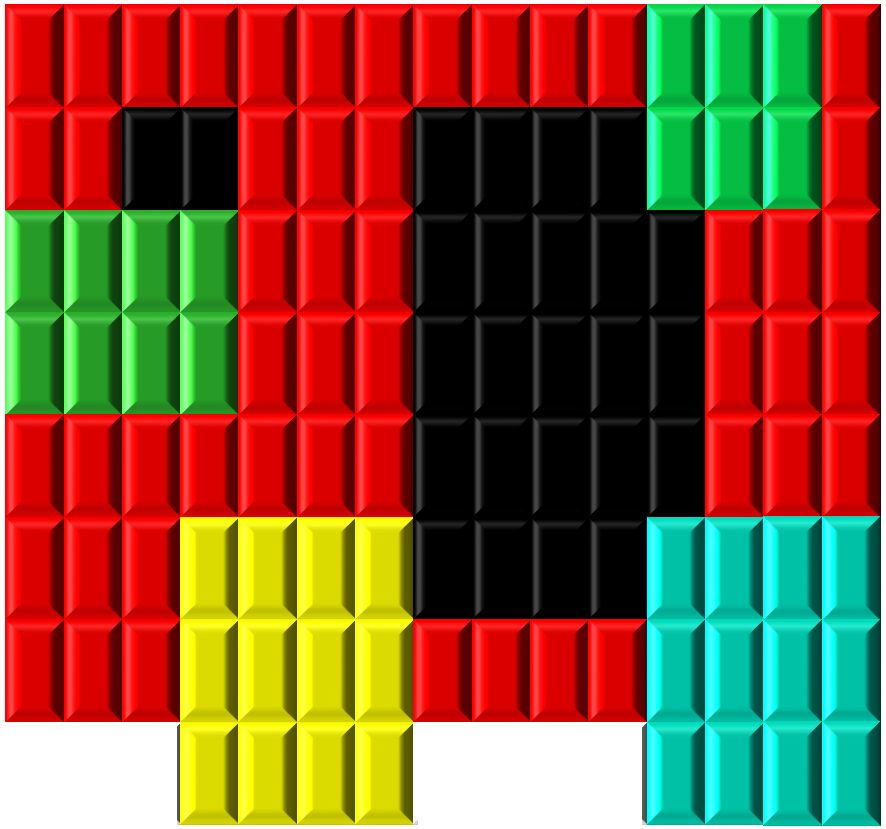


Garner, …, Bauer , Rivera; CCR in revision

Entwicklung von Resistenz – was passiert

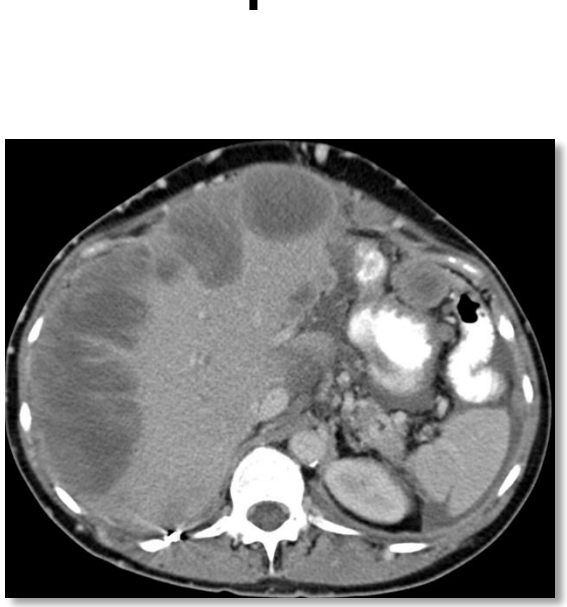


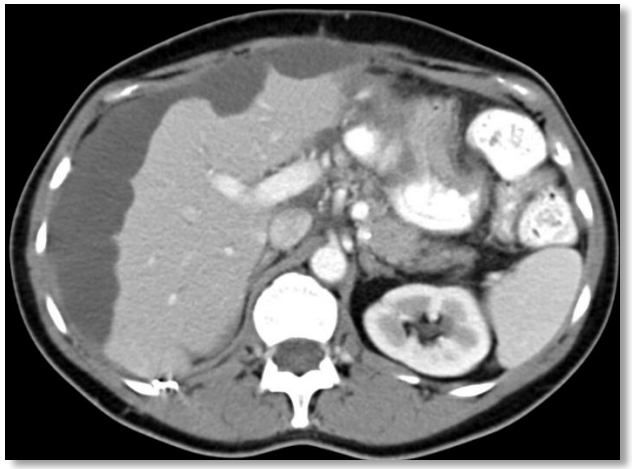
1 Jahr Imatinib

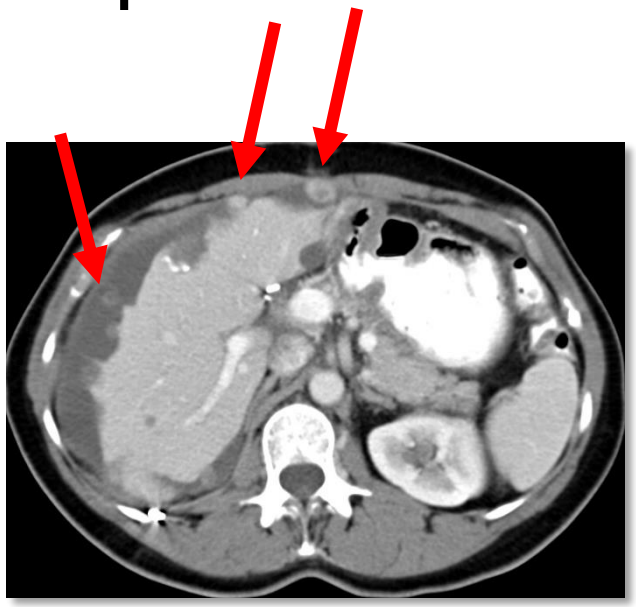


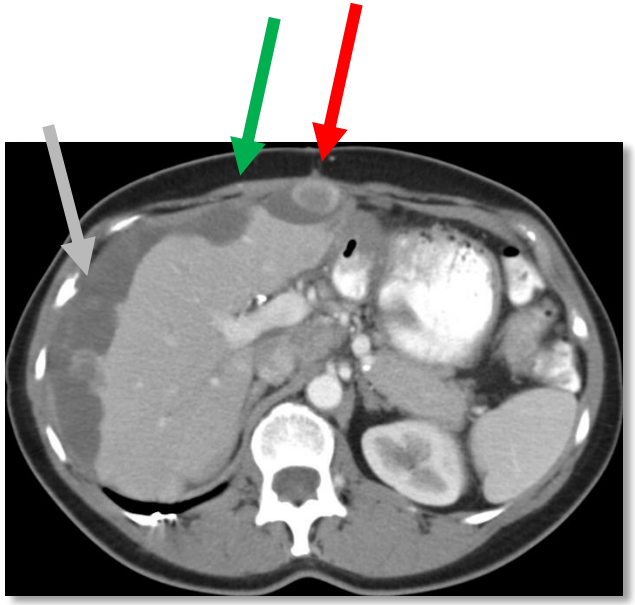
Sichtbares Wachstum

- **Development of resistance to imatinib – concepts**







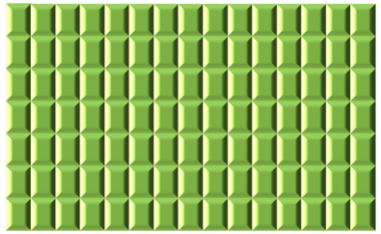


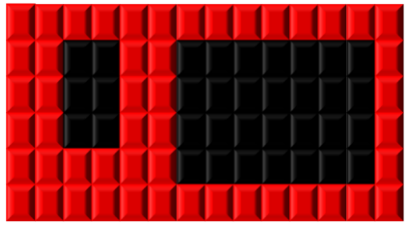
Baseline

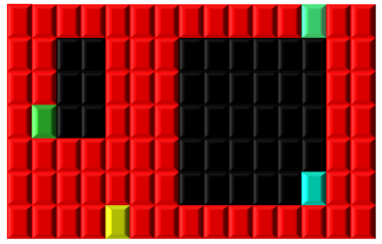
Response to IM

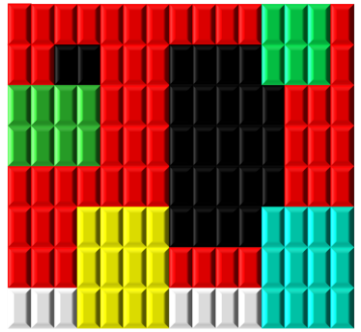
18 months - SU

21 months



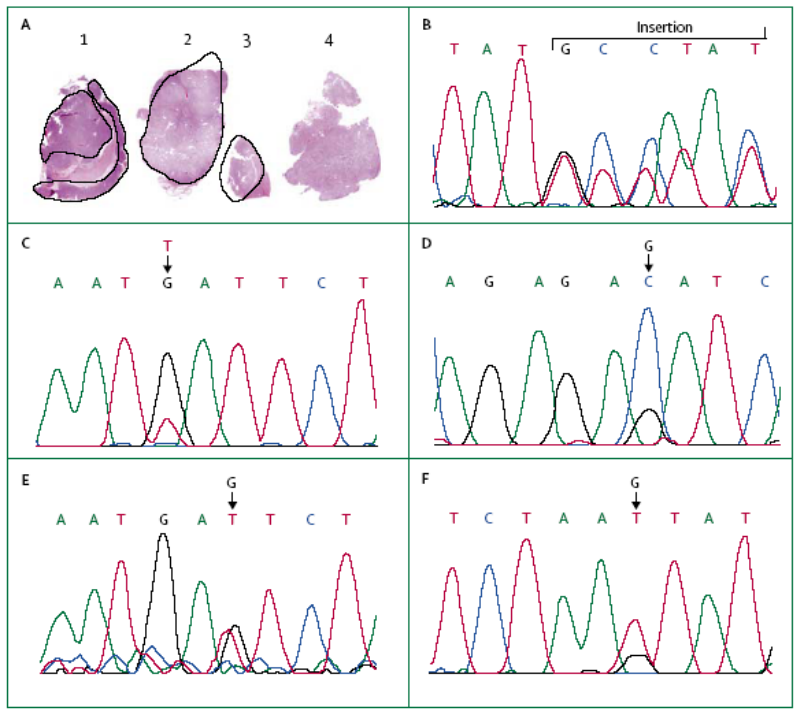






Mechanisms of imatinib resistance

Genomic heterogeneity



insertion Exon 9

D816E

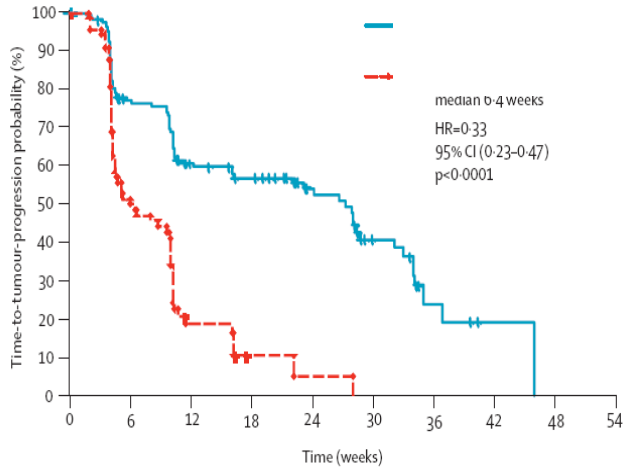
N822K

D820Y

D820E

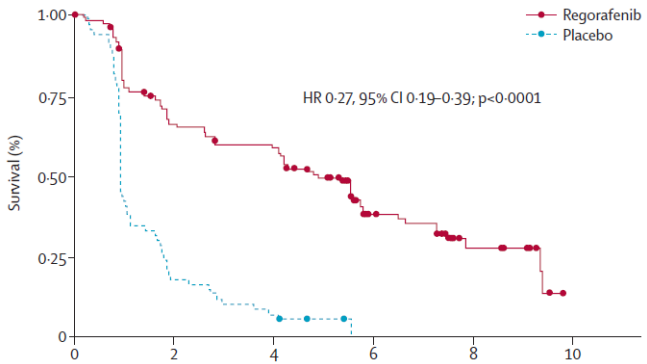
„genomic heterogeneity“

Sunitinib



Median PFS: 6.2 vs 1.2 mo

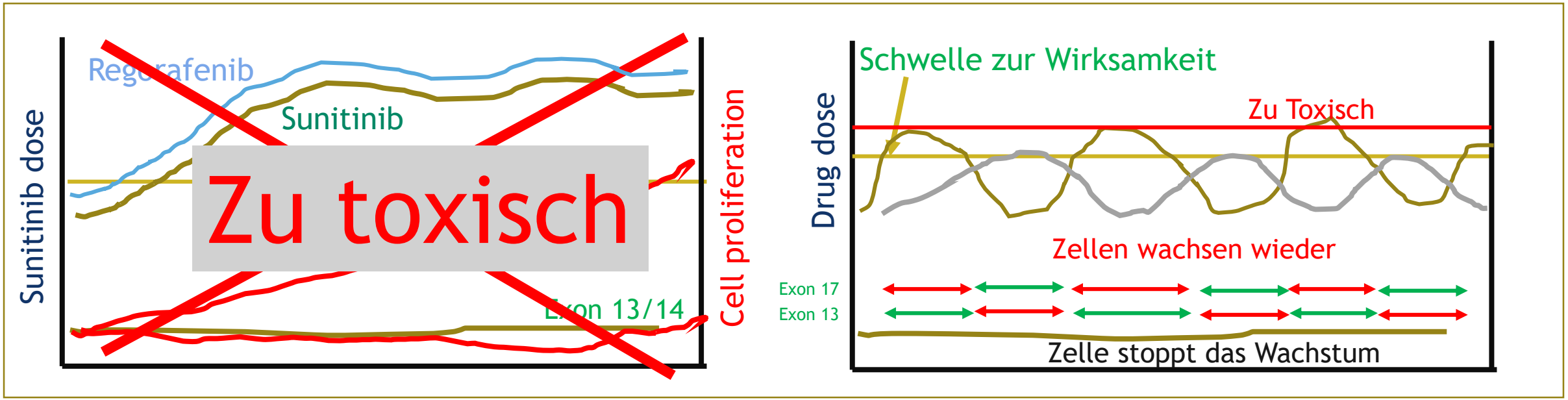
Regorafenib



Median PFS: 4.8 vs 0.9 mo

Wardelmann et al, Lancet Oncol 2005; 6: 249–51;Demetri et al, Lancet 2006; 368: 1329–38; Lancet 2013 381(9863):295-302

Kann man nicht einfach kombinieren?

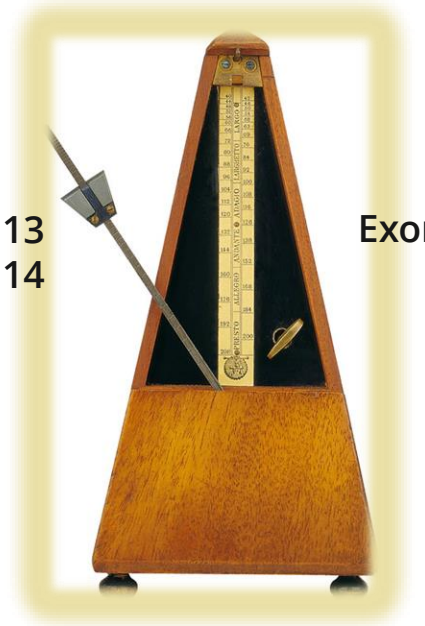


Grundannahmen:

Fixe Kombination ist zu toxisch
Pausen sind möglich
Wechsel funktioniert rechtzeitig

Behandlung von resistenten GIST

Konzept: Metronomische Therapie!



