GIST: Progressive Disease

New Horizons GIST - Vienna/Austria
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GISTs are different…

- Age & co-morbidities
- Stage of diagnosis…
- Tumour burden (tumour mass)
- Location
- Tumour size
- Mitotic Count
- Primary Mutation (KIT, PDGFRA, Wild Type…)
- Metastasis (number, location…)
- Secondary Mutations
- Type of resistance?
- Role of the immune-system?

- Availability & quality of treatment! (e.g. tumour rupture)
- Therapy & side effect mgmt.

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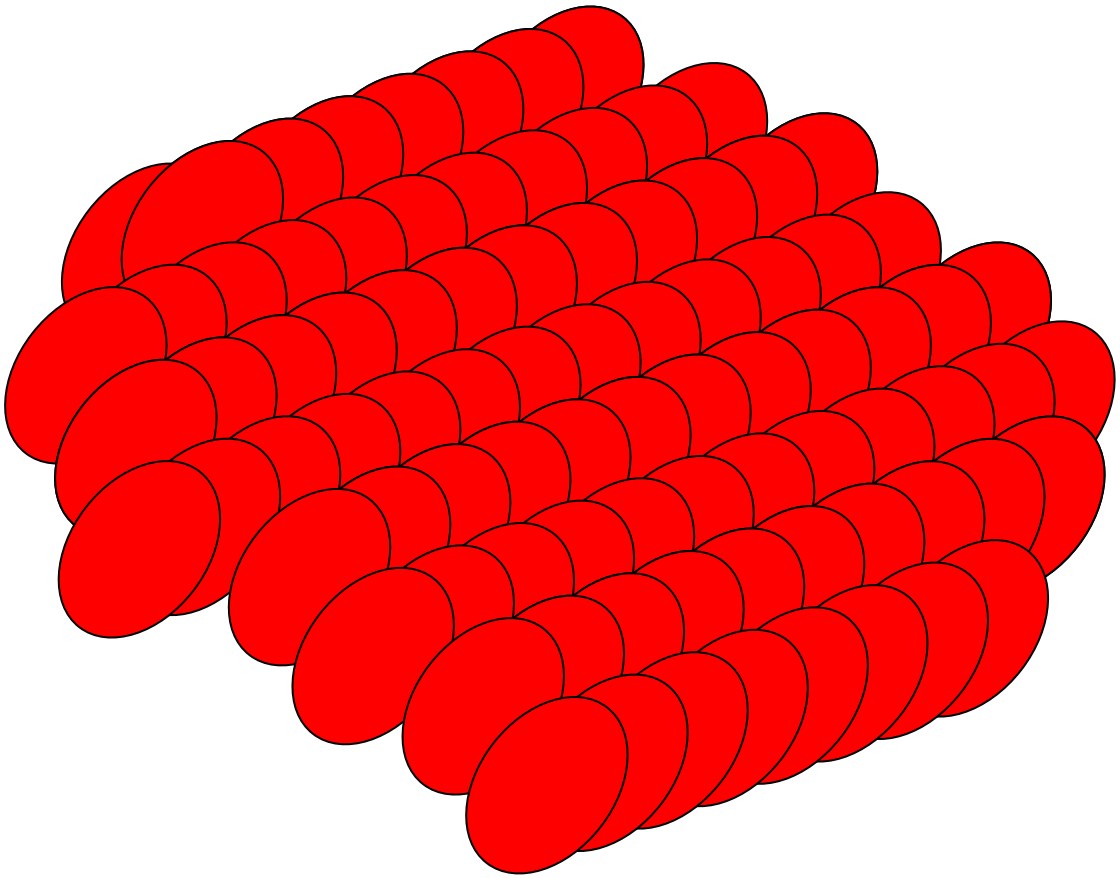
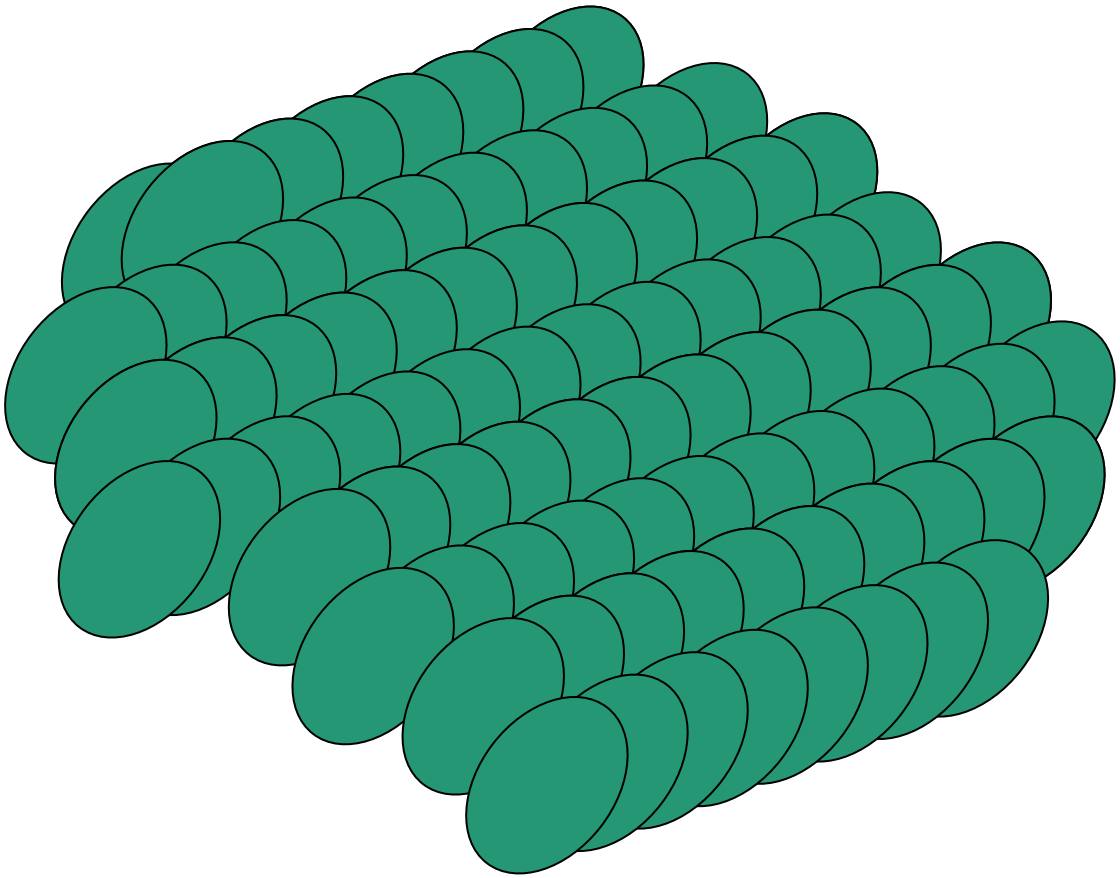
WHAT DOES PROGRESSION MEAN?





