Blazing a New Future
for Patients with Cancer™

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STARTRK2 Clinical Trial: A Basket Study of Entrectinib for the Treatment of Solid Tumors with Specific Gene Rearrangements

Zachary Hornby: Chief Operating Officer, Ignyta, Inc.

Genomically Driven Clinical Trial Paradigms in Oncology

- **Roy's Talk**

Single histology: Squamous lung cancer	**Multiple Markers:** PI3KCA, CDK4/6, FGFR, c-MET, etc.	**Multiple Drugs:** Taselisib, palbociclib, AZD4547, etc.	**"Umbrella Study"** Lung-MAP

One Histology, Multiple Drugs

- **This Talk**

Multiple histologies: All solid tumors	**Few Markers:** NTRK, ROS1, ALK	**Single Drug:** Entrectinib	**"Basket Study"** STARTRK-2

One Drug, Multiple Histologies

Ignyta: Company Overview

Leading oncology precision medicine company

- Ignyta (NASDAQ: RXDX) San Diego-based public biotechnology company focused on precision medicine in oncology

Robust pipeline of molecularly targeted therapies

- Entrectinib: TRK, ROS1, ALK inhibitor with 79% ORR in fusion-positive patients in Ph 1 studies (n=24); achieved complete and durable responses in patients with CNS disease
- RXDX-105: RET inhibitor with 56% ORR in patients fusion-positive patients in Ph 1/1b (n=9)
- RXDX-106: Tyro3, AXL, MerTK (TAM) inhibitor with promising preclinical efficacy as both an immunomodulator and a targeted therapy

Integrated approach to Rx/Dx development

- CAP-accredited, CLIA-certified, QSR-compliant diagnostic lab with multi-modality assays (e.g., NGS, NanoString, FISH, IHC)
- Internal Dx allows Ignyta to illuminate the molecular drivers of cancer and quickly advance the most appropriate molecularly targeted therapies to address them

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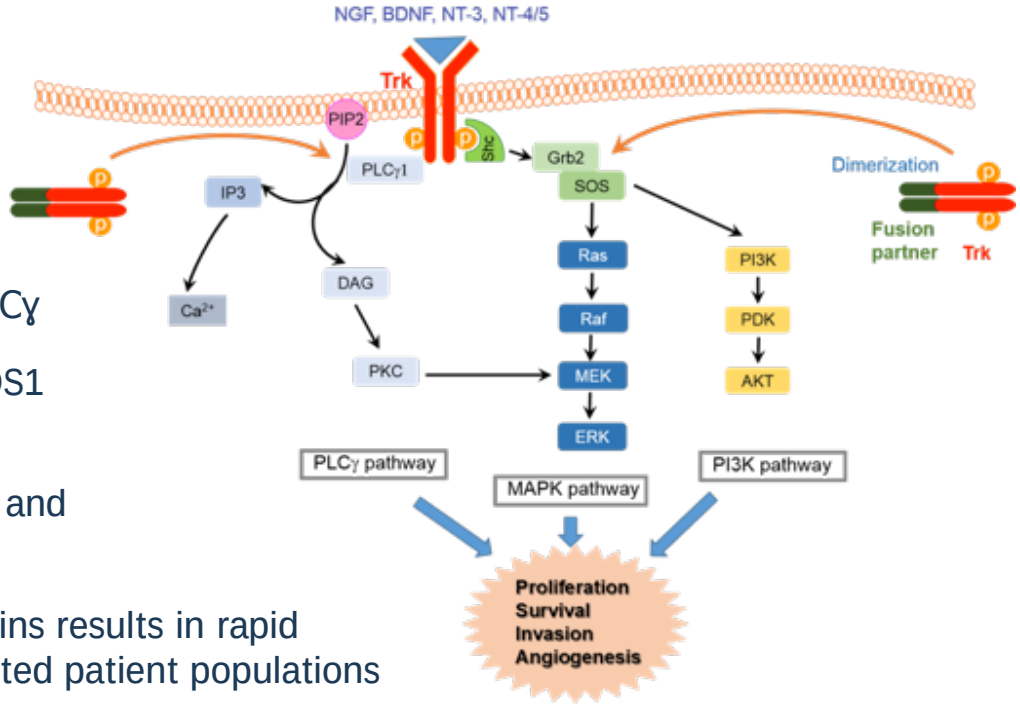
Entrectinib: Investigational, Potentially First- and Best-in-Class TRK Inhibitor and Best-in-Class ROS1 Inhibitor

Most potent, orally available pan-TRK inhibitor in clinical development

Target	TRKA	TRKB	TRKC	ROS1	ALK
IC50* (nM)	1.7	0.1	0.1	0.2	1.6

- TRK, ALK and ROS1, are cell surface receptors that can become rearranged at the genetic level and fused at the protein level
- Fusion proteins homodimerize and constitutively activate downstream oncogenic signaling pathways, MAPK, PI3K, PLCγ
- Entrectinib is the most potent pan-TRK and ROS1 inhibitor in clinical development
- It Demonstrates inhibition of its kinase targets and down-stream effectors
- Entrectinib inhibition of oncogenic fusion proteins results in rapid tumor response in preclinical models and selected patient populations
- Designed to cross blood brain barrier (BBB) and to address primary brain tumors and secondary CNS metastases



* Biochemical kinase assay

Gene Rearrangements Targeted by Entrectinib Are Present Across Many Tumor Histologies