Exon 13
Exon 14

Exon 17

1 week

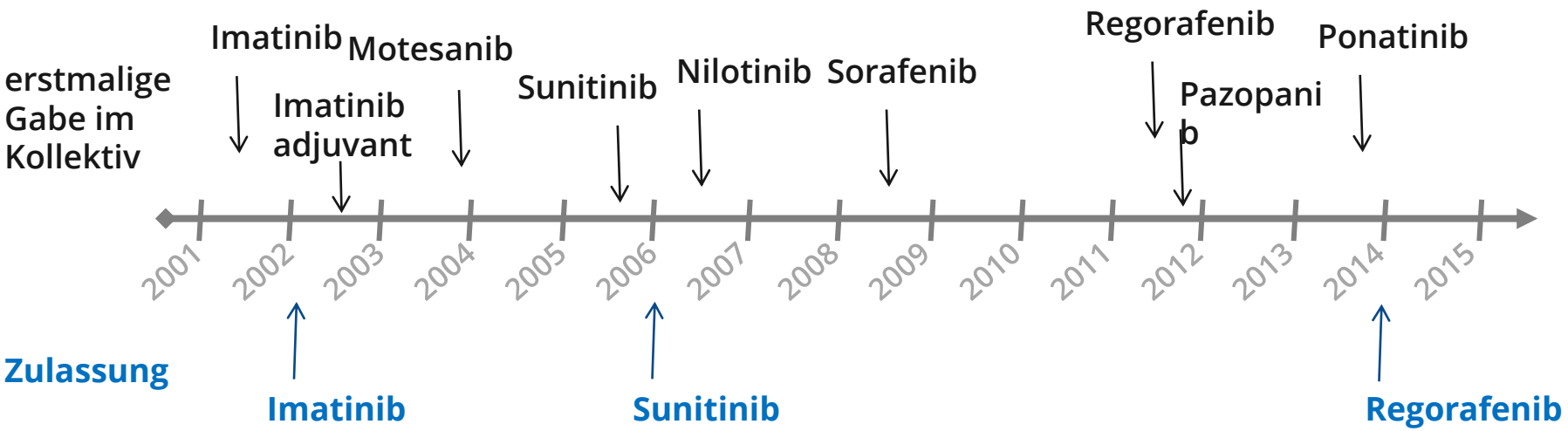
SU	SU	SU	RE	RE	RE	RE
	37.5 mg			120 mg		
Dose escalation	50 mg			160 mg		

SURE Studie – was hats gebracht?

Ansprechend	N (%)
CR + PR	0 (0%)
SD*	4 (33.3%)
PD	8 (66.7%)

mPFS (mo): 1.9 months
(95% CI: 1.4-3.6 months)

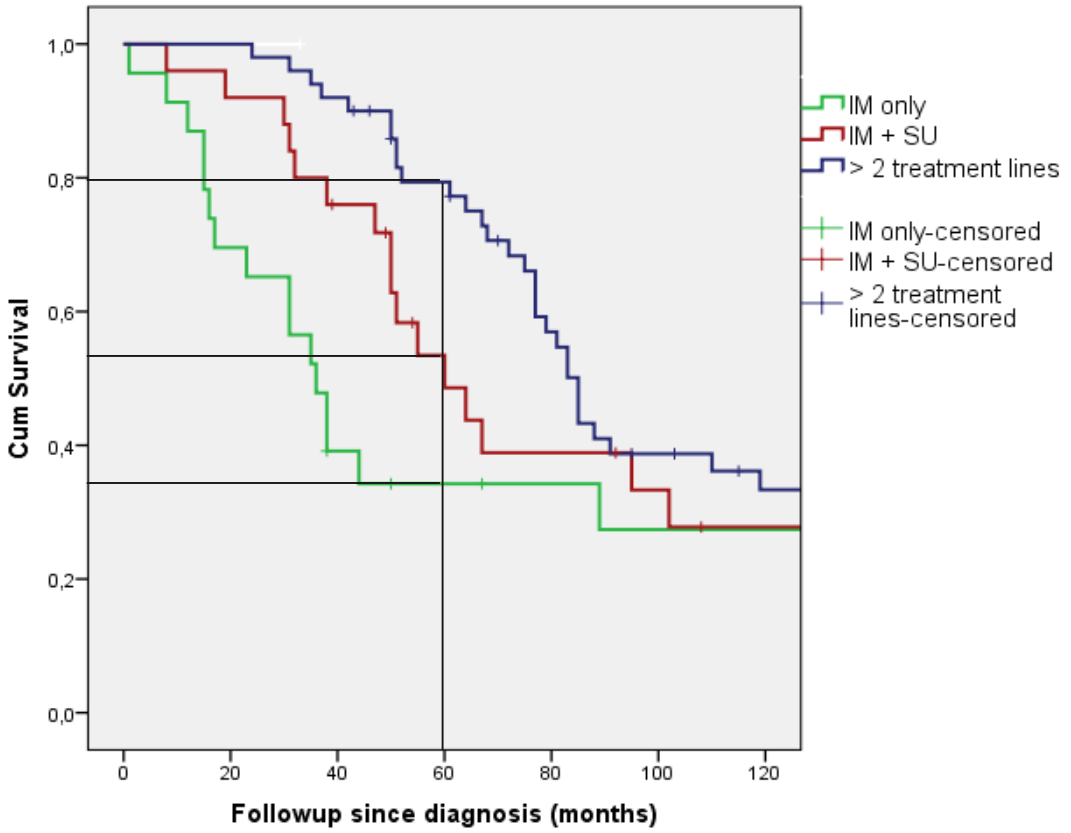
Medikamente gegen GIST über die Zeit



Mehr therapeutische Optionen = längeres Leben

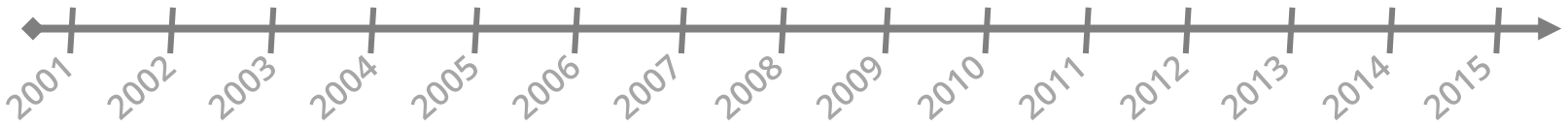
n=99

Einfluss der Zahl der Therapielinien
Auf das Überleben



Medikamente gegen D842V-GIST

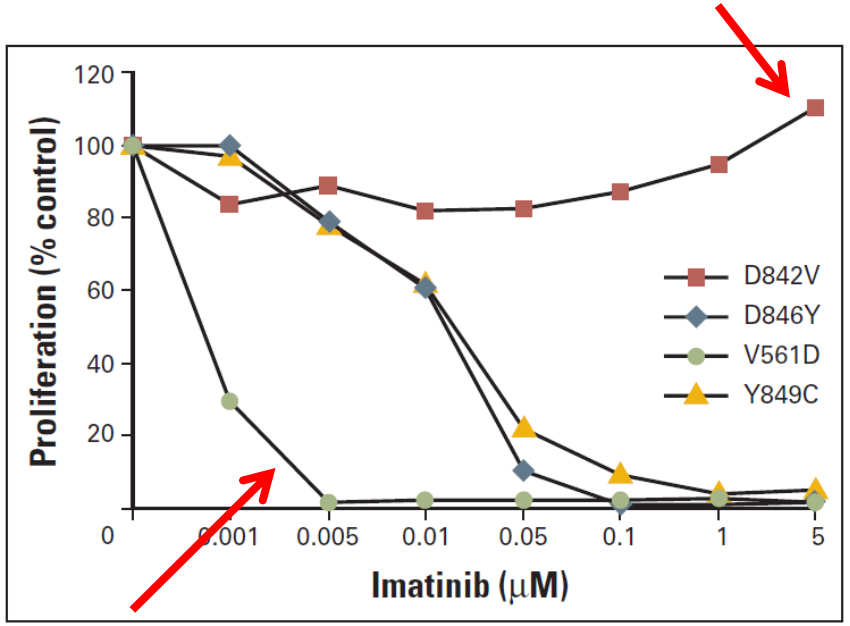
erstmalige Gabe im Kollektiv



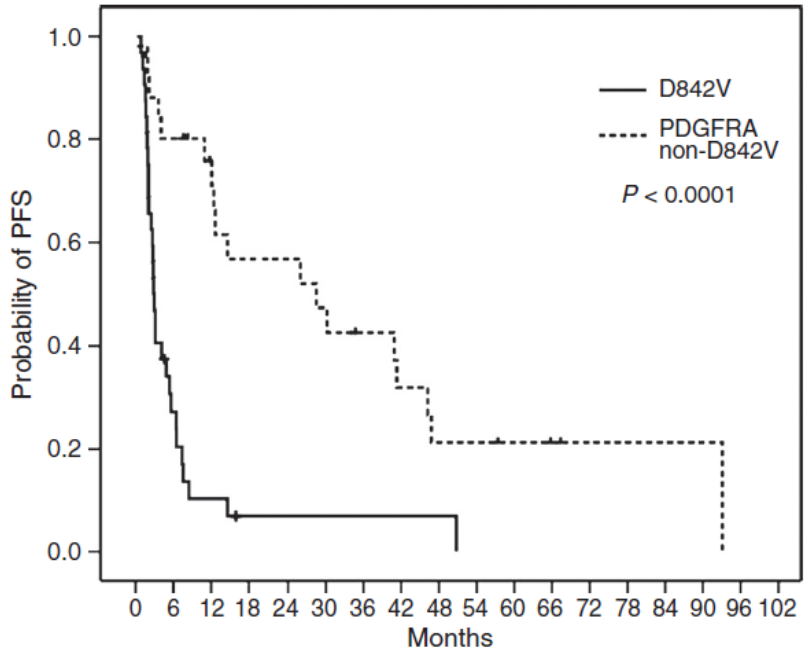
PDGFRA-mutierte GIST

Imatinib funktioniert nicht gegen PDGFRA D842V

Resistenz

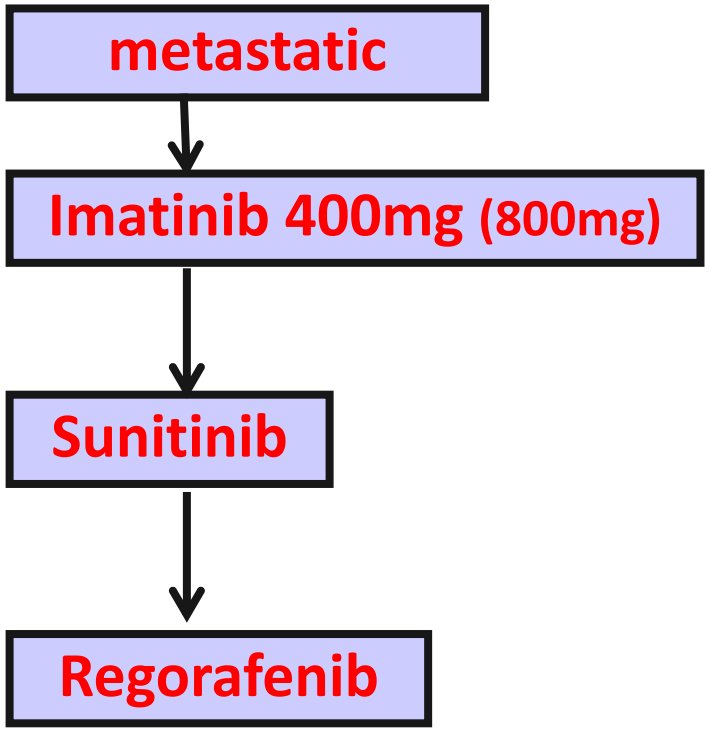


Sensibel



Corless et al, JCO 23 2005

Aktuelle Studienergebnisse bei GIST



1st line

2nd line

3rd line

4th line

>4th line

Intrigue: Ripretinib vs Placebo (Phase III)

Navigator: Avapritinib (Phase II)

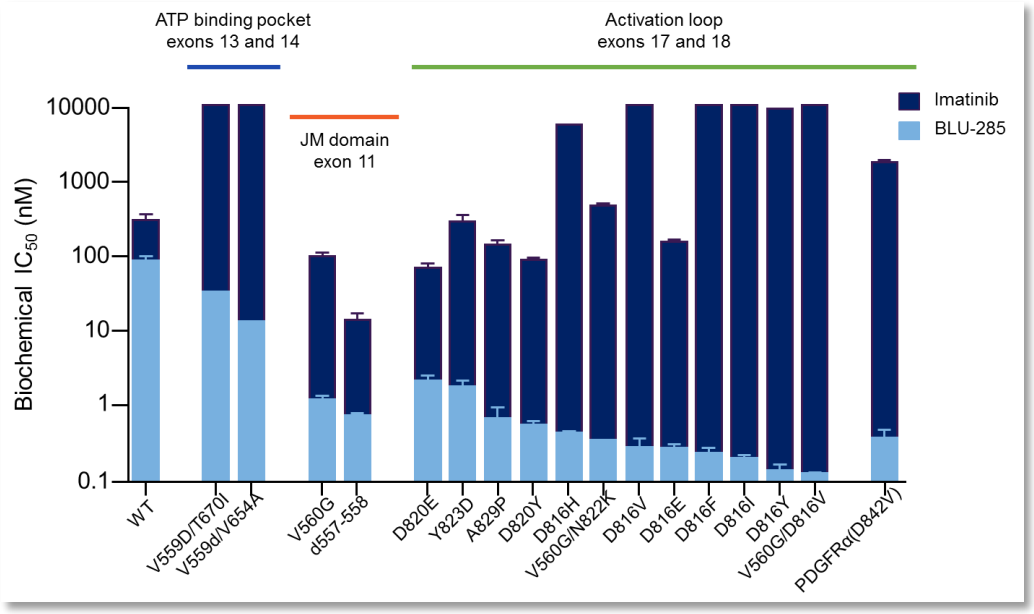
CABO GIST TRIAL (Phase II)

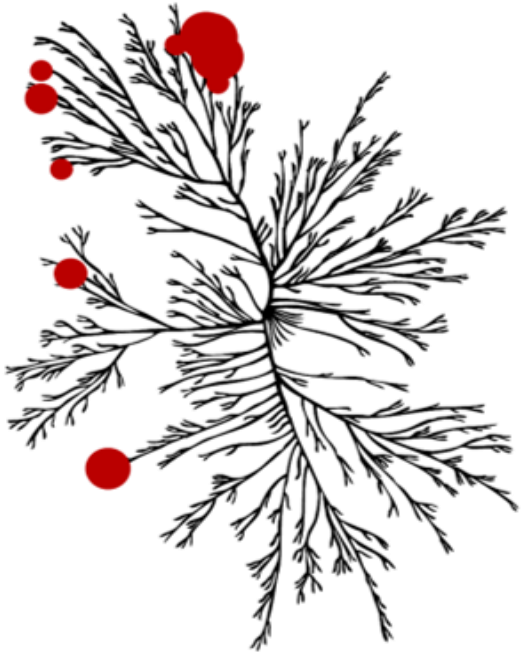
Voyager-Studie: Avapritinib vs Regorafenib (Phase III)

Invictus-Studie: Ripretinib vs Placebo (Phase III)

Neue KIT/PDGFRA-Inhibitoren

Avapritinib (BLU-285)





