

WELCOME to “NEW HORIZONS GIST”
WELCOME at SPAEN “Sarcoma Patients EuroNet” ...

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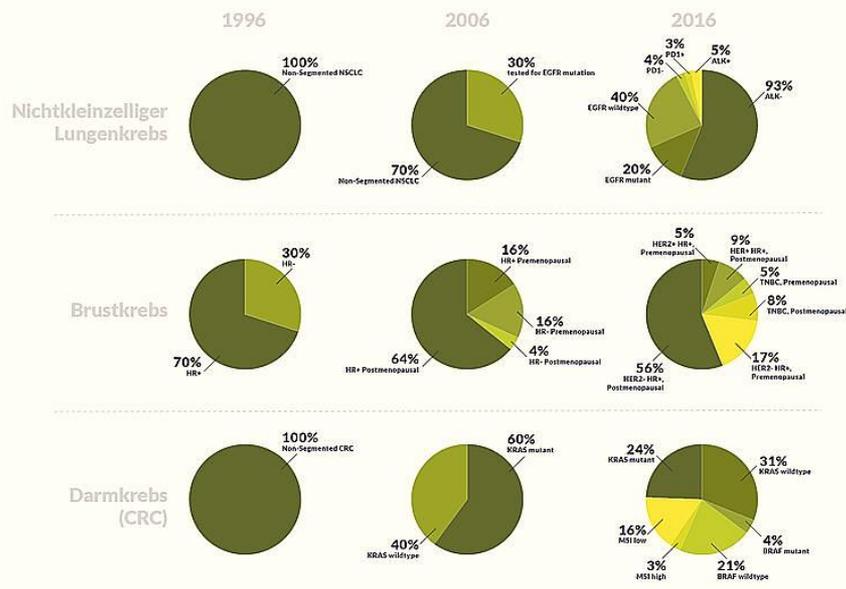
After 18 years a dinosaur in patient advocacy...

- **With NEW HORIZONS GIST right from the start**
- **2003 – 2019 Patient Organization in Germany**
Das Lebenshaus e.V. GIST/Sarcoma
- **Since 1/2020 = Successor – Deutsche Sarkom-Stiftung**
(German Sarcoma Foundation) - Vice-Chair of the Board
- **2009 Co-Founder SPAEN Sarcoma Patients EuroNet e.V.**
Co-Chair with Gerard van Oortmerssen (NL) + fantastic Board/Team
- **“National Center of Cancer Research (NCT)” in Germany:**
Chair of the Patient Advisory Board



Mutation matters - the mutation makes the difference...

Personalized medicine: Therapies are becoming more individual, more targeted



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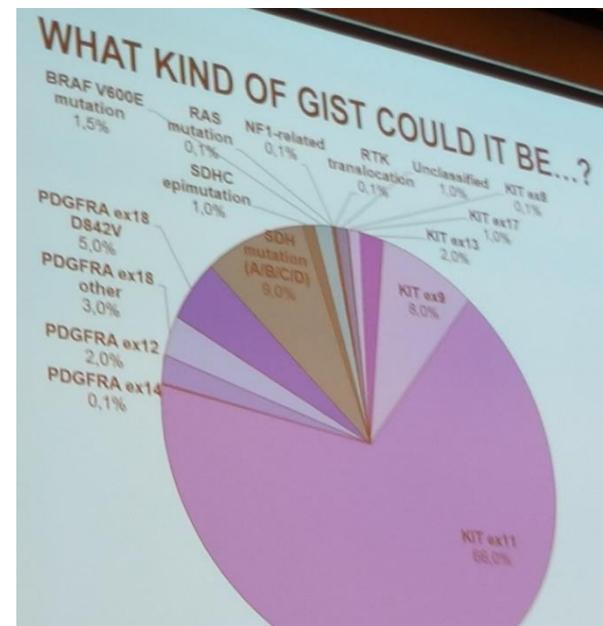
Quelle: DKG FORUM Mai 2017 | Jg. 32 | Nr. 03

Personalized Oncology Precision Oncology Tumor Agnostic Therapies

Mutation matters: Even rare ones are e.g. different...

