Precision Medicine in Sarcoma

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No Conflicts of Interest

CAUSAL: Cohort to Augment the Understanding of Sarcoma Survivorship Across the Lifespan

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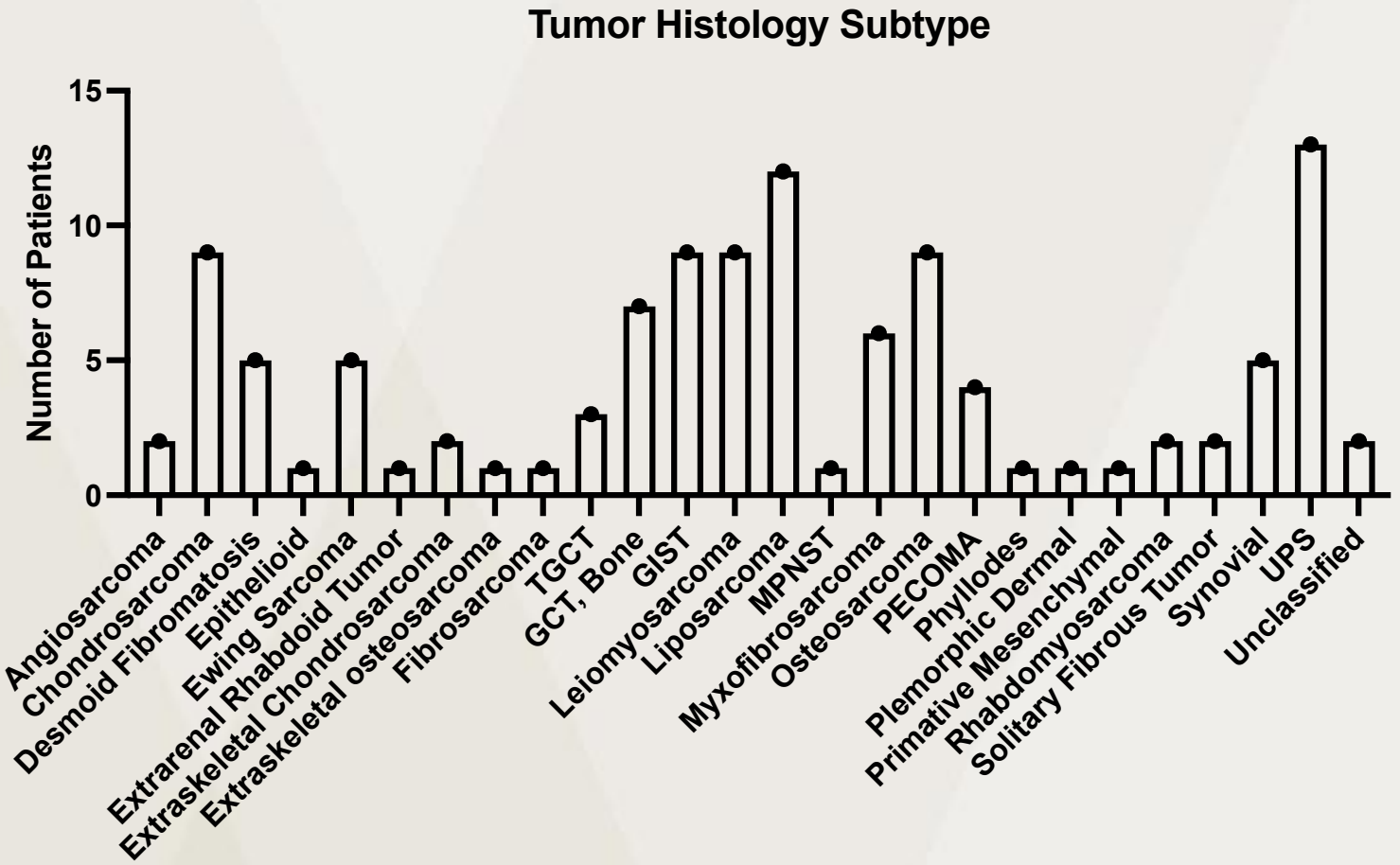
Genomic Landscape of Sarcoma