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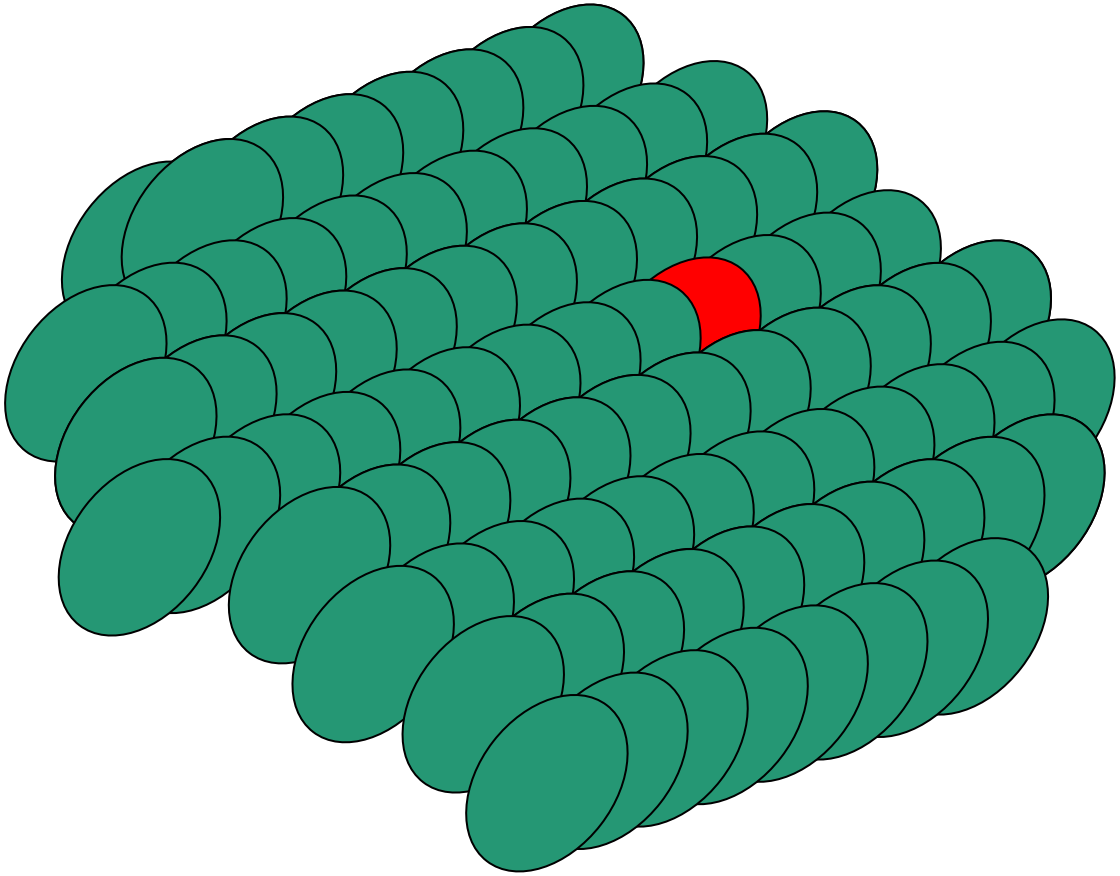
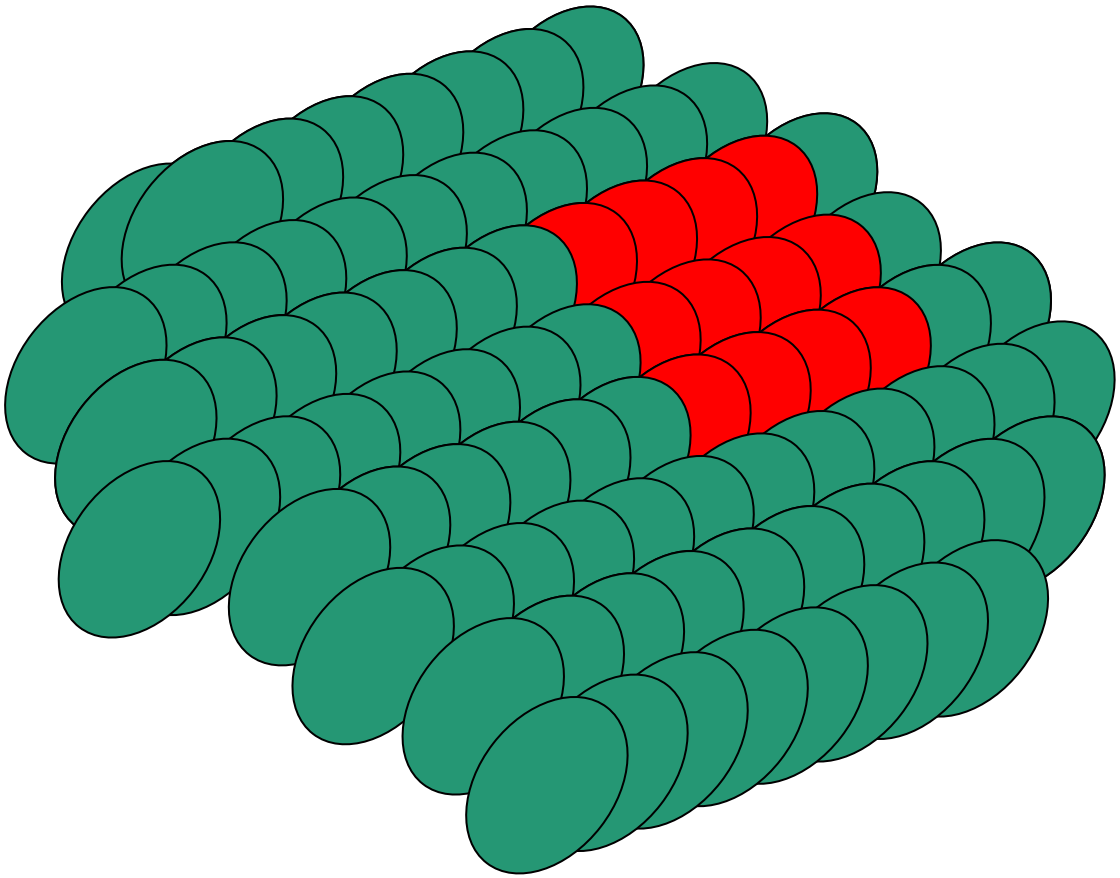
Approved targeted therapies for the treatment of GIST