Ongoing clinical trials

Avapritinib kinome selectivity

NAVIGATOR GIST

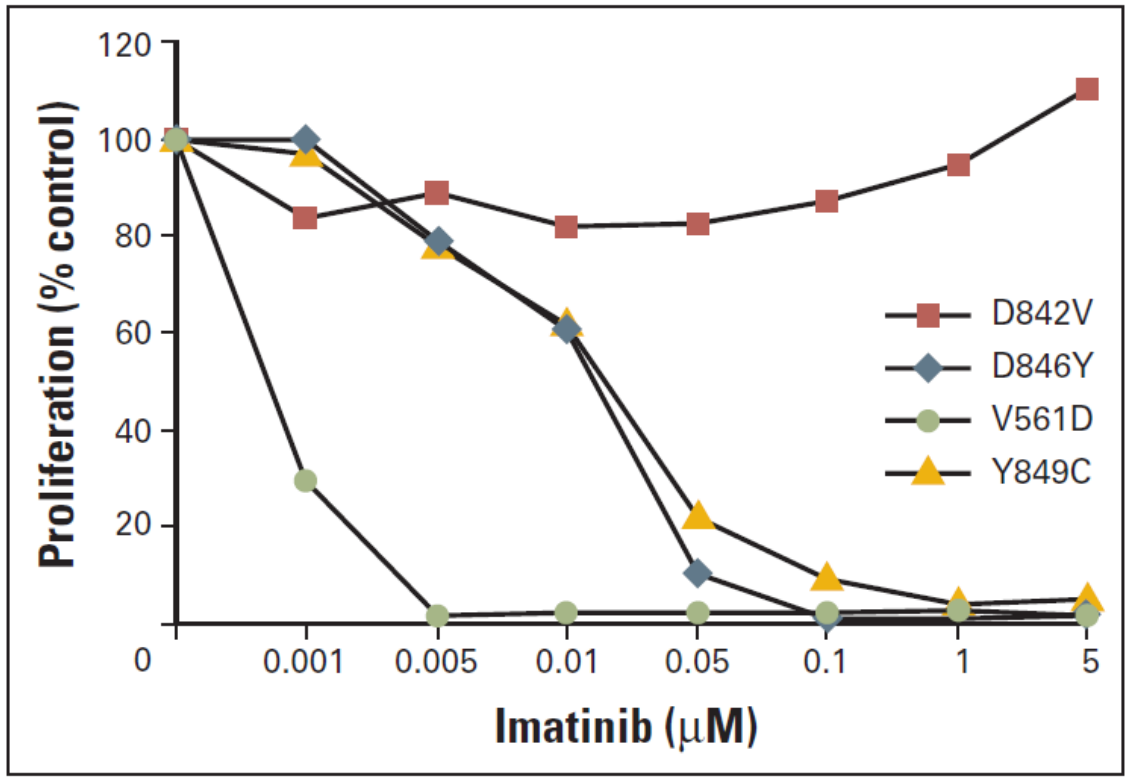
Phase 1 advanced GIST

VOYAGER GIST

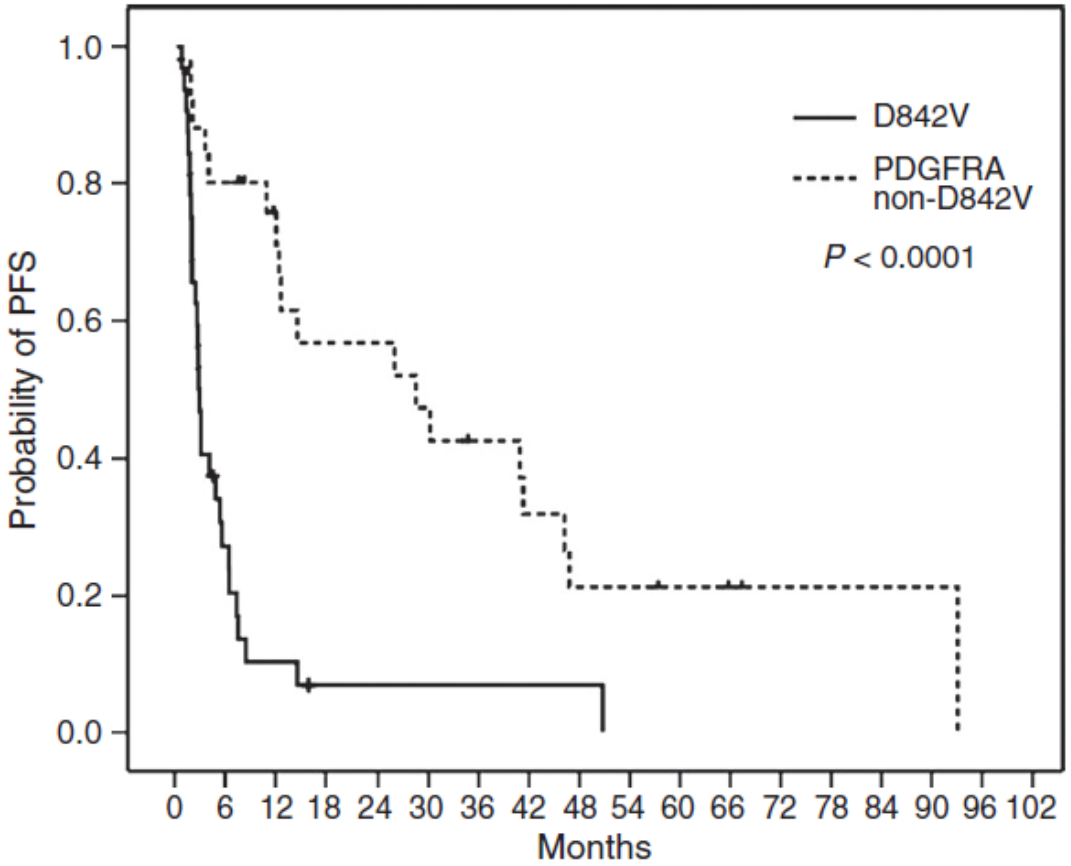
Phase 3 trial of avapritinib vs. regorafenib in 3L and 4L GIST

Approaching cure? Novel KIT/PDGFRA inhibitors

PDGFRA D842V – the former untreatable

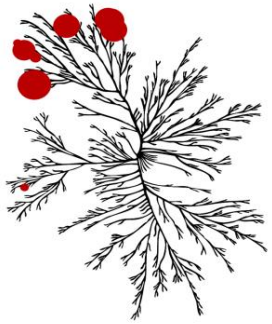
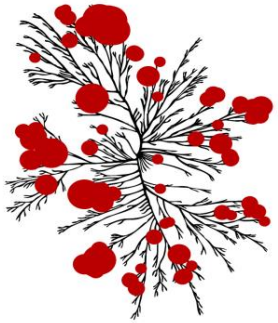
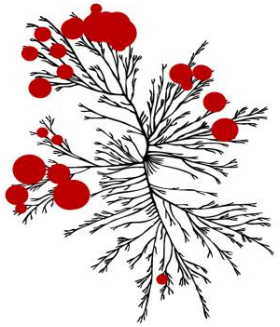
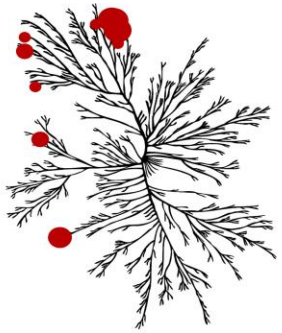
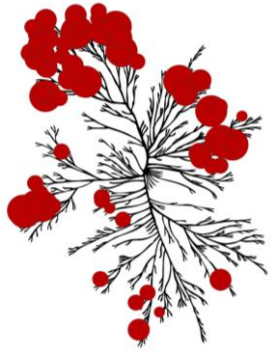
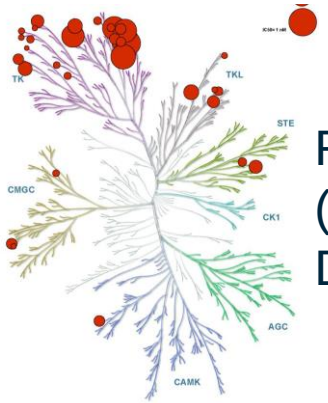


Absolute IM-resistance

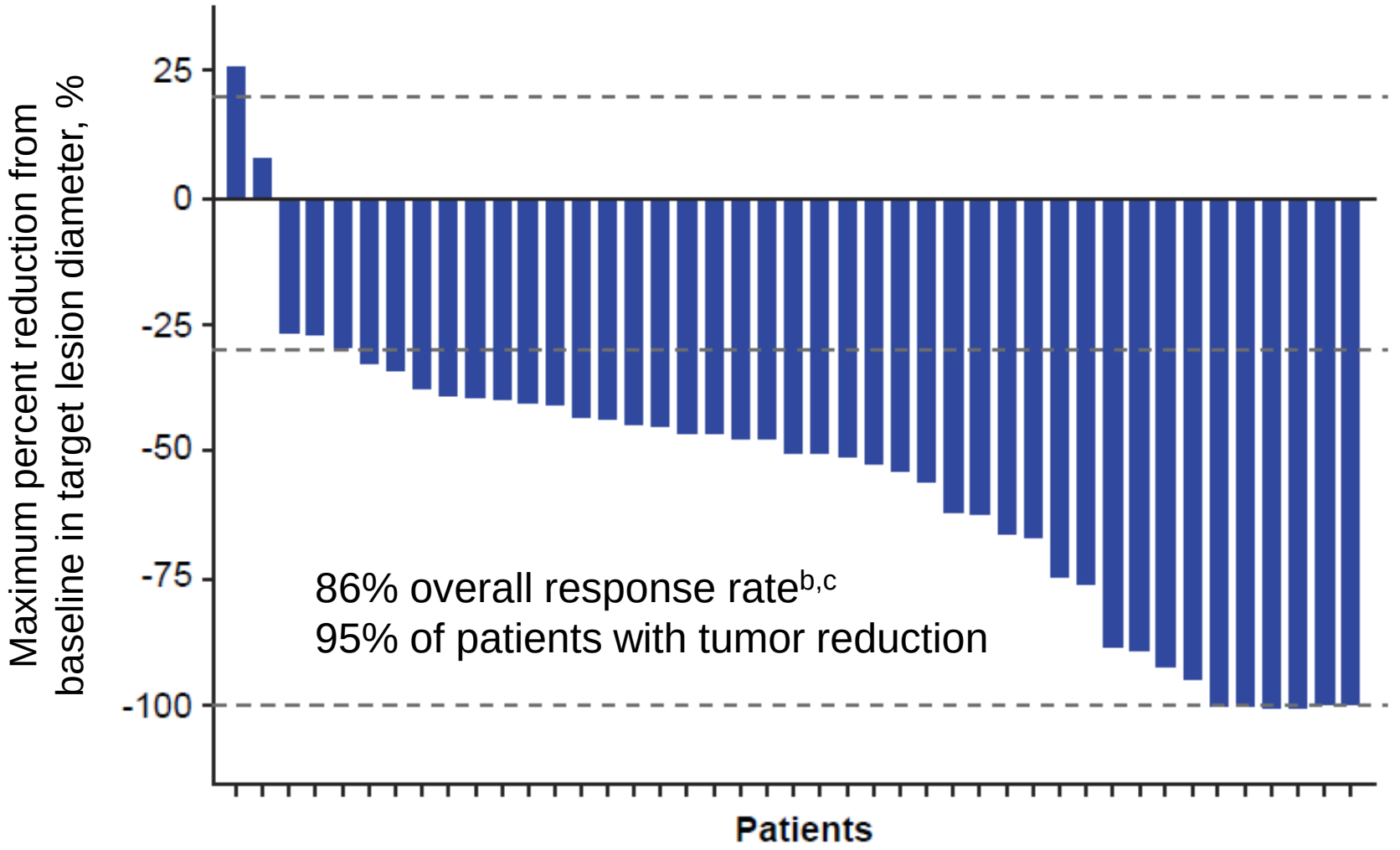


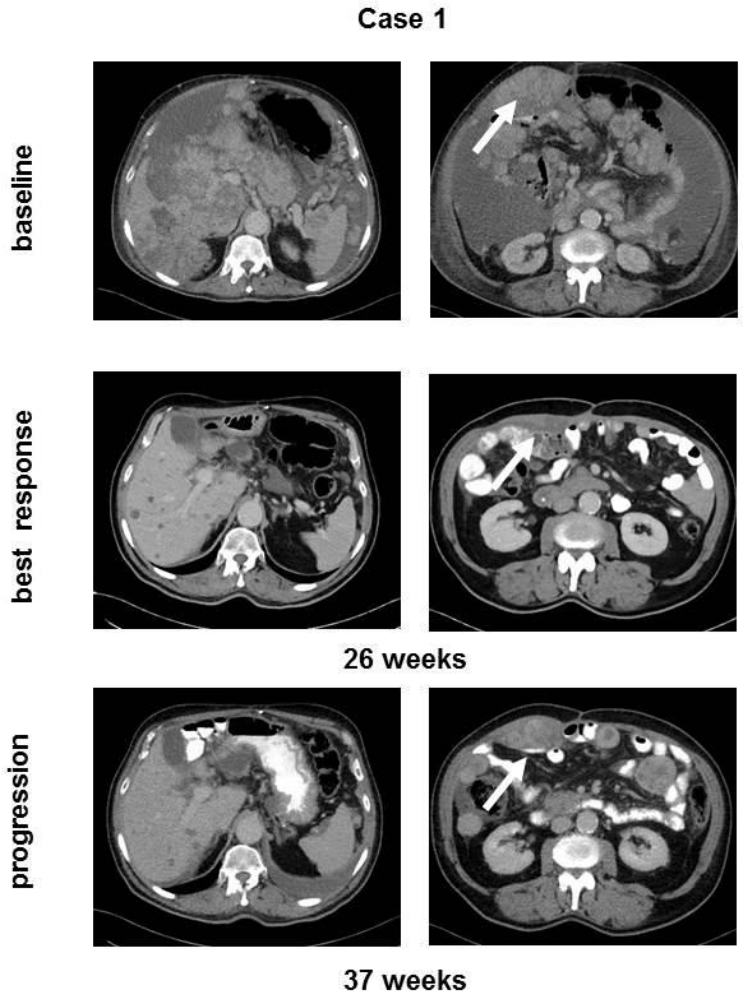
Dismal prognosis

Avapritinib ist ein selektiver KIT-Inhibitor

	Selective therapies	Multi-targeted kinase therapies	
Approved for GIST	 Imatinib	 Sunitinib	 Regorafenib
Investigational for GIST	 Avapritinib	 Ripretinib (according to Blueprint)	 Ripretinib (according to Deciphera)

Avapritinib ist die erste, hoch wirksame Therapie bei D842V-GIST





Avapritinib

AYVAKIT™ avapritinib | tablets

FDA approves avapritinib for gastrointestinal stromal tumor with a rare mutation

Resources for Information | Approved Drugs

Hematology/Oncology (Cancer) Approvals & Safety Notifications

Drug Information Soundcast in Clinical Oncology (D.I.S.C.O.)

Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) Short Description

On January 9, 2020, the Food and Drug Administration approved avapritinib (AYVAKIT™, Blueprint Medicines Corporation) for adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including D842V mutations.

Avapritinib is the first therapy approved for patients with GIST harboring a PDGFRA exon 18 mutation.