CAUSAL: Objectives

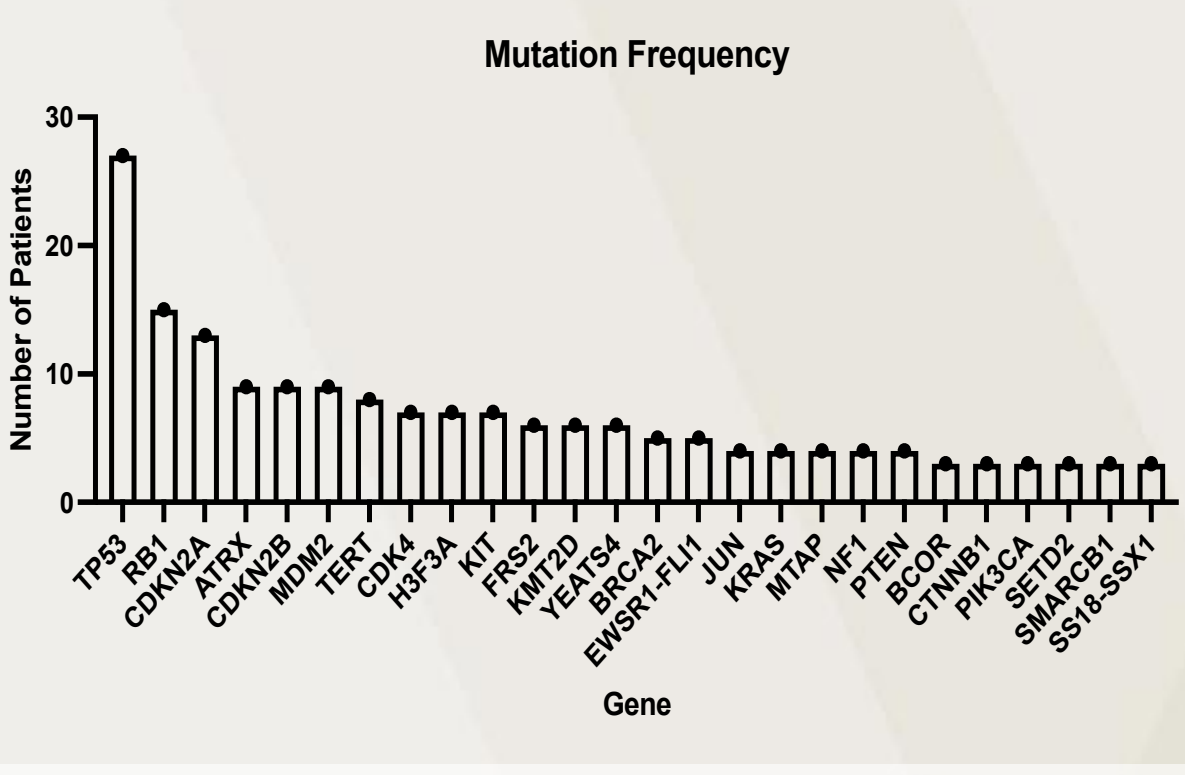
- Develop a systematically study recurrence, organ toxicity, function, quality of life, and survival as well as their predictors.
  - Goal to enroll 2100 sarcoma survivors through the VUMC Sarcoma Treatment Center
- To identify genomic drivers of sarcoma and to use this information to develop personalized liquid biopsy assays for monitoring treatment response, recurrence, and minimal residual disease (MRD).
  - The role of drug metabolism and DNA repair gene functional polymorphism
  - Genetically predicted gene expression levels
  - Polygenic risk scores, on treatment efficacy and therapy-induced normal tissue toxicity

