DISCLOSURES

No financial relationships of commercial interest
OBJECTIVES

1. Overview of NIH Pediatric and Wild-Type GIST Clinic

2. Overview of findings and contributions

3. Highlights

4. Future Considerations
Gastrointestinal Stromal Tumors: GIST

- Most common mesenchymal neoplasms of the gastrointestinal track; but fewer than 1% all GI tumors
- Originates in the Interstitial Cells of Cajal (smooth muscle pacemakers)
- Introduced as a diagnostic term in 1983
- KIT mutations described in 1998

PRESENTATION:

Anemia
Pain
Obstruction
Fatigue
Early Satiety
Incidental Finding
GIST

Stomach

Small Bowel

www.endoskopiebilder.de
Gastrointestinal Stromal Tumors: GIST

Epithelioid

Spindle cell
Gastrointestinal Stromal Tumors: GIST

85%: mutations in KIT
10%: mutations in PGDFRA
→ SURGERY, TKIs

5%: “other”

wildtype, young patients...
Once upon a time…

- The NIH Pediatric and Wild-Type Clinic was established in 2008
the NIH Pediatric & Wildtype GIST Clinic
Established 2008
Our Clinic

**Multidisciplinary**
Pediatric Oncologists, Medical Oncologists, Pediatric Surgeons, Geneticists, Endocrinologists, Genetic Counsellor, Pathologists, Radiologists, Psychologists, Behavioral Therapists, Nurses, Nurse Practitioners, Nutritionists, Dermatologists, Pain Specialists, Care Coordinators...

**Multi-Institutional**
National Cancer Institute / Clinical Center / NICHD, Dana Farber Cancer Institute / Boston Children’s Hospital, Fox Chase Cancer Center, St. Jude Children’s Research Hospital, Memorial Sloan Kettering Cancer Center, Huntsman Cancer Institute, Children’s Hospital Los Angeles, Sylvester Comprehensive Cancer Center, and others...

**Embraced a Collaborative Model**
Within and across specialists, institutions and community organizations

**Reached out to patients, physicians and advocates**
Findings

The vast majority (84%) of the “wild-type” GISTs are **SDH deficient**
- 75% SDH mutations
- 25% SDHC promoter hypermethylation

Other molecular features are “**rare**” but increasingly being described: NF1, BRAF, ARID1A, ARID1B, CBL, PIK3CA, HRAS, NRAS, KRAS, FGFR1, MAX, MEN1, fusions (ETV6-NTRK and others)

Often an indolent disease: **most patients survive with disease progression**. No improvement seen with extensive surgical resections. Intractable pain, obstruction and bleeding remain considerations for surgical intervention.

This approach to improve outcomes in rare diseases works...!
Frequency of SDHB-negative and SDHB-positive gastric GISTs as a function of age

Miettinen et. al.
Am J Surg Pathol. 2011
Examples of immunohistochemically SDHB-negative and SDHB-positive gastric GISTs. A to D, SDHB-negative cases with staining limited to blood vessels, lymphohistiocytic infiltration, smooth muscle, or hepatocytes. C, Liver metastasis with positive hepatocytes. Note a faint cytoplasmic blush in panel D. E to H, SDHB-positive spindle cell and epithelioid GISTs with granular cytoplasmic staining of various intensities in tumor cells and vessel walls.

Miettinen et. al
Am J Surg Pathol. 2011
Findings

- Best screening tool is SDHB IHC
- Critical importance of molecular characterization
- Most SDH mutations are **GERMLINE**
  - Implications for genetic counseling
- SDH Deficient GISTs are overwhelmingly **gastric** in location and most are **multifocal** and/or metastatic at presentation (only one small bowel SDH deficient GIST)
- Poor response to imatinib; definite responses to sunitinib and regorafanib - likely due to effects on VEGF
- Other trials (linsitinib, vandetanib) have been negative
- Guadecitabine trial ongoing
Findings

This approach to improve outcomes and improve knowledge in rare diseases works
Highlights

- Collaboration
- Genetic Testing and Counselling
- SURGICAL strategy
- Models
- Awareness
Awareness: leveraging social media platforms

**FACEBOOK LIVE EVENT**

Live from the NIH GIST Clinic

**June 19, 3:30 pm ET**

- **Fernanda Arnaldez, M.D.**
  National Cancer Institute

- **Margaret Von Mehren, M.D.**
  Fox Chase Cancer Center

- **Becky Owens**
  GIST Support International
Future Considerations

Mission of the NIH Pediatric and Wild-Type GIST Clinic: improving outcomes, quality of life, empowering patients and families

Consortium: how to better serve the GIST community

This model to be implemented in other rare malignancies in the context of the Moonshot® Initiative

Future clinical trials based on model-generated data: how to optimize
SDH Deficiency Leads to expression of multiple targets
Carney-Stratakis Syndrome:

- GIST, paragangliomas
- Germline mutations in succinate dehydrogenase
- AD with incomplete penetrance