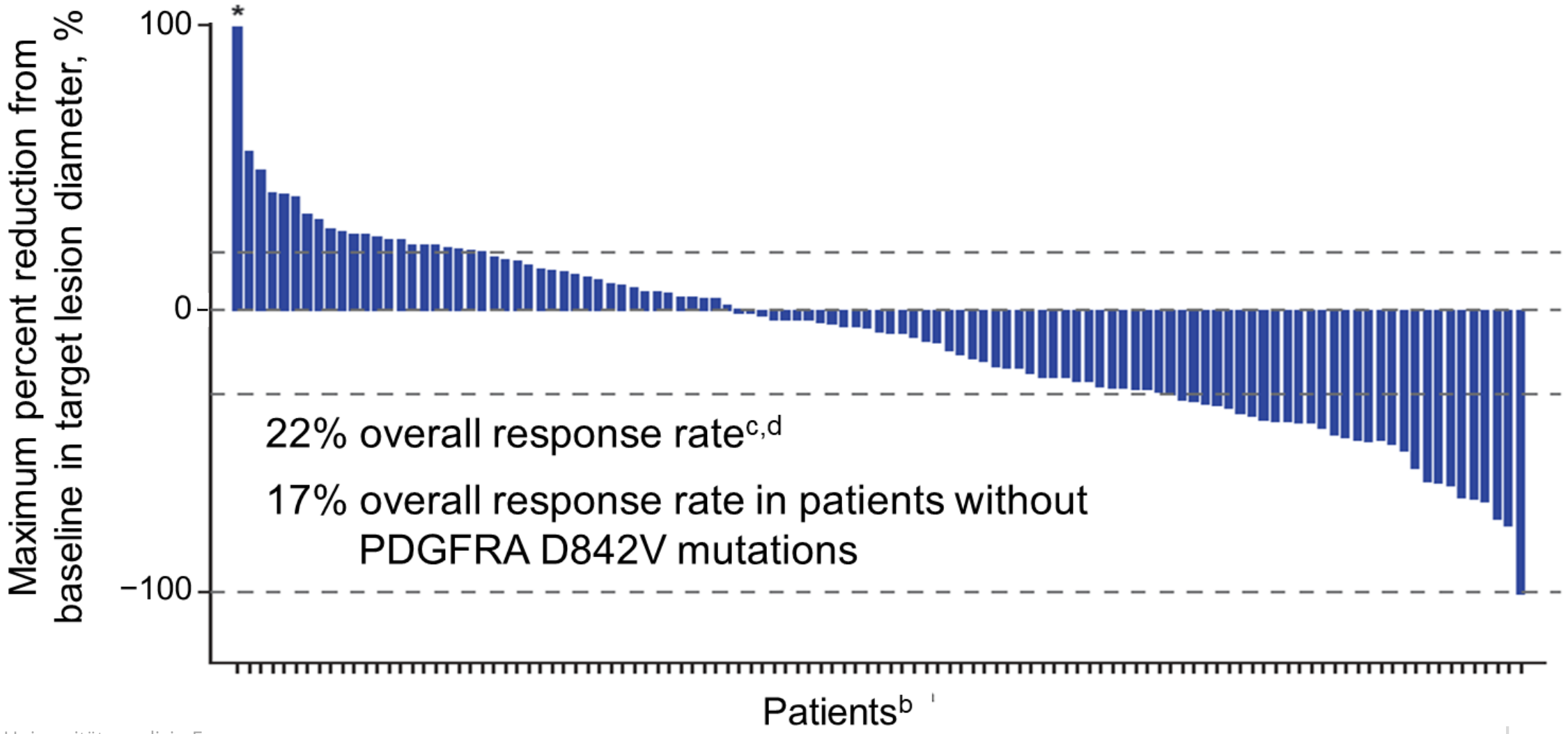
Efficacy was investigated in NAVIGATOR (NCT02508532), a multi-center, single-arm, open-label trial enrolling 43 patients with GIST harboring a PDGFRA exon 18 mutation, including 38 patients with PDGFRA D842V mutations. The trial initially enrolled patients at a starting dose of 400 mg orally once daily, which was later reduced to the recommended dose of 300 mg orally once daily due to toxicity. Patients received avapritinib until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall response rate (ORR) based on disease assessment by independent radiological review using modified RECIST 1.1 criteria. An additional efficacy outcome measure was response duration.

For patients harboring a PDGFRA exon 18 mutation, the ORR was 84% (95% CI: 69%, 93%), with 7% complete responses and 77% partial responses. For the subgroup of patients with PDGFRA D842V mutations, the ORR was 89% (95% CI: 75%, 97%), with 8% complete responses and 82% partial responses. The median response duration was not

Content current as of:
01/09/2020

Regulated Product(s)
Drugs
Oncology

Avapritinib führt auch zu Tumorschrumpfung bei Patienten mit KIT-Mutationen und Vorbehandlung



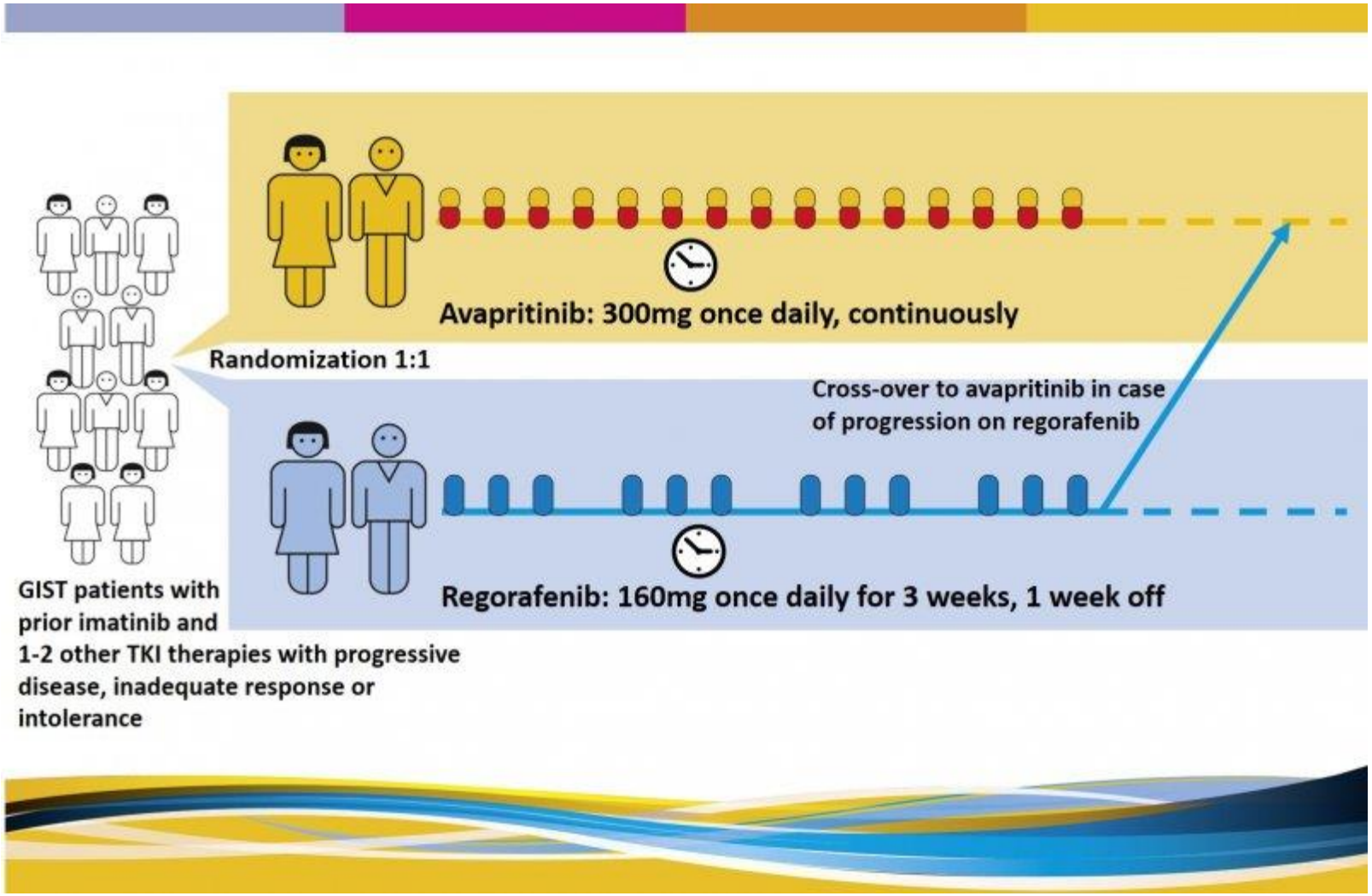
Nebenwirkungen von Avapritinib

n (%)	Safety Population (N=204)			
	All AEs		Treatment-related AEs	
	All Grades[b]	Grade ≥3[c]	All Grades[b]	Grade ≥3[c]
Übelkeit	131 (64)	5 (3)	121 (59)	-
Fatigue	113 (55)	15 (7)	96 (47)	13 (6)
Blutarmut	102 (50)	58 (28)	74 (36)	33 (16)
Kognitive Störungen [a]	84 (41)	8 (4)	84 (41)	8 (4)
Ödeme um die Augen	83 (41)	-	82 (40)	-
Erbrechen	78 (38)	4 (2)	65 (32)	-
Verminderter Appetit	77 (38)	6 (3)	58 (28)	-
Durchfall	76 (37)	10 (5)	65 (32)	6 (3)
Vermehrtes Tränen	67 (33)	-	62 (30)	-
Wassereinlagerungen	63 (31)	-	55 (27)	-
Gesichtsödem	50 (25)	-	49 (24)	-
Verstopfung	46 (23)	-	-	-
Schwindel	45 (22)	-	-	-
Haarfarbe anders	43 (21)	-	42 (21)	-
Bilirubin erhöht	43 (21)	9 (4)	-	8 (4)
Bauchschmerzen	41 (20)	11 (5)	-	-

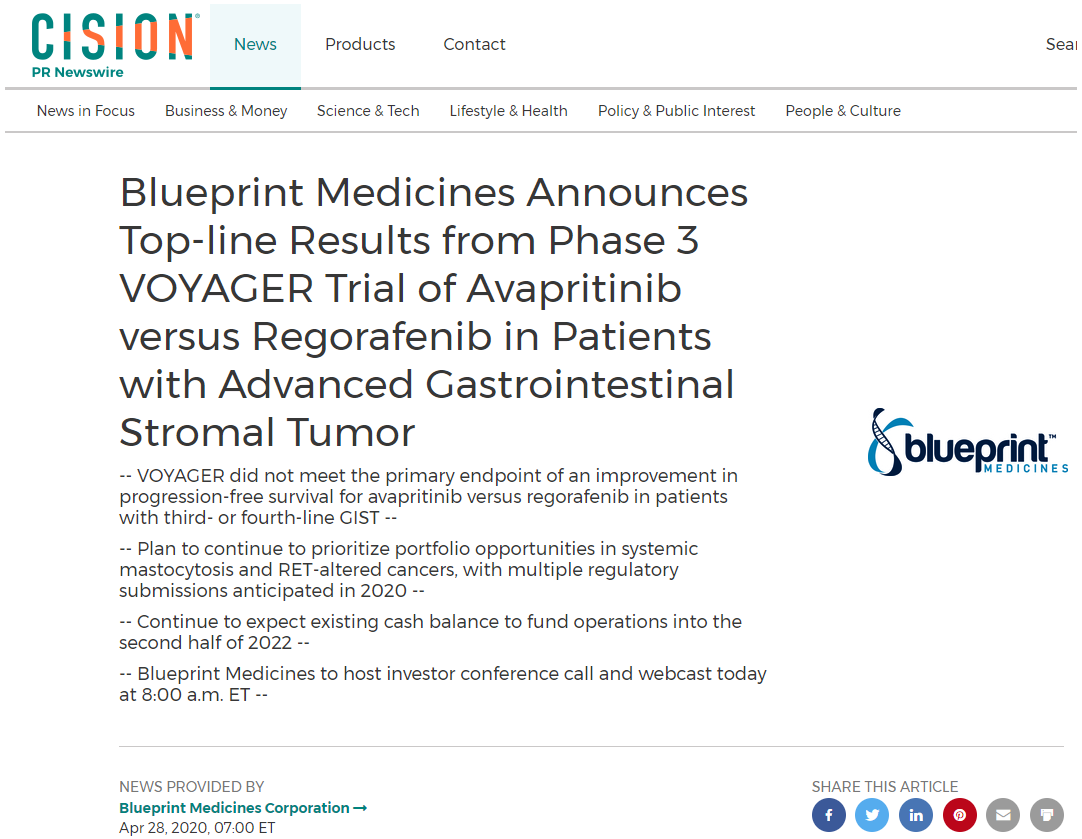
a

Gedächtnisstörungen(29%)
Kognitive Störungen (11%)
Verwirrtheit (7%)
Enzephalopathie (1%).

Voyager-Studie



Voyager-Studie



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Blueprint Medicines Announces Top-line Results from Phase 3 VOYAGER Trial of Avapritinib versus Regorafenib in Patients with Advanced Gastrointestinal Stromal Tumor

blueprint MEDICINES

-- VOYAGER did not meet the primary endpoint of an improvement in progression-free survival for avapritinib versus regorafenib in patients with third- or fourth-line GIST --

-- Plan to continue to prioritize portfolio opportunities in systemic mastocytosis and RET-altered cancers, with multiple regulatory submissions anticipated in 2020 --

-- Continue to expect existing cash balance to fund operations into the second half of 2022 --

-- Blueprint Medicines to host investor conference call and webcast today at 8:00 a.m. ET --

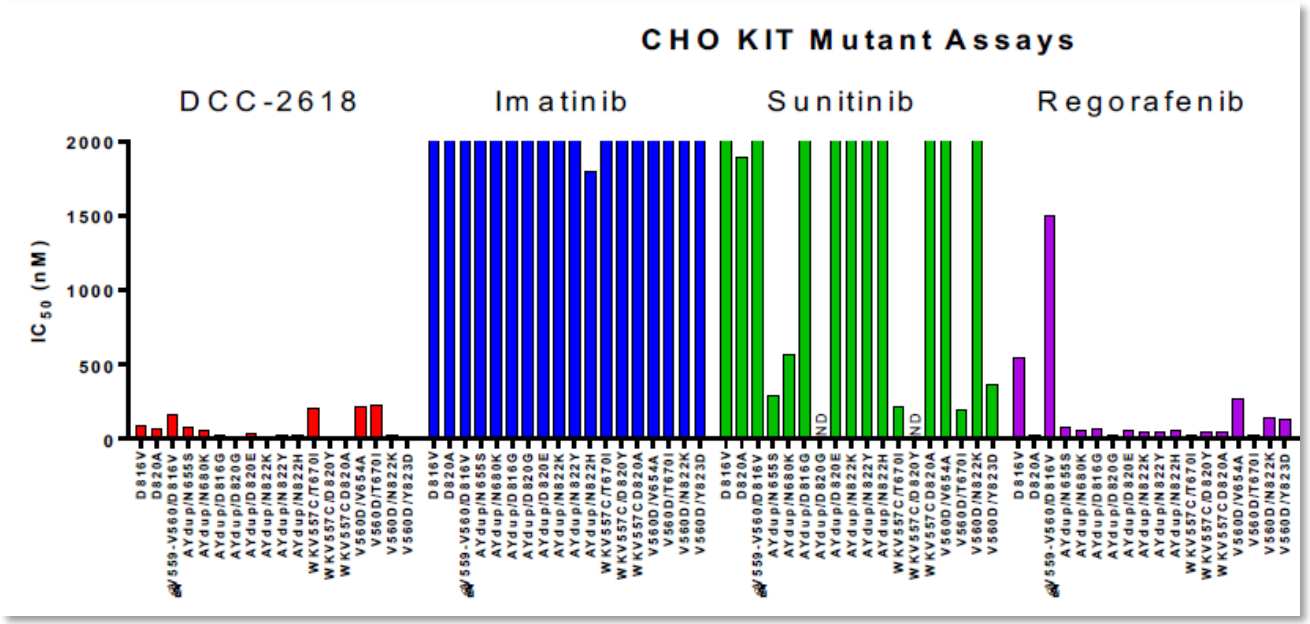
NEWS PROVIDED BY
Blueprint Medicines Corporation →
Apr 28, 2020, 07:00 ET