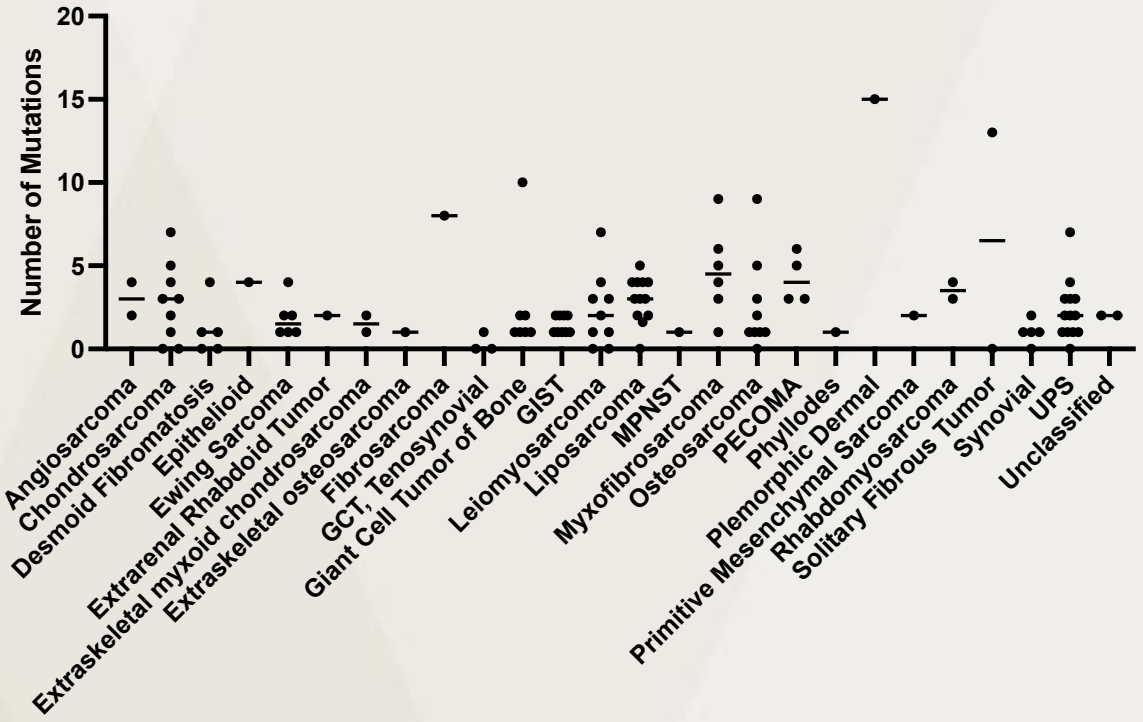
Initial Sequencing Cohort

- NGS with Tempus Labs, Inc. –
  - xT 648 Gene Panel
  - RNA (Altered Splicing from RNA Sequencing)
  - RNA Expression (Under/Over Expression)
- As of 04/19/2023:
  - Patients Sequencing Requested: 186
  - Patients DNA Sequencing Completed: 114
  - Patients with DNA Mutations: 101
  - Patients with RNA Available: 78
  - Patients with RNA Alterations: 68