- Research code:	STI-571 	SU 11248 	BAY 73-4506 
- Active agent:	imatinib (mesylate)	sunitinib (Malate)	regorafenib
- Product name:	Gleevec® / Gleevec™	Sutent®	Stivarga®
- Manufacturer:	Novartis	Pfizer	Bayer
- Approvals:	CML + rare cancers	Met. kidney cancer (mRCC)	Met., colon cancer (mCRC)
	adjuvant GIST therapy	Prog. NET of the pancreas	
	1st-line mets. GIST	2nd-line mets. GIST	3rd-line mets. GIST
- Tyrosine kinase-inhibitor - targets:	KIT, PDGFR, Bcr-Abl	KIT, PDGFR, VEGF, FLT, RET, CSF	RET, VEGFR1-3, KIT, PDGFRA+B, FGFR1-3, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, SAPK2, PTK5, abl
- Dosage form:	Oral	Oral	Oral
	100mg, 400mg	12.5mg, 25mg, 50mg	40mg
	Tablets	Capsules	Tablets
- Therapy:	Contin., daily	Cycle – 6 weeks	Cycle - 28 days - 4 weeks
		4 wk. ther. - 2 wk. break	21 days ther. - 7 days break)
- Standard dosage:	400mg or 800 mg/day	50mg/day for 4 weeks.	160mg/day for 21 days
- Dosage in clinical practice:	400mg minimum dose 800mg exon 9	37.5mg/day contin. Individual dosing	dose reductions (120/80) Individual dosing