Change in knowledge in almost 20 years – even in rare cancers such as GIST:

66,0%	KIT Exon 11 (Diverse)	
8,0%	KIT Exon 9	
2,0%	KIT Exon 13	
1,0%	KIT Exon 17	
0,1%	KIT Exon 8	
5,0%	PDGFR Exon 18 D842V	
3,0%	PDGFR Exon 18 (Diverse)	
2,0%	PDGFR Exon 12	
1,0%	PDGFR Exon 14	
9,0%	SDH Mutation (A/B/C/D)	
1,5%	BRAF V600E	(1,5% von 1.200 = 18)
1,0%	SDHC Epimutation	
1,0%	Unclassified	
0,1%	RAS-Mutation	
0,1%	NF1-related	
0,1%	RTK Translocation	



Quelle: CTOS 2019
Kohorte Heinrich/Corless

Prolog: Mutational Testing in GIST (1)

- **PATHOLOGISTS**
- **Determines the location of the mutation in the genes and in the receptor protein**
- **Important to assess the course of the disease / to make a decision for/against a therapy option**
- **Is carried out on the tumor tissue by pathologists**
 - **fresh tissue e.g. sample (biopsy) or surgery (resection)**
 - **tumor samples embedded in paraffin**
 - (...including older ones...)
 - (...in many pathological institutes for at least ten years...)
- **The expertise and experience of pathologists with mutational testing in GIST are very important!**



Prolog: Mutational Testing in GIST (2)

■ ONCOLOGISTS

It's not just nice to know the mutational status –
mutational status matters!

It determines the GIST-therapy in many cases...

“exon 11 mutation” respond well to imatinib

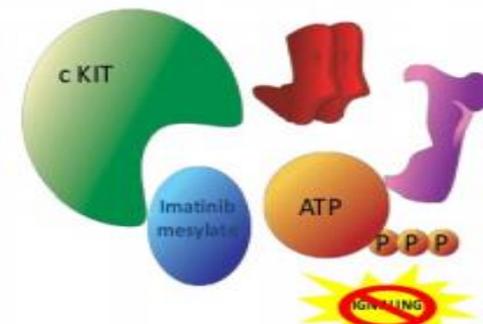
“exon 9 patients” should be treated with 800mg imatinib

GIST exon 18 D842V do not respond to imatinib

Avapritinib would be the choice of treatment...

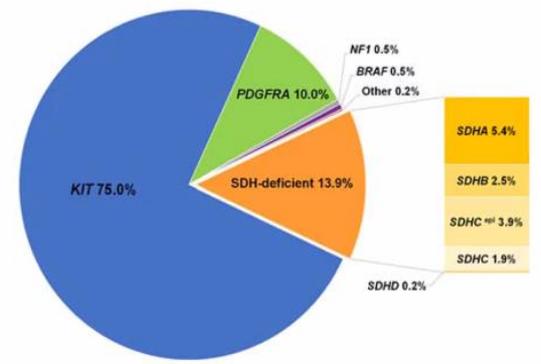
■ IN MANY COUNTRIES

- Mutation analysis part of optimal therapy management at GIST!
- Newly diagnosed patients in particular should find out about their primary mutation at the time of diagnosis
- But - we also know: There are big differences between countries (20/30% - 90%)