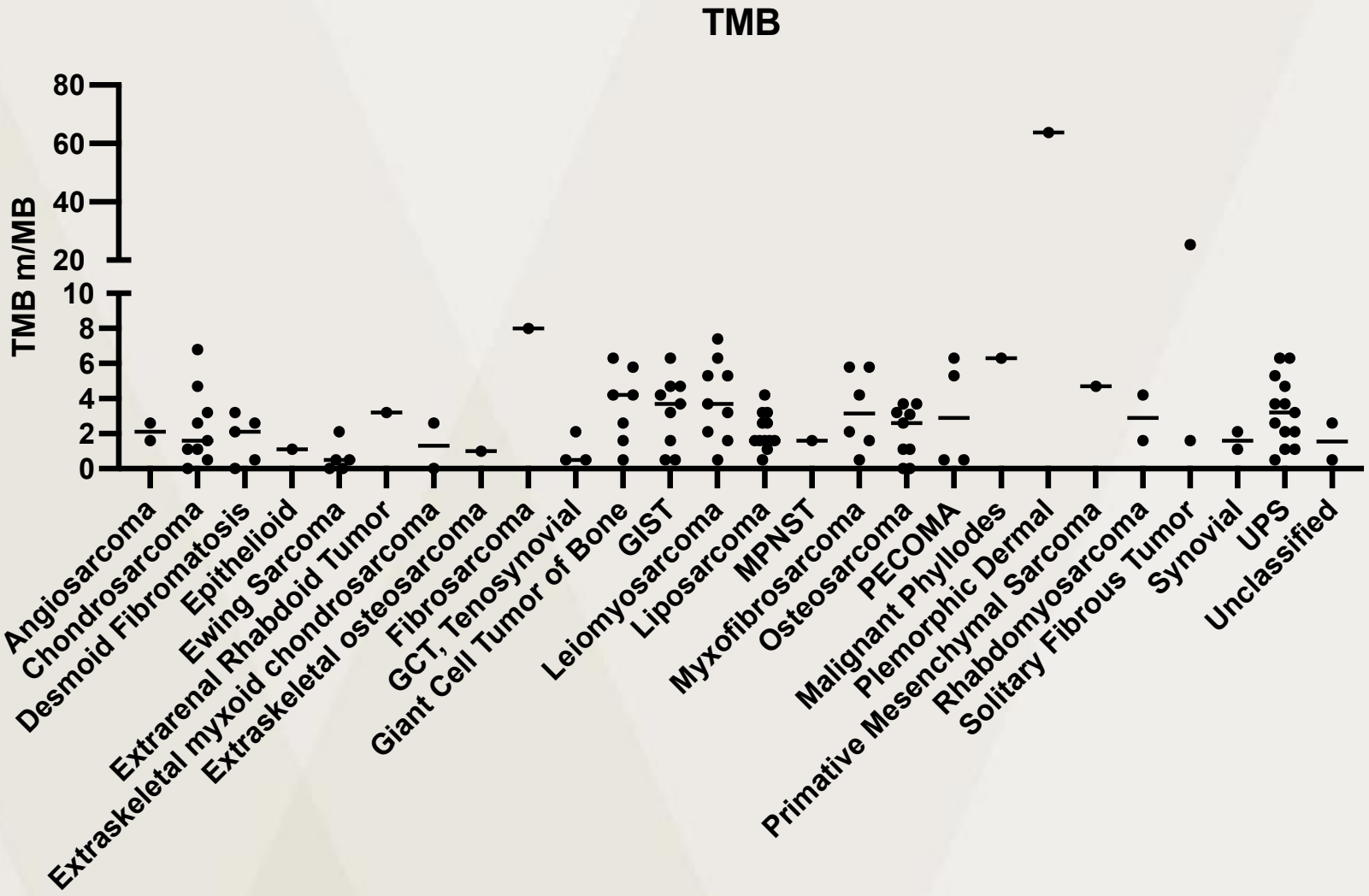
Mutations & Patient Distribution





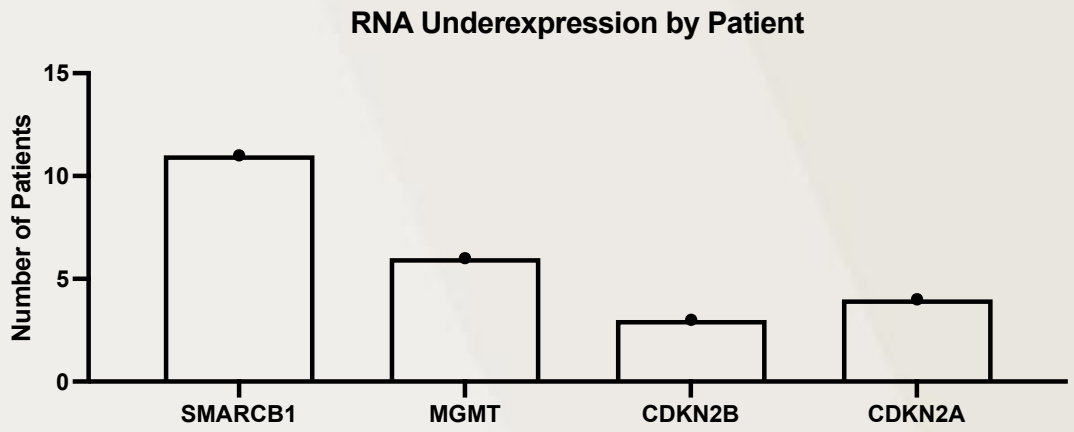
MSI/TMB