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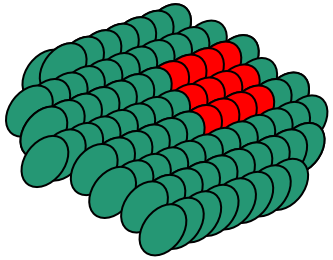
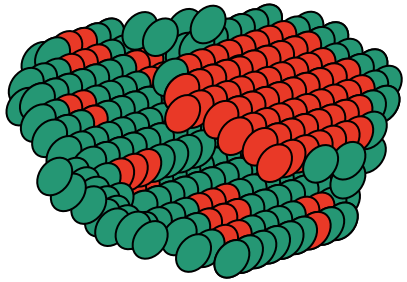
Types of Progression

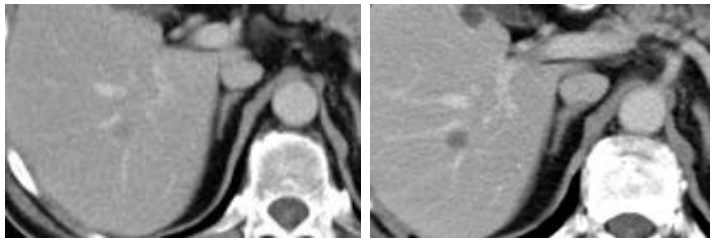
- **Local (focal) progression: Progressive disease – in one location**



- **Systemic progression Progressive disease (at the same time) in several places**



- **False or pseudo-progression**



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Types of Progression

- New lesions / metastases
- Intratumoral "nodes" (lesion in a lesion)
- Increase in tumor size
  (Not due to fluid increase!)
- Increase in tumor density

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Imatinib Resistance & Secondary Mutations

- **Initial:**
  Few patients do not tolerate imatinib at the beginning

- **After 2- 3 years,**
  successfully treated tumours are becoming resistant

- **But also:**
  10% of all GIST-patients with metast. disease are longterm responder (> 15 years)
  Unfortunately, we do not know (…in advance…)
  who these patients are and why they are stable for so long!?

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PROGRESSIVE DISEASE:

WHAT TO DO?

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Testing / verification of progression

Is it really a progressive disease?

- **Adherence (therapy loyalty)?**
- **Confirmed progression?**
- **Histology confirmed?**
- **Factors such as**
  Complementary therapies?
- **Symptoms present?**
- **Imminent danger?**

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Testing / verification of progression

Progressive disease >>> not appropriate / useful:

- **Headless / operational action**
  (not just switching the therapy)
- **Pressure by the treating physician**
- **Opportunity: Time for a second opinion ...**

Depending on <u>individual</u> “patients situation" may also be an option:

Treatment Beyond Progression! >>> Reichardt data

"Watch closely and wait - before therapy change ..."

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General recommendation…

Because we only have three approved treatment options:

Get the most out of every therapy –

use the therapy as long as possible!!!