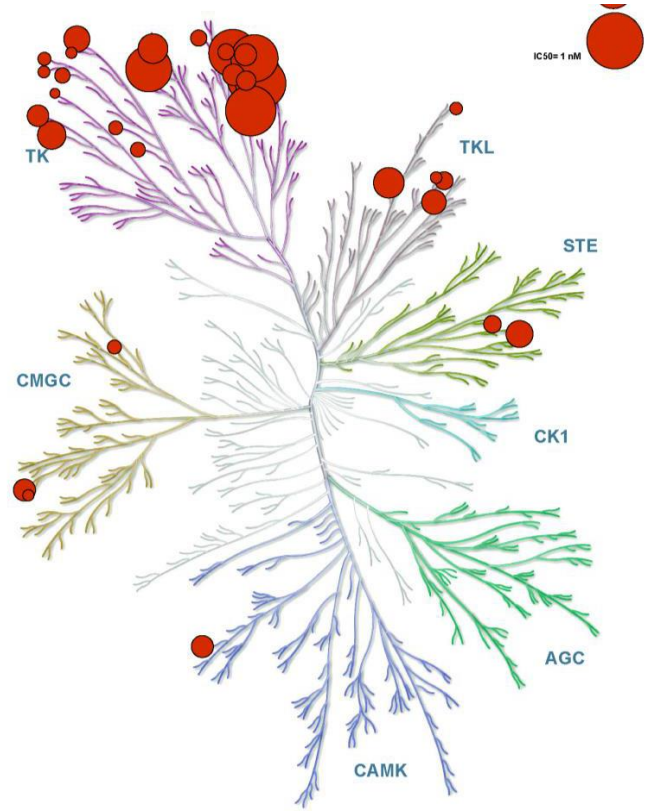
SHARE THIS ARTICLE

- Studienziel nicht erreicht
- Avapritinib ist nicht besser als Regorafenib
- Regorafenib bleibt der Standard 3. Linie
- Ausführliche Ergebnisse noch nicht vorhanden
- Keine Zulassung für KIT-mutierte GIST
- CUP nur noch für PDGFR-mutierte Patienten

Neue KIT/PDGFRA Hemmstoffe

Ripretinib (DCC-2618)





Ongoing clinical trials

Ripretinib kinome selectivity

INVICTUS
≥4th line

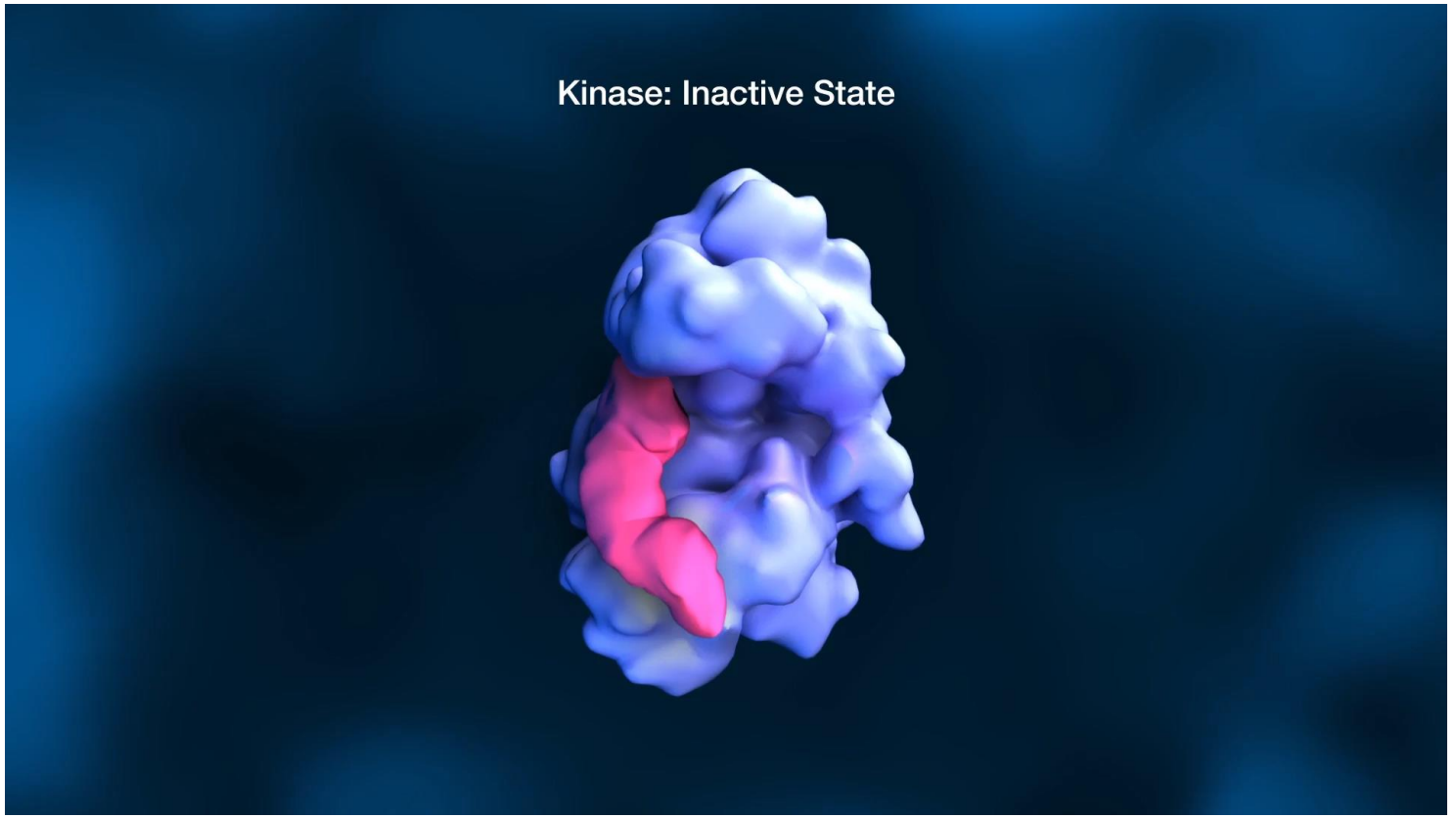
INTRIGUE
2nd-line

Janku et al, European Journal of Cancer 2016, Vol. 69, S1 pS4

INVICTUS:
A Phase 3, interventional, double-blind, placebo-controlled study to assess the safety and efficacy of ripretinib (DCC-2618) in patients with advanced gastrointestinal stromal tumors (GIST) who have received treatment with prior anticancer therapies (NCT03353753)

Jean-Yves Blay, Steven Attia, Sebastian Bauer, Ping Chi, Gina D'Amato,
Suzanne George, Hans Gelderblom, Michael C. Heinrich, Robin L. Jones, Peter Reichardt, Patrick Schoffski, Cesar Serrano, John Zalcberg, Julie Meade, Kelvin Shi,
Rodrigo Ruiz-Soto, Margaret von Mehren

Ripretinib - Bindungsmechanismus



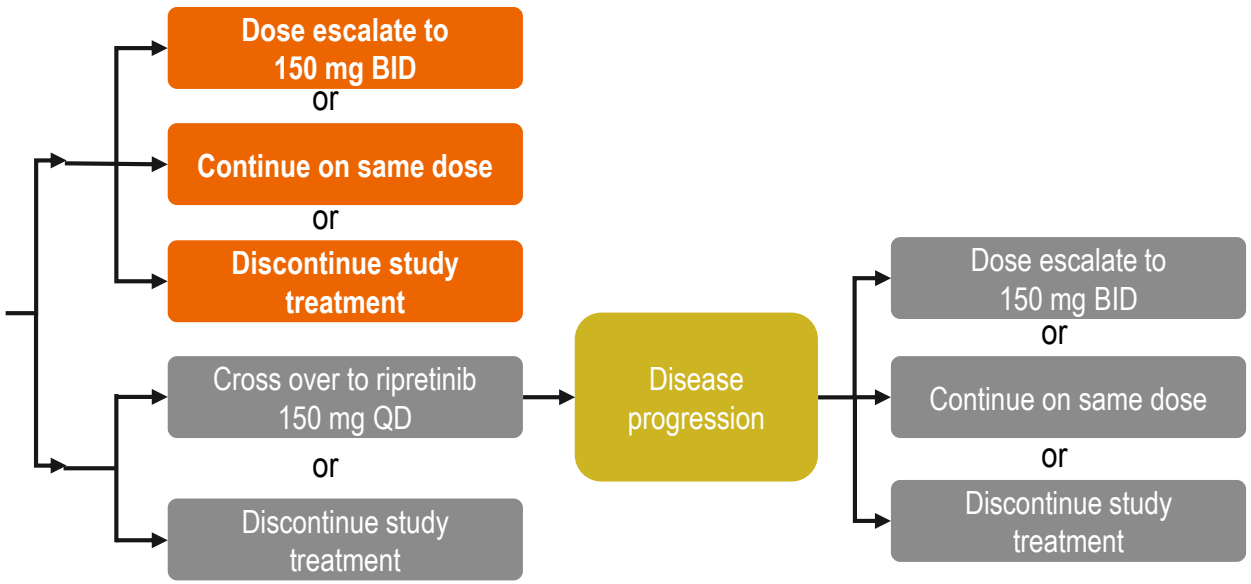
Smith BD, et al. *Cancer Cell*. 2019;35:738-751.

Evaluated ripretinib as ≥4th line therapy in patients with advanced GIST

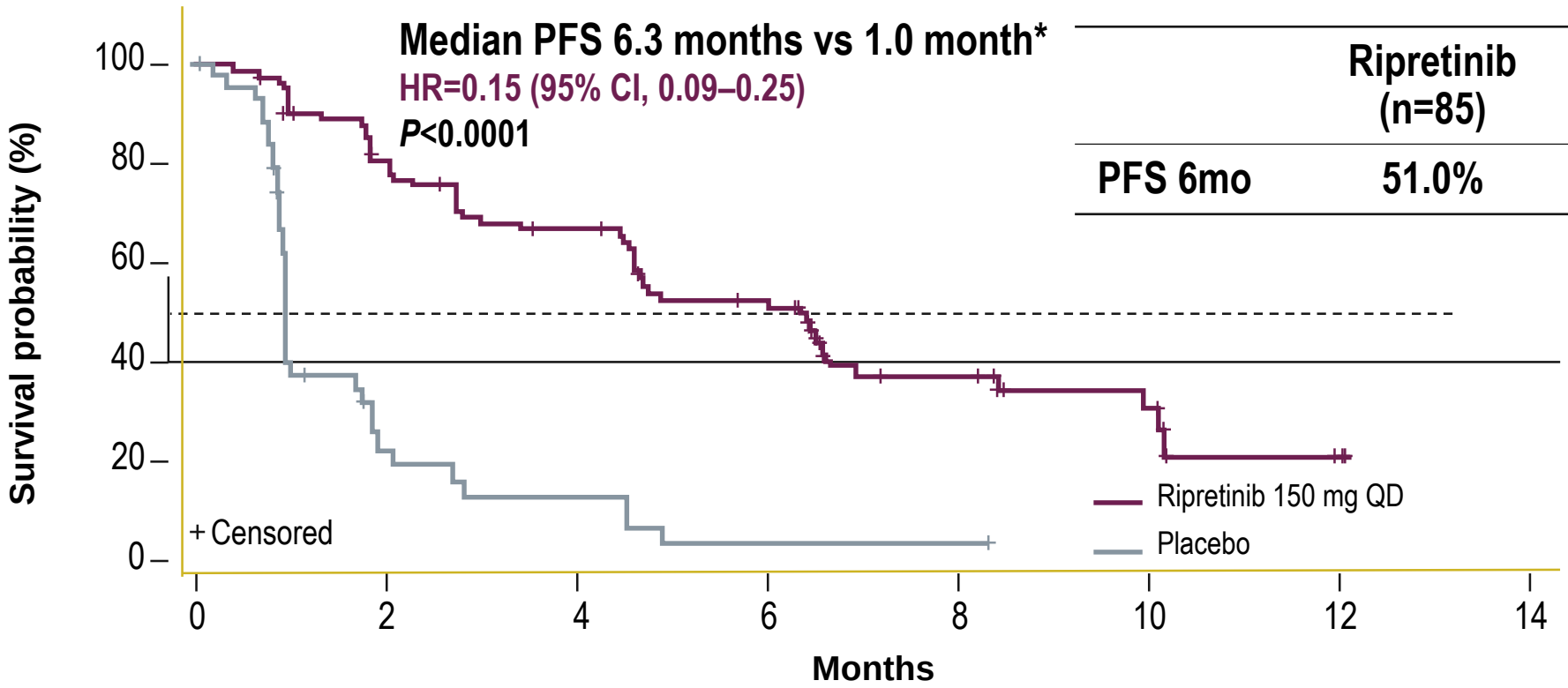
INVICTUS: Randomisierte Phase III-Studie

Ripretinib received (n=85)

Placebo received (n=43)