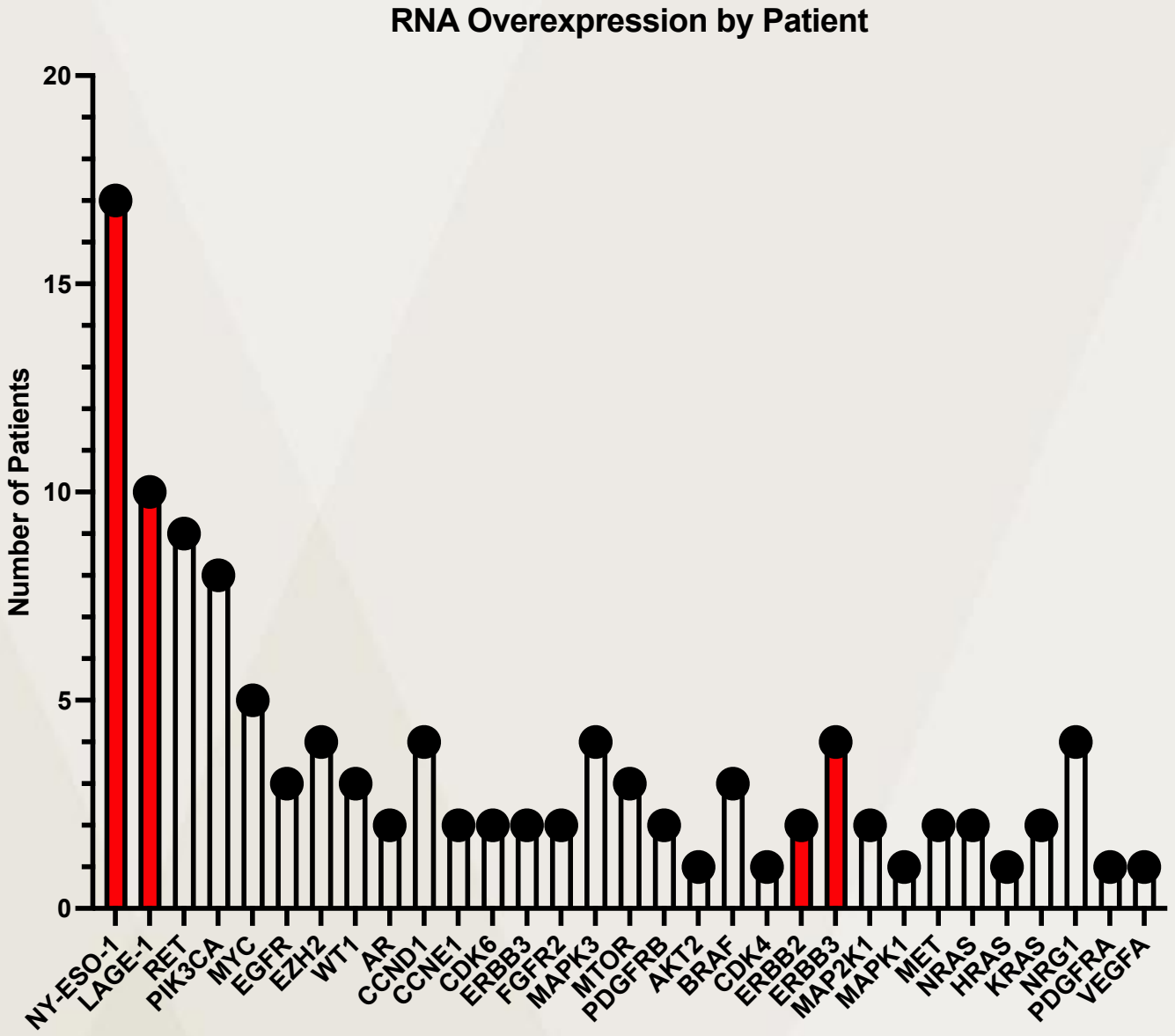
- All Tumors MSI-Stable
- Average TMB
  - 3.51 m/MB
- Highest TMB 63.7
  - Only 2 tumors with TMB >10