Important tools:

- **Treatment by an experienced GIST-physician-/team**
- **Individual therapy- and side effect management (individual dosing, reduce side effects, increase compliance)**
- **Available systemic treatment options (incl. clinical trials)**
- **Local interventions**

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Progressive Disease

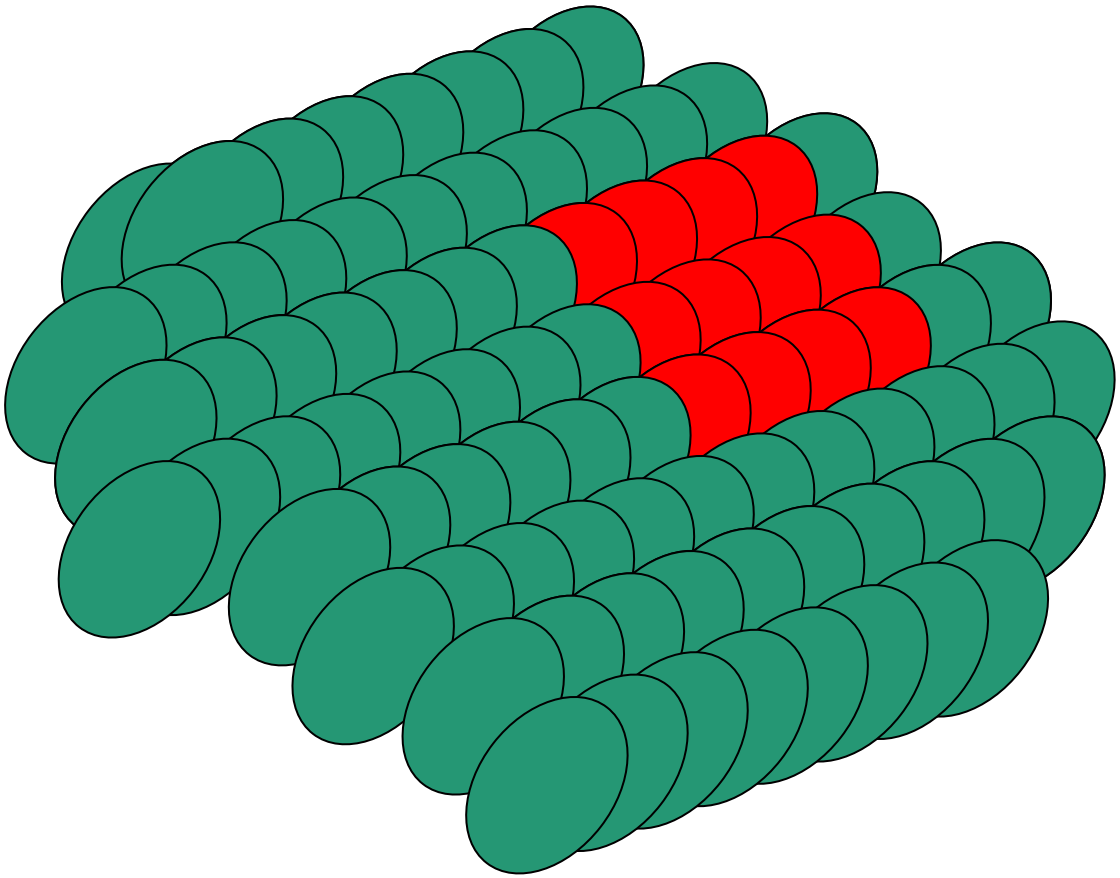
DRUG STANDARD OPTIONS?