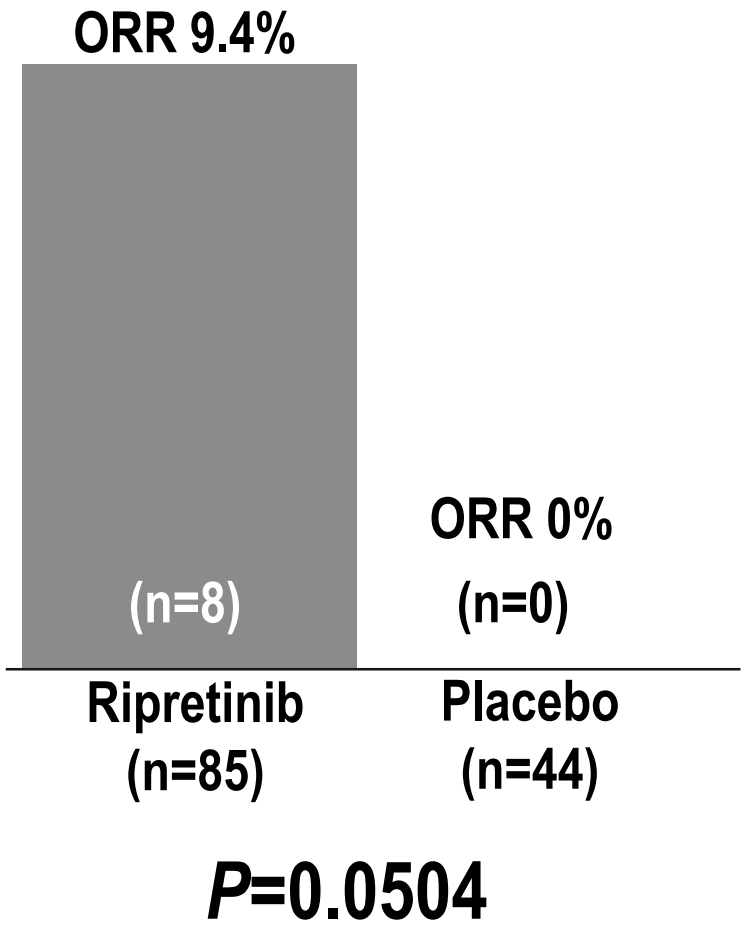
Ergebnisse INVICTUS

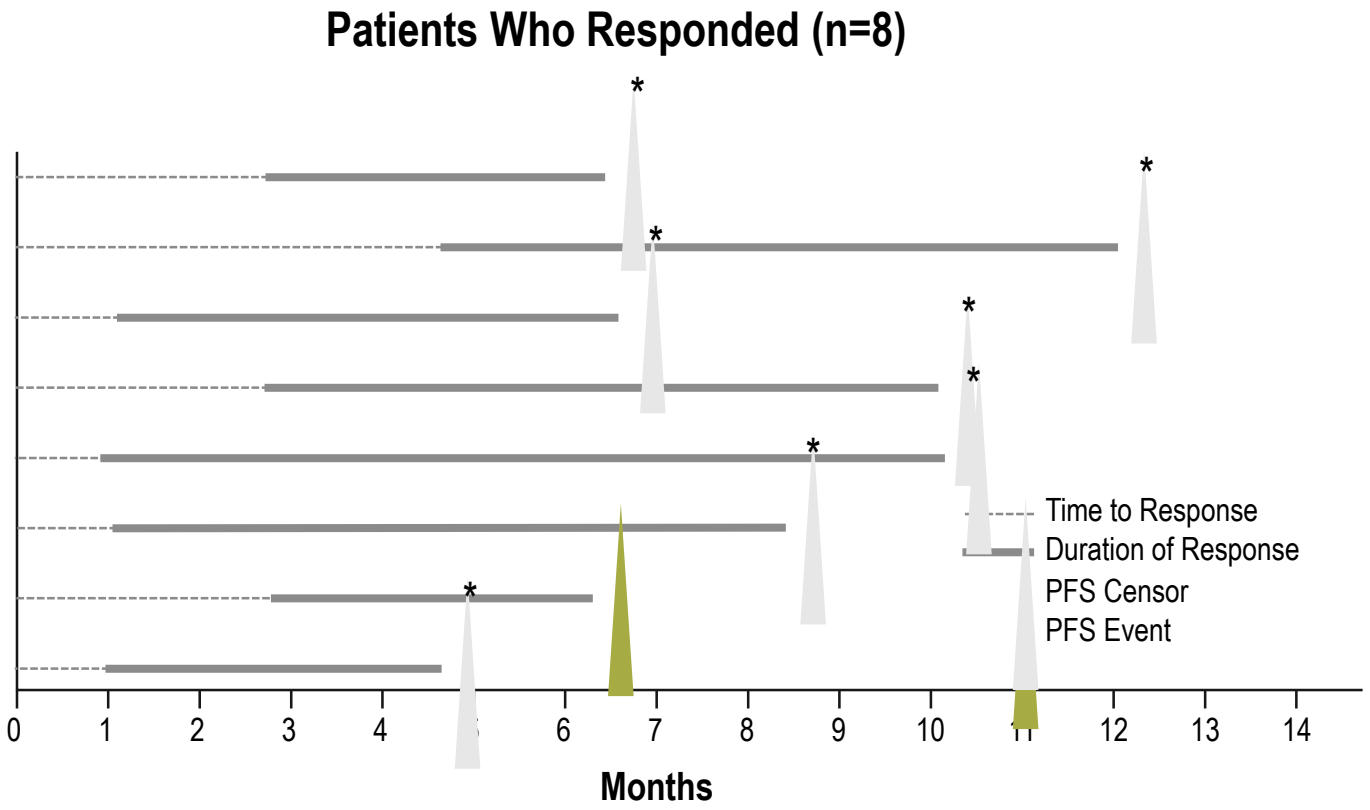


	Ripretinib (n=85)	Placebo (n=44)
PFS 6mo	51.0%	3.2%

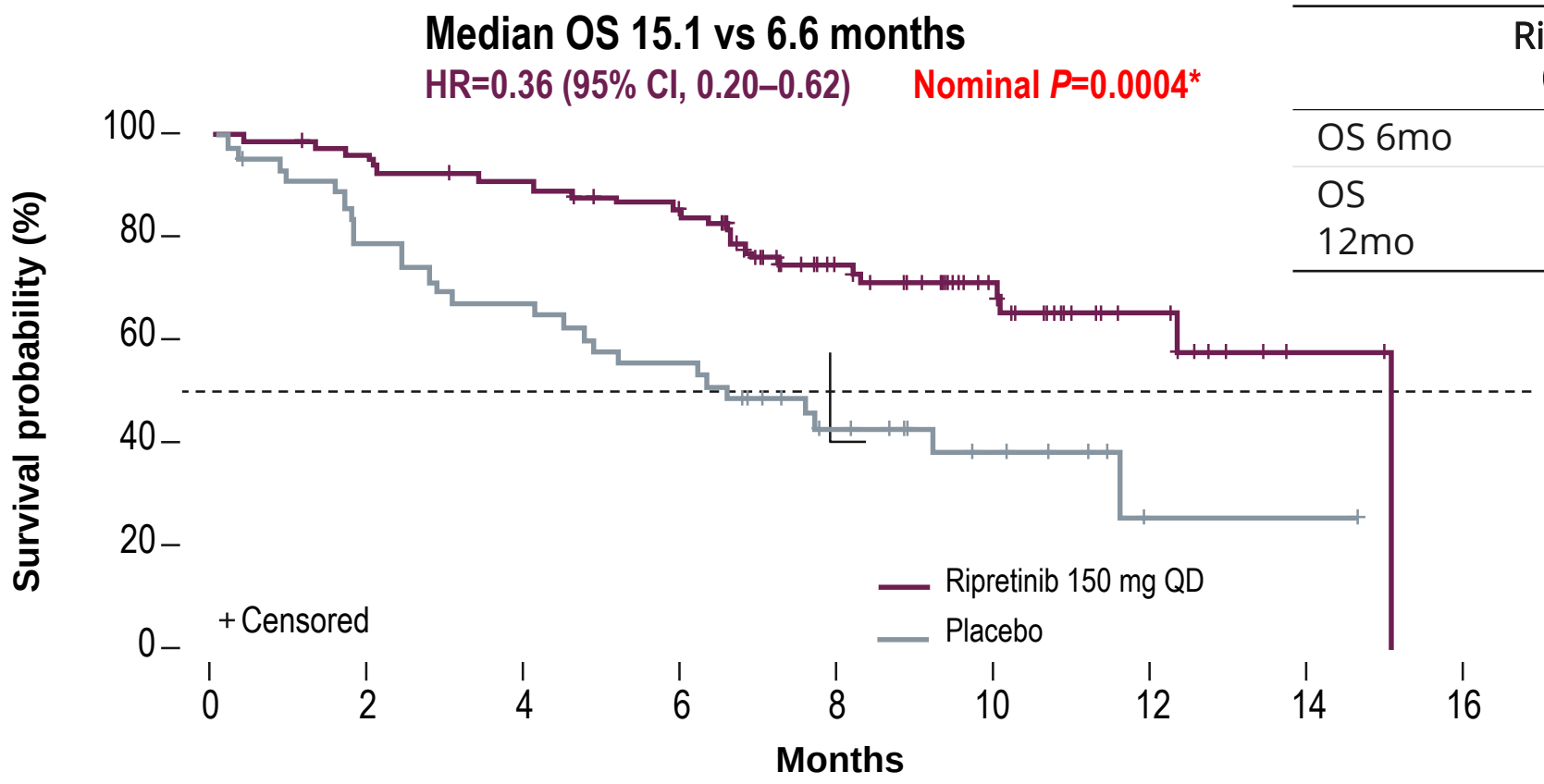
*Double-blind period.

Schrumpfungsrate Ripretinib (Remission)





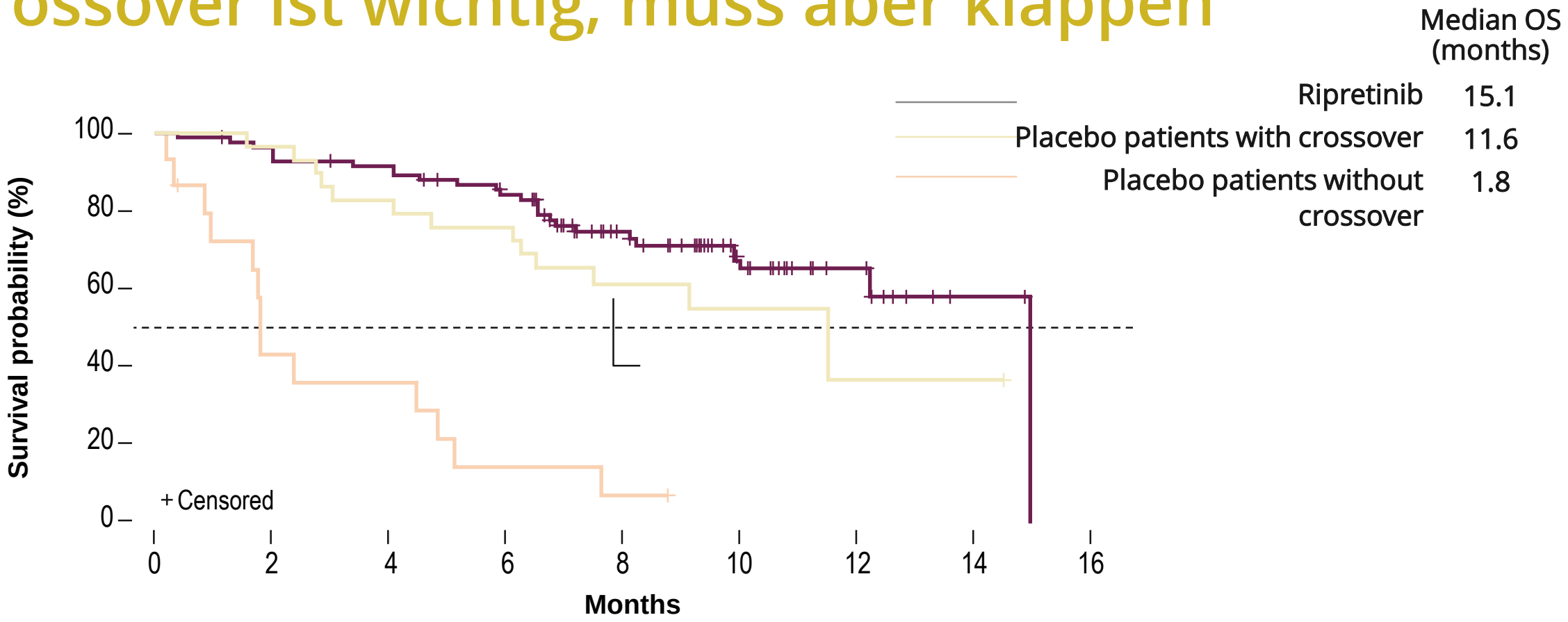
Überlebenskurve



	Ripretinib (n=85)	Placebo (n=44)
OS 6mo	84.3%	55.9%
OS 12mo	65.4%	25.9%

*Due to hierarchal testing procedures of the end points, the OS end point could not be formally tested because the ORR was not statistically significant.

Crossover ist wichtig, muss aber klappen



Bedeutung für zukünftige Studien?

Was sind die Nebenwirkungen? (ausgewählt)

		Ripretinib	Placebo
Häufig:	Haarausfall (mild)	52%	5%
	Fatigue (leicht)	42%	23%
	Übelkeit (leicht)	39%	12%
	Muskeklschmerzen (leicht)	32%	12%
	Durchfall (selten Erbrechen)	28%	14%
	Hand-Fuß-Syndrom	21%	0%
	Gewichtsverlust	19%	12%
	Mundschleimhautenzündungen	11%	0%
Schwerere Nebenwirkungen:		50%	44%
Nebenwirkungen mit Behandlungsabbruch:		8%	12%

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Newsroom

Currently Reading
FDA Approves Qinlock (Ripretinib) For Gastrointestinal Stromal Tumors
May 18, 2020 – Gianna Melillo

Study Describes Use of Liquid Biopsy in Patients With Solid Tumors
May 15, 2020 – AJMC Staff

What We're Reading: Trump to Revamp National Stockpile; NIH

Newsroom – Published on: May 18, 2020

FDA Approves Qinlock (Ripretinib) For Gastrointestinal Stromal Tumors

Gianna Melillo

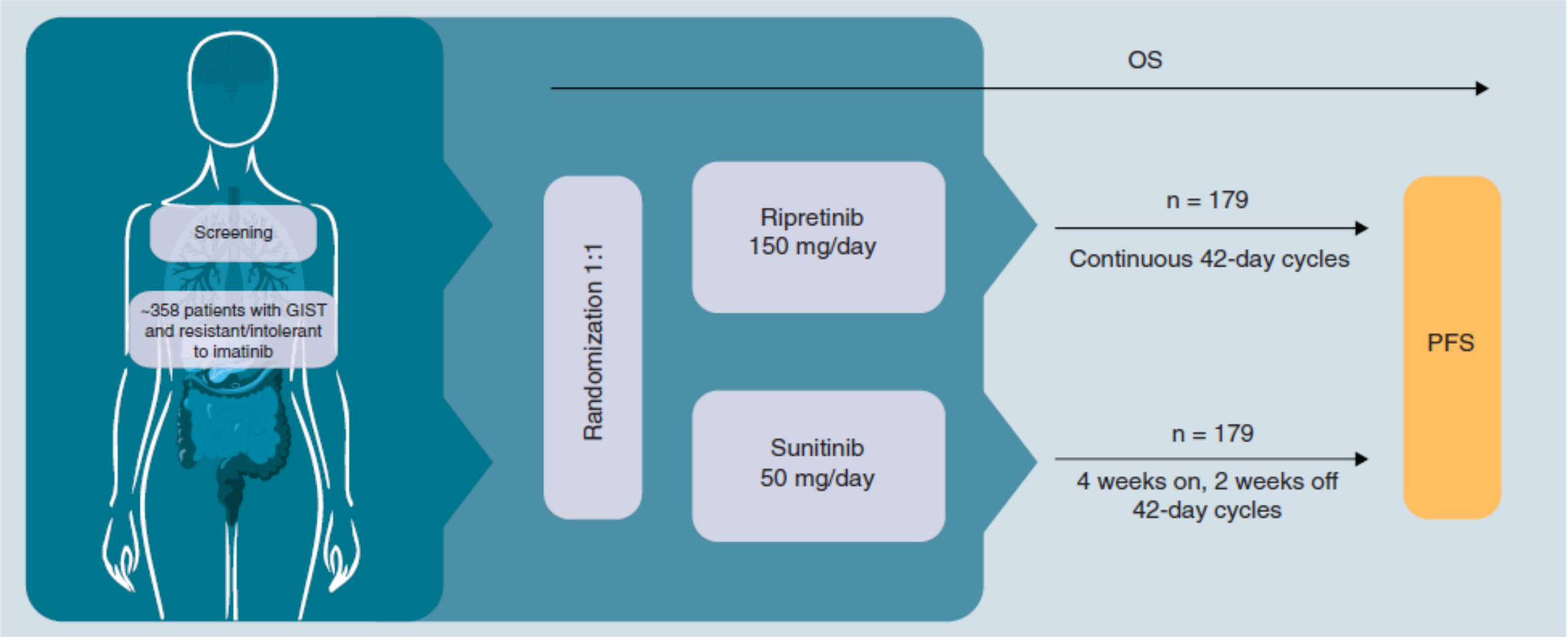
The FDA approved Deciphera Pharmaceuticals' ripretinib (Qinlock), the first drug for fourth-line treatment of advanced gastrointestinal stromal tumors (GISTs). The medication is only indicated for adults who have previously received treatment with 3 or more kinase inhibitor therapies, including imatinib.

The FDA recently approved Deciphera Pharmaceuticals' ripretinib (Qinlock), the first drug for fourth-line treatment of advanced gastrointestinal stromal tumors (GIST). The medication is only indicated for adults who have previously received treatment with 3 or more kinase inhibitor therapies, including imatinib.

Between 4000 to 6000 adults are diagnosed with a GIST in the United States each year. The tumors occur when abnormal cells form in gastrointestinal tract tissues. Although GISTs are most common in the stomach, small intestine, and large intestine, the tumors can originate in any place along the gastrointestinal tract.