RNA Expression

- 24 Transcripts under expressed
- 109 Transcripts overexpressed
  - 33 Possible Targets pending IHC validation





ESMO Score for Clinical Actionability of molecular Targets (ESCAT)

- Tier I:
  - Mutation-Drug match has improved outcomes in clinical trials
- Tier II:
  - Mutation-Drug match has activity, but needs further investigation
- Tier III:
  - Alteration suspected to improved outcomes based on trials in another tumor type or with similar molecular alteration
- Tier IV:
  - Pre-Clinical Evidence of Action

ESCAT: Tier I - II

Diagnosis	Gene	Alteration	Variant Allele Fraction	Drug	ESCAT Tier	ClinVar Prediction
GIST	KIT	p.W557R	41.6%	Imatinib	I-A	P/LP
GIST	KIT	p.V559A	40.6%	Imatinib	I-A	P/LP
GIST	KIT	p.K558_V559delinsN	37.1%	Imatinib	I-A	Uncertain
GIST	KIT	p.A502_Y503dup	22.0%	Imatinib	I-A	New
GIST	KIT	p.V555_K558del	18.1%	Imatinib	I-A	New
GIST	PDGFRA	p.D842V	40.2%	Avapritinib	I-B	P
Liposarcoma	CDK4	CNG		Palbociclib	I-B	N/A
Liposarcoma	CDK4	CNG		Palbociclib	I-B	N/A
PEComa	BRCA2	CNL		Olaparib	II	P
Unclassified	BRCA2	p.S611*	41.6%	Olaparib	II	P
Chondrosarcoma	IDH1	p.R132C	20.1%	Ivosidenib	II-B	P/LP

Outcomes of Patient Sequencing

- 31.5% (36 of 114) of patients had potentially actionable DNA mutations,
  - 14 tier I
  - 6 tier II (2 Based on TMB)
  - 15 tier III
  - 1 tier IV
- 34.6% (27/78) of patients had potential targets based on RNA expression.
  - IHC validation of potential targets
- 55.2% (63/114) patients had either a potential DNA or RNA target
- 7.9% (9/114) had multiple RNA or DNA targets

Conclusions & Future Directions

- Additional sequencing in soft tissue and bone sarcoma is needed to help investigate histologic subtypes
  - Can lead to meaningful treatment options based on ESCAT Scoring
- Clinical course
  - Do patients respond as expected given mutational profile
  - Explore new mutations –
    - GoF Exon 11, GoF Exon 9 – GIST
    - MGA-NUTM1 – Primitive Mesenchymal Neoplasm
- RNA Seq Analysis for additional biologic subtyping
  - Cluster histologic subsets based on gene expression

Thank you!

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