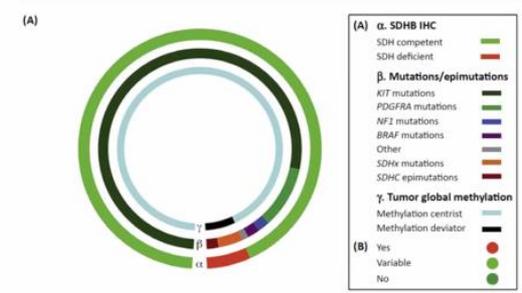


Frequency of SDH alterations in GIST



I. M. Schaefer et al. 2017 Adv. Anat. Pathol

Gastrointestinal Stromal Tumors (GISTs): Two Distinct Clusters



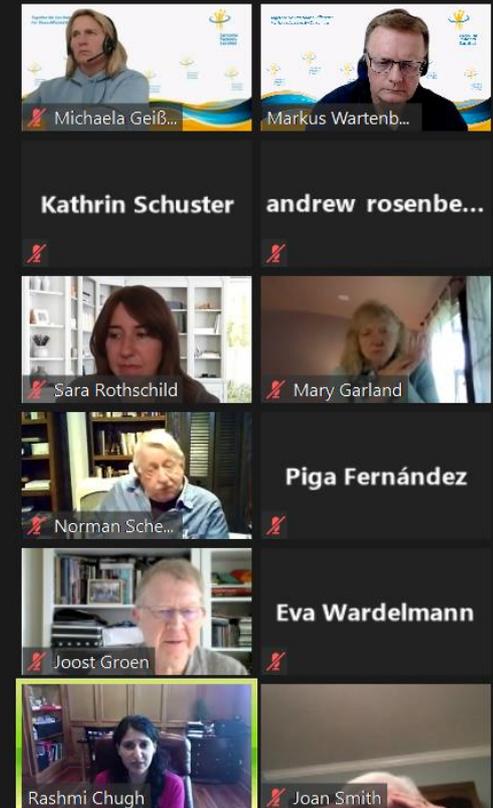
	SDH-competent GIST					SDH-deficient GIST	
	KIT	PDGFRA	NF1	BRAF	Other	SDHx	SDHCme
Median age <30 years	●	●	●	●		●	●
Female predominance	●	●	●	●		●	●
Gastric location	●	●	●	●		●	●
Multifocal lesions	●	●	●	●		●	●
Mainly epithelioid	●	●	●	●		●	●
Plexiform histology	●	●	●	●		●	●
Lymph node mets	●	●	●	●		●	●
Paragangliomas	●	●	●	●		●	●
Imatinib resistant	●	●	●	●		●	●

Mei et al. 2018 Cell Press Reviews

Primary GIST Mutations: Initial Management strategies

Mutation	Management
KIT Exon 11	Imatinib 400 mg daily
KIT Exon 9	Imatinib 400 mg daily (escalate to 800 mg as tolerated)
PDGFR α Exon 18 (D842V) *	Avapritinib
PDGFR α Exon 18 (non-D842V)	Imatinib
PDGFR α non-Exon 18	Imatinib
SDH deficiency *	VEGFR-directed therapies Sunitinib/Regorafenib
KIT Exon 13	Imatinib

Primary
mutation status
must useful to
recognize
Imatinib
Resistance*



Michaela Geiß... Markus Wartenb...

Kathrin Schuster andrew rosenbe...

Sara Rothschild Mary Garland

Norman Sche... Piga Fernández

Joost Groen Eva Wardelmann

Rashmi Chugh Joan Smith

Immunohistochemistry (IHC) vs. Mutational testing: Different tests, different questions, different answers

	Immunohistochemistry (staining for <u>KIT protein</u>)	Mutational testing (DNA sequencing of <u>KIT gene</u>)
Tests for:	expression of <u>KIT protein</u> by the tumour cells	mutations in the <u>KIT gene</u> in the tumour cell DNA
Tells us:	whether the tumour is a GIST (often, merely confirming the diagnosis)	whether the tumour is a <u>KIT-mutant</u> GIST (and, if so, identifies the mutation)*
Requires:	tumour sample (biopsy or surgery)	tumour sample (e.g., FFPE: Formalin-Fixed Paraffin-Embedded)
Performed by pathology lab?	always	sometimes; LRG strongly recommends that patients push to have mut. testing done!

9

Participants in the Zoom meeting:

- Michaela Geiß...
- Markus Warte...
- David Josephy
- Peter Reichardt
- Denisse Mont...
- Norman Sche...
- Joan Smith
- Zoltan Kalo
- Mary Garland
- Judith Robins...
- Laura Occhiuz...