Over the past 20 years, the FDA approved targeted therapies imatinib, sunitinib, and

Ripretinib in der Zweitlinien-Therapie



Approaching cure? Novel KIT/PDGFRA inhibitors

Response rates in imatinib-resistant GIST

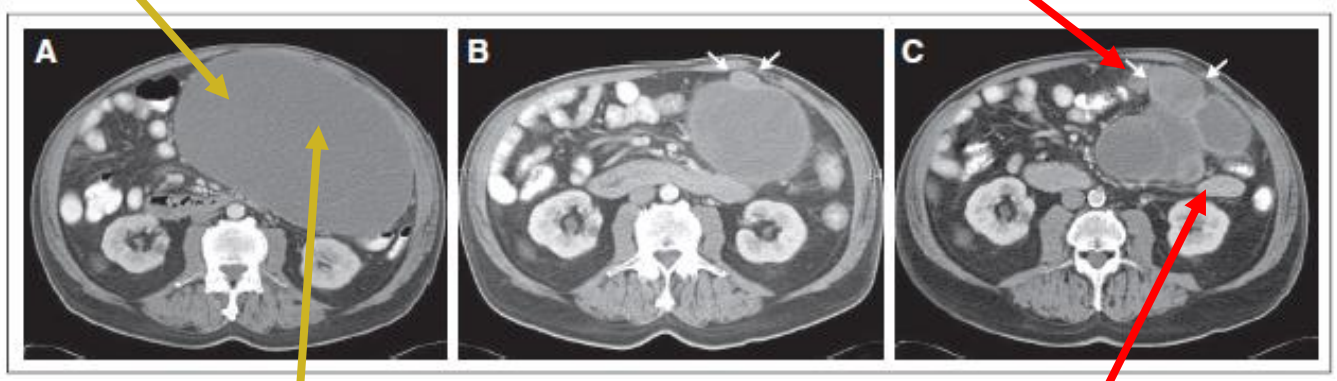
Drug name	Line of treatment	ORR	Ref	
Sunitinib	2	7%	Demetri and colleagues[61]	6.2 mo
Regorafenib	3	5%	Demetri and colleagues[64]	4.8 mo
Ripretinib	2	18%	George and colleagues[74]	9.6 mo
Ripretinib	3	24%	George and colleagues[74]	
Ripretinib	⩾4	9%	George and colleagues[74]	6.0 mo
Avapritinib	3/4 regorafenib-naïve	26%	Heinrich and colleagues[75]	8.6 mo
Avapritinib	⩾4	20%	Heinrich and colleagues[75]	3.7 mo
ORR, overall response rate.				
Cabozantinib	**3**	**7%**	**Schöffski**	**5.5mo**

Ther Adv Med Oncol
2019, Vol. 11: 1–13

KIT / PDGFRA sind nicht das einzige Problem…

hzg KIT ex 11: E554_V559del

KRAS G12R



hzg PTEN C124S missense mut

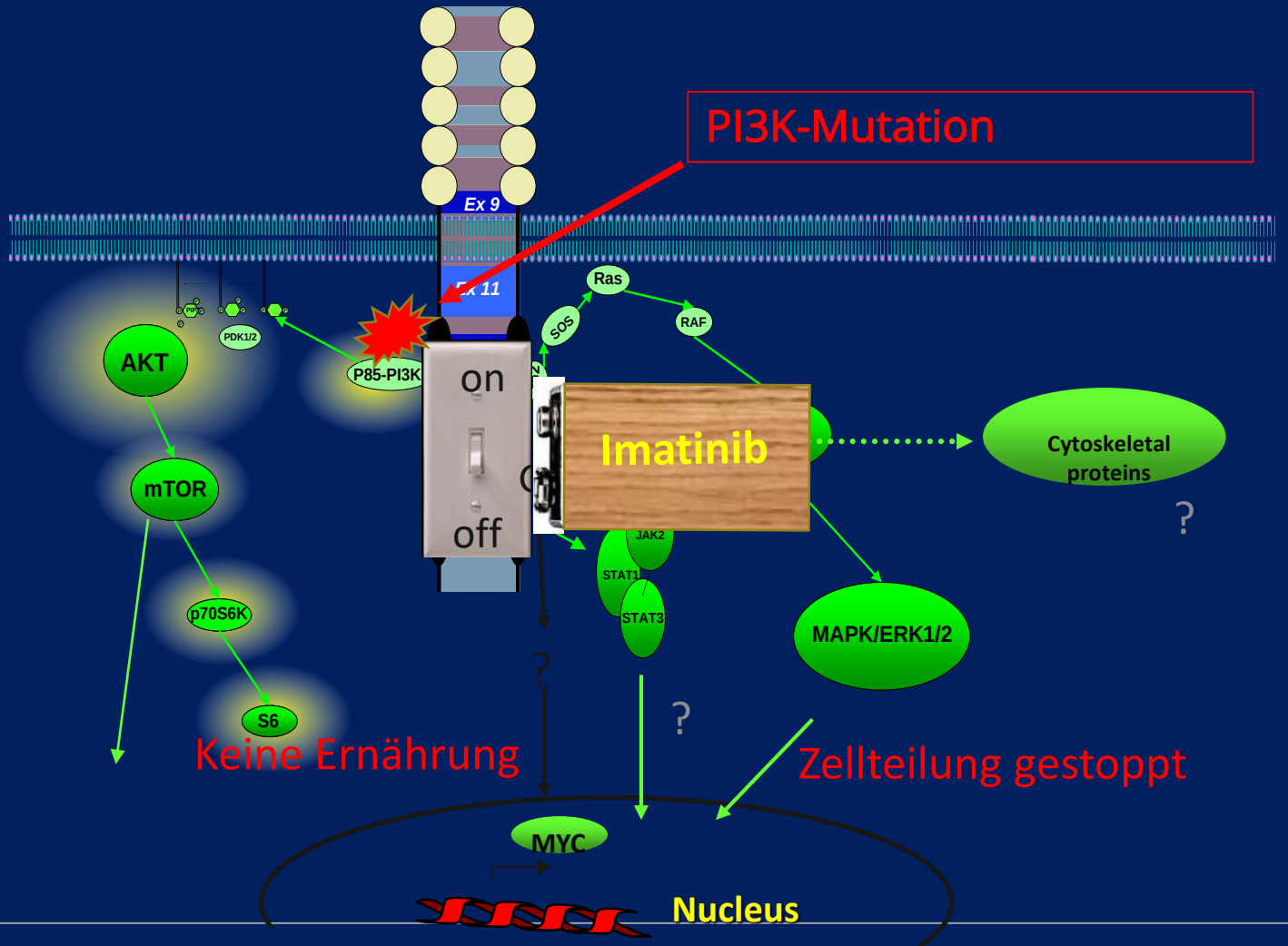
KIT T670I

Patient	Gene	AA-change	AF [%]	KIT/PDGFRA mutation
1	AKT3	F27I	13	PDGFRA – D842V + V658A
2	BRAF	V600E	60	WT
3	BRAF	V600E	32	WT
4	KRAS	G13D	36	KIT – e11 + N822K
5	PIK3CA	H1065Y	33	KIT – e11 + N822K
6	PIK3CA	H1047R	21	KIT – e11
7	PIK3CA	H1047R	81	KIT – e11
8*	NF1	M1981V	5	KIT – e11 + Y823E
9*	NF1	I719fs	32	KIT – e11 + D820Y + A829P
10	PTEN	I122S	78	KIT – e11
11	TSC1	E479del	46	PDGFRA – D842V
12	TSC2	A1719T	58	PDGFRA – D842V

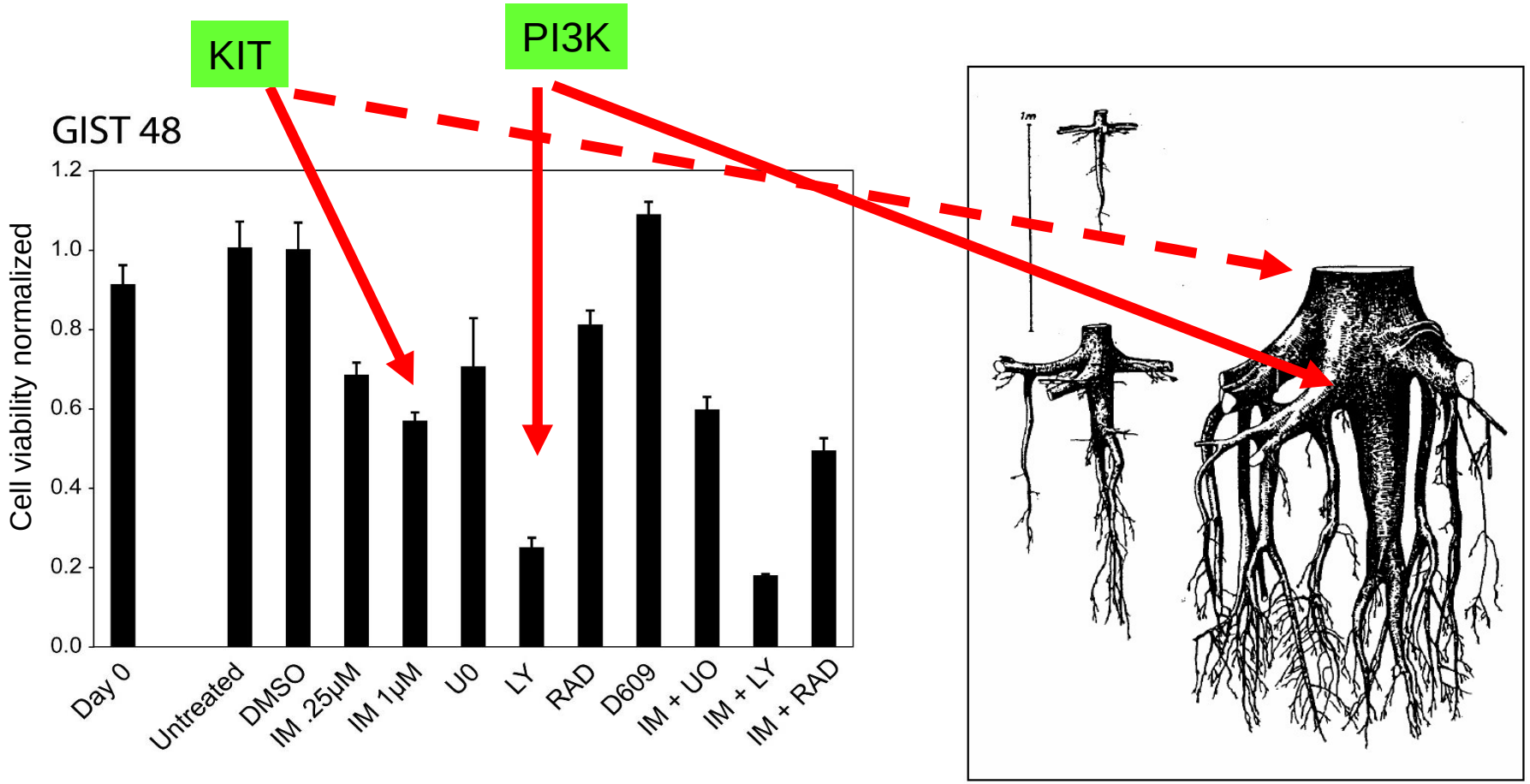
Serrano et al J Clin Oncol. 2015 Aug 1;33(22):e93-6

Mühlenberg, Mol Cancer Ther. 2019 Jul 15 epub ahead

Resistenz UNABHÄNGIG von KIT



Angriff auf die KIT-Botenstoffe!
PI3K und MEK-Inhibitoren als Kombinationswirkstoffe?



Imatinib-resistant GIST

Bauer / Fletcher et al, Oncogene 2007 26:7560-8

A phase II study of MEK162 (binimetinib [BINI]) in combination with imatinib in patients with advanced gastrointestinal stromal tumor (GIST)

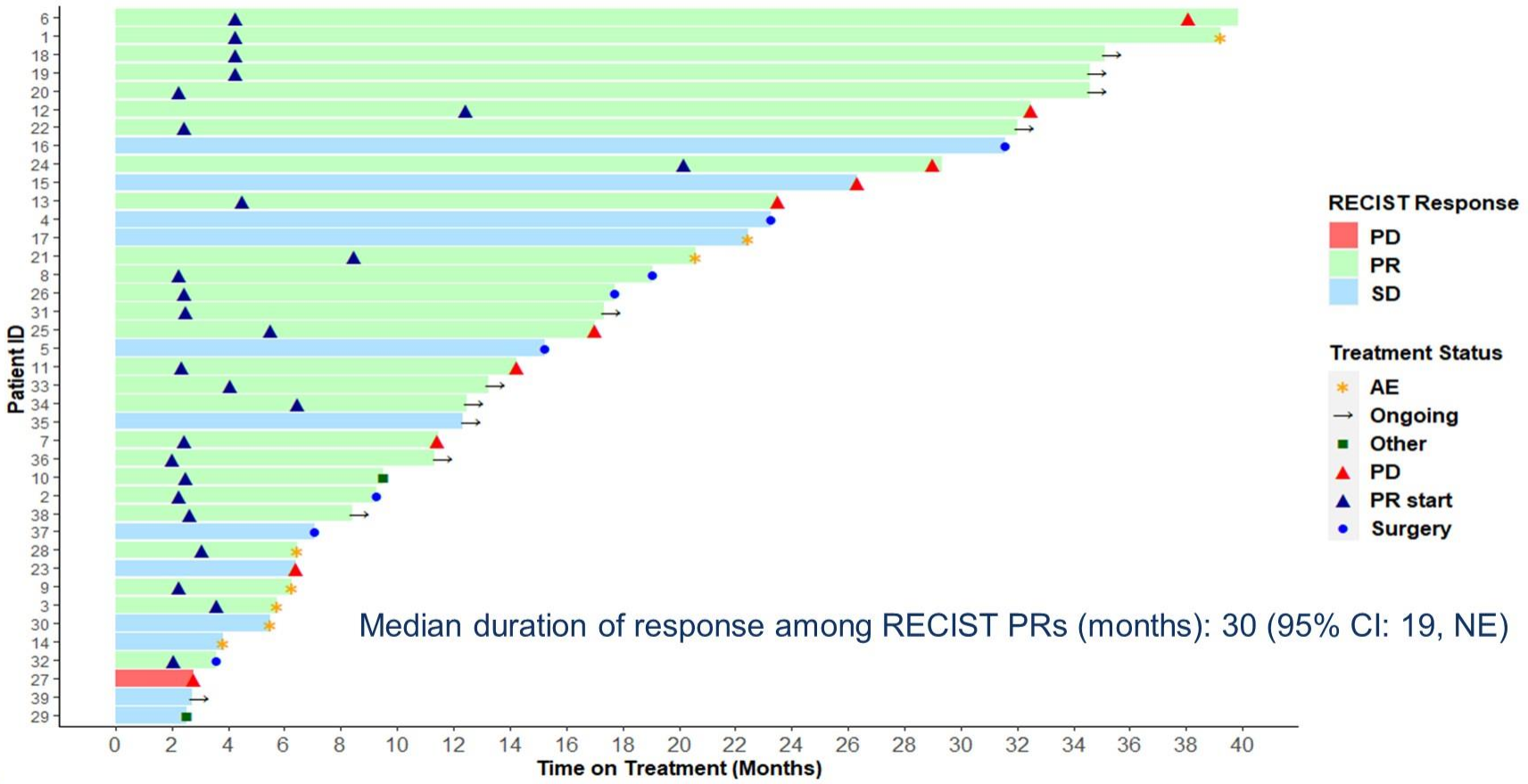
Ping Chi, Li-Xuan Qin, Ciara Kelly, Sandra P. D'Angelo, Mark A. Dickson, Mrinal Gounder, Mary L. Keohan, Sujana Movva, Benjamin A Nacev, Aimee Crago, Sam Yoon, Gary Ulaner, Moriah Martindale, Kashfia N. Haque, Mercedes M. Condy, Haley T. Phelan, Matthew D. Biniakewitz Samuel Singer, Sinchun Hwang, Cristina R. Antonescu, William D. Tap

Memorial Sloan Kettering Cancer Center

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: Ping Chi, MD, PhD

Duration of Responses



Median duration of response among RECIST PRs (months): 30 (95% CI: 19, NE)