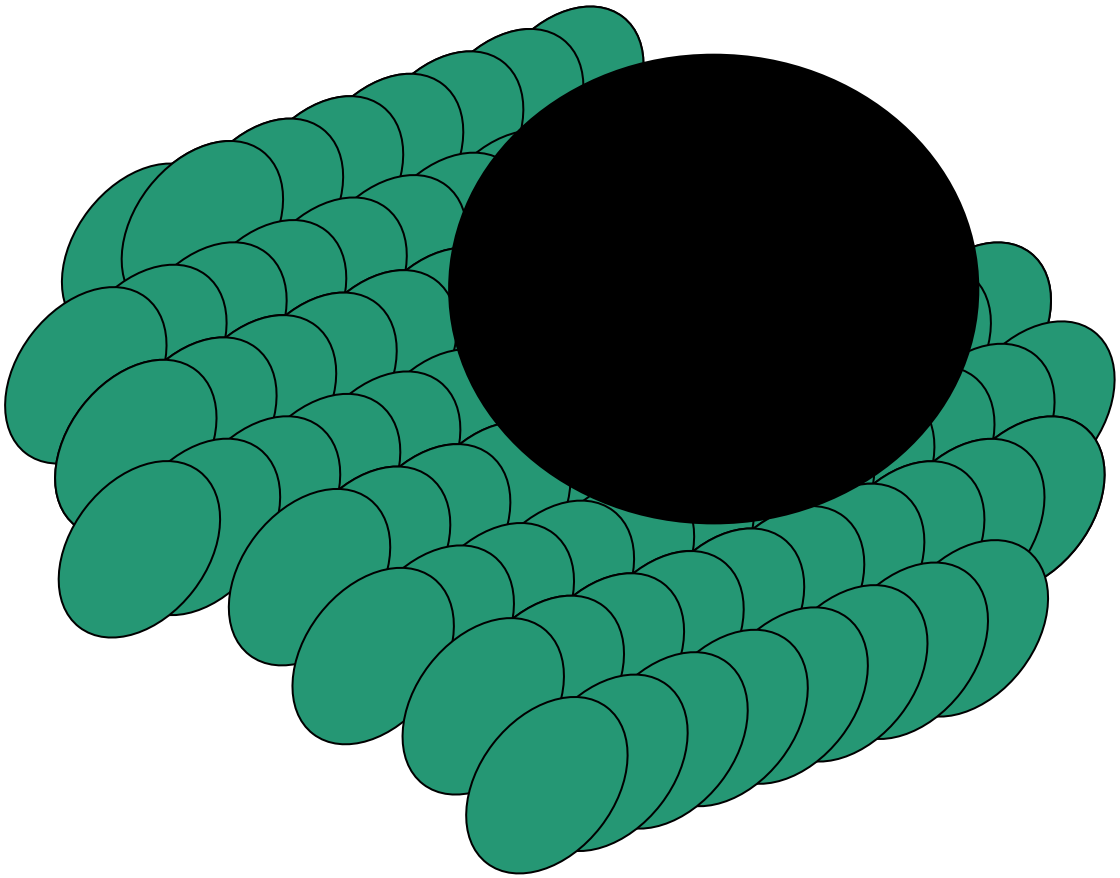
- Increasing the imatinib-dose
- Changing systemic treatment to sunitinib (approved)
- Changing systemic treatment to regorafenib (approved)

MORE DRUG OPTIONS?

- Using already tested GIST-treatments such as Afinitor, Tasigna etc. (off lable)
- New options: Participating in a clinical trial – if available
- After all therapy-options: Reintroducing imatinib or other agents

LOCAL INTERVENTIONS / ACTIONS?





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Local options / actions

- Operation / resection — Knife / Laser
- „Cooking" of single metastases in the liver
  - RFA Radio-frequency ablation — heat
  - 3D-guided RFA — heat
  - LITT (laser) — heat
- Internal radiation by SIRT (seeds) — radiation

  (Selective internal radiation therapy) with SIR-Spheres microspheres
- Chemo-embolization — cytostatics
- Extremely rare = bone mets. >>> radiation

- Transplant (liver) - no option

Objective: Maintain systemic treatments as long as possible…

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Progressive disease: Some open questions (1)

- **Who are the patients – benefitting from an Imatinib-therapy as long-term patients? What are the main factors for long-term responses?**
- **When are we able to measure an upcoming progression (much earlier) by blood test as a standard procedure?**
- **How can we prevent resistance or delay resistance?**
- **Does it make sense to change a therapy before resistance comes up?**
- **How can we educate doctors and patients better to use the three approved therapies as effective as possible? (Therapy & Side Effect Mgmt.!)**
- **What is the next generation of effective GIST-therapies? Immuno-oncology? Switch Pocket Inhibitors? Others?**

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Progressive disease: Some open questions (2)

- **What are the best „end of life“ options for GIST-patients without further options?**
- **What are solutions for countries where the standard therapies are not available or not affordable? What about the ethical responsibility of pharma companies to offer their drugs in drug assistance programmes?**
- **How can patients be sure that they receive generics with active agents and not counterfeits or substandard qualities? (Countries outside the EU, developing countries, etc.)**
- **Research in GIST has a lot to do with coincidences, individual expert initiatives, company decisions, etc. Are there chances for an international, better coordinated (overall) research plan in GIST? (Research priorities developed by experts & patient advocates together?)**