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: Ping Chi, MD, PhD

Resistance Mechanisms

Patient ID	Treatment duration (wks)	Best RECIST response	MSK-IMPACT	
			Diagnosis	Progression
27	11	+27.1%	NF1 exon36 p.L1587*; NF1 exon37 p.T1646fs*52 (sporadic)	NF1 exon36 p.L1587*; NF1 exon37 p.T1646fs*52 Primary resistance
23	26	+11.4%	KIT exon9 p.A502_Y503dup; SETD2 exon12 p.W2016*	KIT exon9 p.A502_Y503dup; SETD2 exon12 p.W2016*; MED12 exon3 p.E79D; CSDE1 exon20 p.M829I
7	46	-36.5%	KIT exon9 p.A502_Y503dup; MGA exon4 splicing variant p.G698fs; RB1 deep del	KIT exon9 p.A502_Y503dup; MGA exon4 splicing variant p.G698fs; CDKN2A/2B deep del
11	57	-61.0%	KIT exon11 p.W557_K558del; CDKN2A/B deep del; TEK deep del; NKX2-1 deep del; TSC1 exon6 p.T130Rfs*22	KIT exon11 p.W557_K558del; KIT exon17 p.N822K; CDKN2A/B deep del; TEK deep del; TSC1 exon8 splicing variant p.X246_splice
25	68	-30.7%	KIT exon11 p.Q556_I571del; RB1 exon22 p.V742F	KIT exon11 p.Q556_I571del; KIT exon13 p.V654A; RB1 deep del
13	94	-50.0%	KIT exon11 p.V559A; CDKN2A/B deep del	Not available
15	105	-13.3%	KIT exon11 p.E554_K558del; CDKN2A/B/C deep del	KIT exon11 p.E554_K558del; KIT exon13 p.V654A; CDKN2A/B/C deep del; NCOR1 exon37 p.Y1814*
24	117	-31.1%	KIT exon11 splicing variant p.X550_splice; KIT exon11 p.P551_K558delinsQ; CDKN2A/B del	KIT exon11 splicing variant p.X550_splice; KIT exon11 p.P551_K558delinsQ; KIT exon17 p.N822K; CDKN2A/B del; MAX del
12	130	-30.4%	KIT exon11 p.E562_L576del; CDKN2A del	Not available
6	159	-58.8%	KIT exon11 p.W557_K558del; CDKN2A/B deep del	KIT exon11 p.W557_K558del; KIT exon13 p.V654A; CDKN2A/B deep del

11536: Lower-dosing ponatinib in pre-treated GIST: Results of the POETIG phase II trial

Authors: Johanna Falkenhorst1,2, Rainer Hamacher1,2, Peter Reichardt3, Anja Selig3, Philipp Ivanyi4, Bernd Kasper5, Peter Hohenberger10, Barbara Hermes6, Karina Kostbade1,2, Daniel Pink7, Heiko Suelberg8, Martin Metzenmacher 2, Martina Crysandt9, Sebastian Bauer1,2

1: Sarcoma Center, West German Cancer Center, University Hospital Essen, Germany; 2: Sarcoma Center, Medical Oncology, University Hospital Essen, Germany; 3: Sarcoma Center, Helios Klinikum Berlin Buch, Berlin, Germany; 4: Department for Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany; 5: Sarcoma Unit, Interdisciplinary Tumor Center, Mannheim University Medical Center, Mannheim, Germany; 6: Center for Soft Tissue Sarcoma, GIST and bone sarcoma, University Hospital Tübingen, Tübingen, Germany; 7: Sarcoma Center Berlin-Brandenburg, Helios Klinikum Bad Saarow, Bad Saarow, Germany; 8: X-act Cologne Clinical Research GmbH, Cologne, Germany, 9: Medizinische Klinik IV, University Hospital Aachen, Aachen, Germany; 10: Div. of Surgical Oncology & Thoracic Surgery, Medical Faculty Mannheim, University of Heidelberg

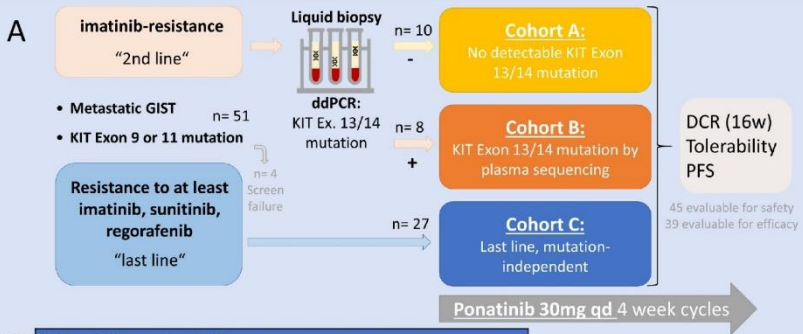
Background:

- Metastatic gastrointestinal stromal tumors (GIST) eventually progress during imatinib treatment.
- Subsequent treatments are associated with limited duration of disease control.
- Ponatinib: KIT inhibitor with a strong activity against secondary mutations in exon 17, including the highly resistant D816 mutations of KIT.
- Doses of 45mg led to cardiovascular and pancreatic AEs in previous trials including ALL and CML patients.

Methods:

- Investigator-initiated multicenter single-arm phase 2 trial conducted in Germany (NCT03171389) evaluating safety and activity of lower-dosing ponatinib in GIST patients (Figure 1)

A



B

Patient Characteristics		
Age	Median:	60 years (38-86)
Gender	Male:	27 (60 %)
	Female:	18 (40 %)
Primary Tumor localization	Gastric:	11 (24.4 %)
	Sm. intestine:	26 (57,8 %)
	Rectum:	1 (2.2%)
	Other:	1 (2.6%)
	unknown:	6 (13.3 %)
No of pre-treatments (Cohort C)	Median	4 (3-5)

Figure 1: Methods A: study flowchart – second and last line patients were included, 2nd line was divided by detection of KIT exon 13/14 mutations in plasma by ddPR. Ponatinib was administered orally 30mg qd **B: Patient characteristics.**

Conclusions:

Lower-dosing **ponatinib (30mg qd)** in metastatic GIST patients was **tolerable,** led to a median **PFS of 15.6 weeks (last line)** and **long-lasting disease control** in a subset of patients.

Future Directions for Research:

Characterize long-term responders for better patient selection

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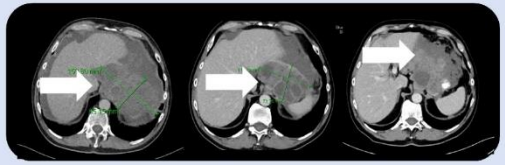
Interim Results (Figure 2, cut-off 30th of April 2020):

Figure 2: A: Adverse events (AEs) grades 3/4, severe adverse events (SAEs) and thrombembolic events Grade 3/4 (one case of myocardial infarction, rated not related) in all cohorts. **B: CT scans of Patient treated in cohort B**: 68-year old male patient with peritoneal metastasis showing long-term disease control (60w). **C: Kaplan Meier Curve**: median PFS depicted and written below. **D: Waterfall plots** (RECIST response) at 16 weeks divided by cohorts.

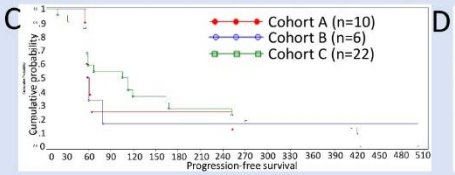
A

Adverse Events	No.	%
Patients with AEs Grade 3/4	30	66.7
AEs Grade 3 occuring in >10% of patients		
GGT increase	6	13.3
Hypertension	7	15.6
Lipase increase	6	13.3
Pain	10	22.2
AEs Grade 4		
Anemia	1	2.2
Depression	1	2.2
Vomiting	1	2.2
SAE	22	48.9
Thrombembolic events Grade 3/4	1	2.2

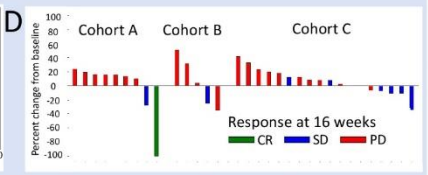
B



C

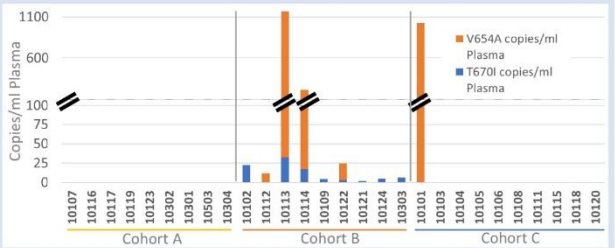


D



Median progression-free survival (interim analysis): Cohort A (n=10): 59.5 (57-158.5) days; Cohort B (n=6): 59 (57-79) d; Cohort C: 109 (57-252) d (25%-75% quantile)

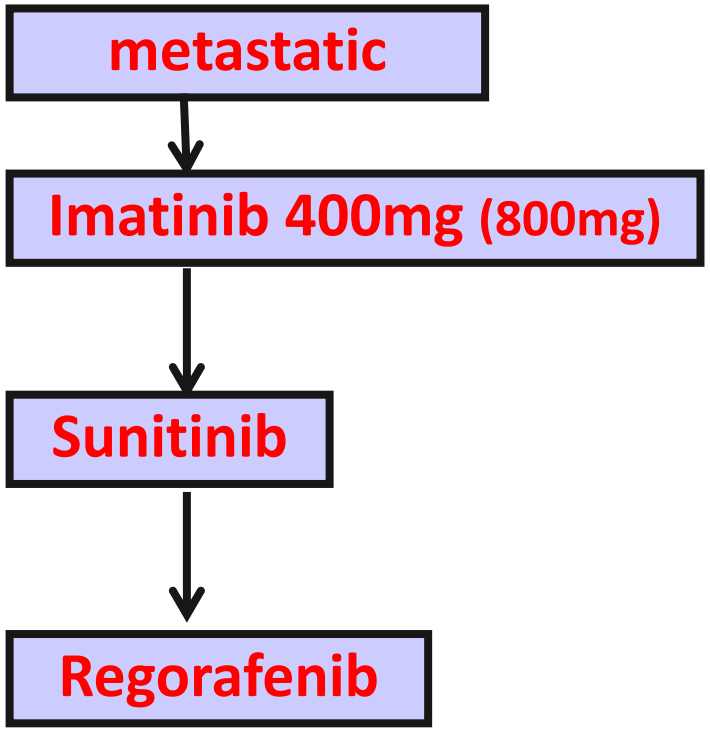
Figure 3: Droplet digital PCR (ddPCR) results for specific KIT mutations in Exon 13 (p.V654A) and 14 (p.T670I) in a subset of patients.



Zusammenfassung

- Resistenz betrifft die meisten Patienten mit GIST
- Avapritinib ist der neue Standard für Patienten mit GIST und PDGFRA D842V-Mutation (aktuell nur CUP)
- Ripretinib (INVICTUS TRIAL) ist der neue Standard aber der Viertlinien-Therapie (EAP bald verfügbar)
- Aktuelle klinische Studien: INTRIGUE in der zweiten Therapielinie (nach Imatinib-Versagen)
- CRENOGIST-Studie bei D842V GIST
- KIT-unabhängige Resistenz wird wichtiger werden mit besseren KIT-Inhibitoren
- Molekularpathologie wird immer wichtiger um die Resistenz zu verstehen, Kombinationen kommen

Trials: KIT/PDGFRA in 2020



1st line

2nd line

3rd line

4th line

>4th line

localized

PDGFRA D842V: CRENOGIST

SSG XXII:
Imatinib 3 vs 5 years
(HR-Patienten)

Intrigue: Ripretinib vs Placebo (Phase III)

COMPASS?

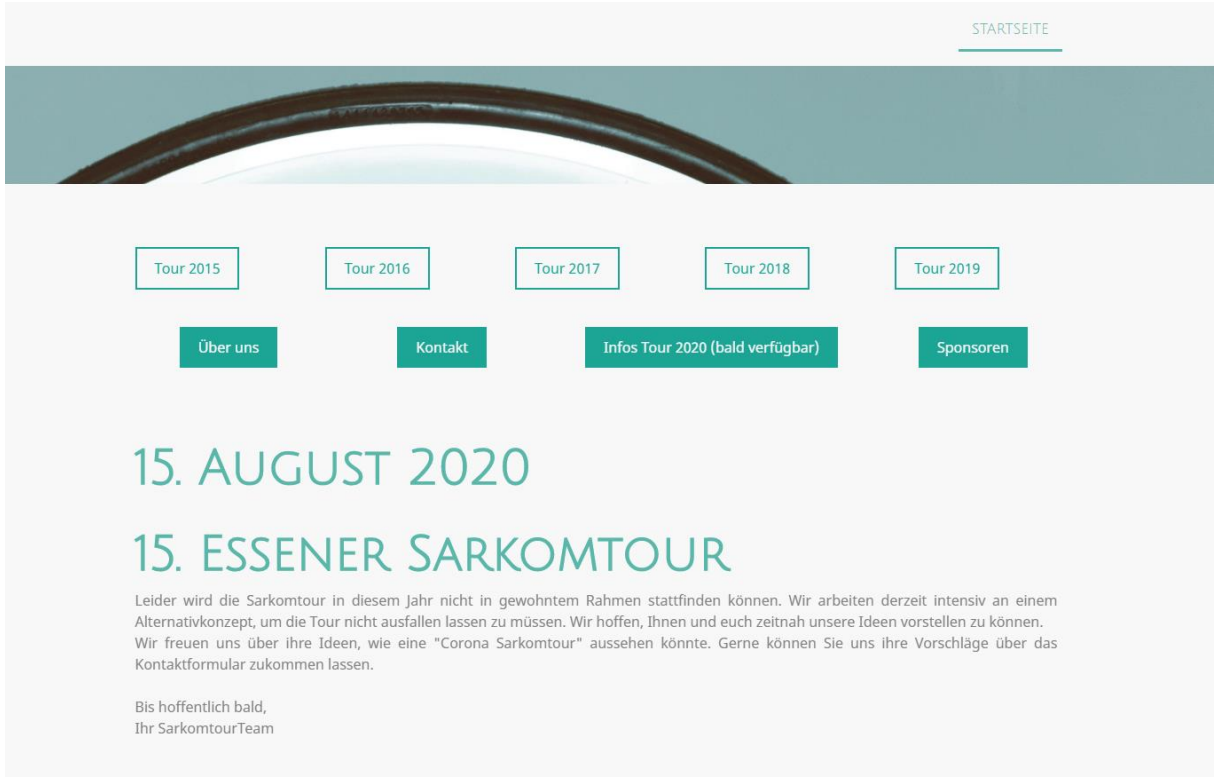
Avapritinib Compassionate Use Programm

Ripretinib Compassionate Use Programm

Westdeutsches Tumorzentrum

Deutsche Sarkomstiftung

Stiftung Universitätsmedizin



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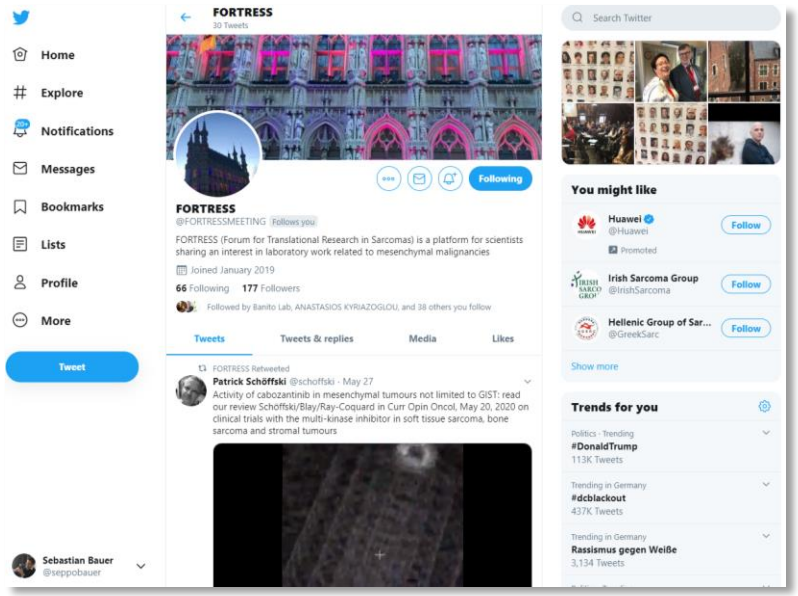
- The FORTRESS-experiment



Austausch, Infrastruktur, Seed-Funding