	NTRK1	*NTRK2*	*NTRK3*	*ROS1*	*ALK*
NSCLC (adeno, large cell NE)		<1%		1-2%	3-7%
CRC		<1%		<1%	<1%
Salivary gland – NOS			3%		
Sarcomas (including GIST)	1-9%		2-11%	2-3%	1-5%
Astrocytoma		3%			
Glioblastoma	1-3%			1%	
Melanoma (Spitz)	16%			17%	10%
Cholangiocarcinoma	4%			9%	2%
Papillary thyroid carcinoma	5-13%		2-14%		7%
Breast – NOS					2%
Mammary analog secretory carcinoma [MASC]			90-100%		
Juvenile/secretory breast			92%		

- **NTRK Fusions have now been detected in >30 solid and hematological malignancies**

Source: TCGA, AACR GENIE, Literature, Foundation Medicine, Ignyta proprietary analysis

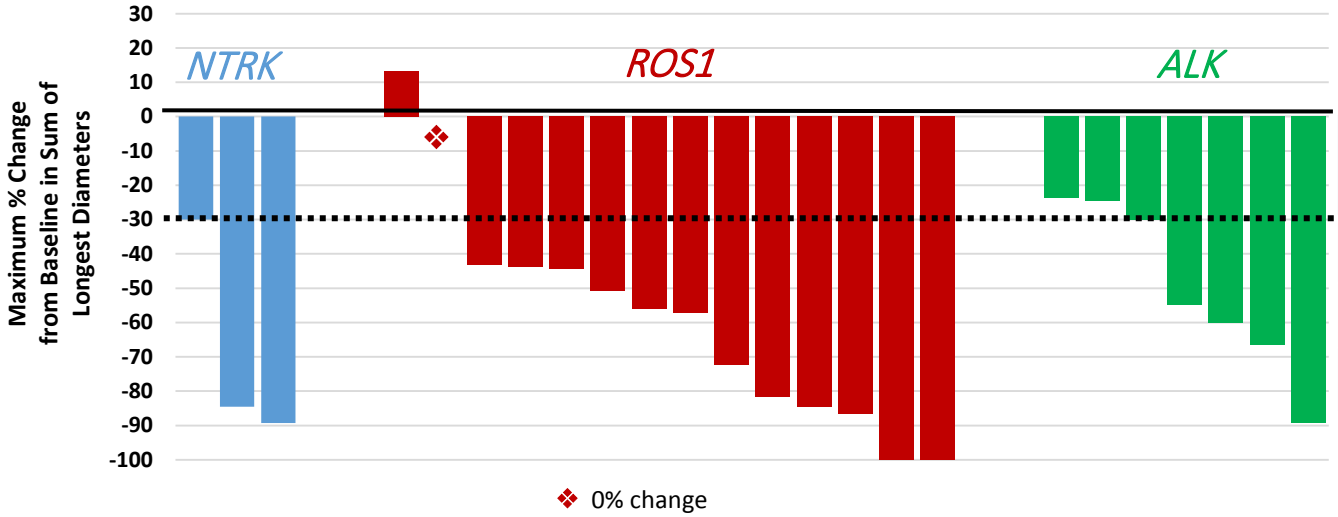
Entrectinib Is Highly Potent against All Tested NTRK Fusions

Entrectinib exhibits high anti-proliferative potency (0.1-5 nM range) regardless of the identity of the fusion partners or tissue of origin

Cell Lines	Fusion	IC50 (nM)
Ba/F3 (+mIL3)		>1000 (control)
Ba/F3-TPM3-NTRK1	*TPM3-NTRK1*	2.5
Ba/F3-LMNA-NTRK1	*LMNA-NTRK1*	1.4
Ba/F3-ETV6-NTRK1	*ETV6-NTRK1*	2.5
B3/F3-BCAN-NTRK1	*BCAN-NTRK1*	0.1
Ba/F3-SQSTM1-NTRK1	*SQSTM1-NTRK1*	0.7
Ba/F3-SCYL3-NTRK1	*SCYL3-NTRK1*	1.3
Ba/F3-VCL-NTRK2	*VCL-NTRK2*	4.3
Ba/F3-AFAP1-NTRK2	*AFAP1-NTRK2*	2.7
Ba/F3-ETV6-NTRK2	*ETV6-NTRK2*	4.5
Ba/F3-ETV6-NTRK3	*ETV6-NTRK3*	4.5
CUTO-3	*MPRIP-NTRK1*	1.1
KM12	*TPM3-NTRK1*	4.5

Situational Challenge: the Targets Are Real, and the Drug Is Active, but How Do We Find, Enroll and Study the Patients

TRK/ROS1/ALK Inhibitor-Naïve *NTRK*-, *ROS1*-, and *ALK*-Rearranged Extracranial Tumors (n=24)



Fusion	Confirmed Responses (n)	ORR (%)
NTRK1/3	3/3	100%
ROS1	12/14	86%
ALK	4/7	57%

79% ORR in Phase 1

Challenge: how to design a registration-enabling clinical program and diagnostic approach that finds, and enrolls, these individually rare (within specific histologies) but collectively numerous patients?

- Many of the relevant tumor types (e.g., head and neck cancers) are not frequently genetically tested
- No individual tumor type has sufficient patient numbers to enroll a complete clinical study
- Some of the biomarkers (NTRK) are not on many diagnostic panels

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Solution: Multifactorial Approach to Enable Ease of Detection, Awareness, Enrollment and Analysis

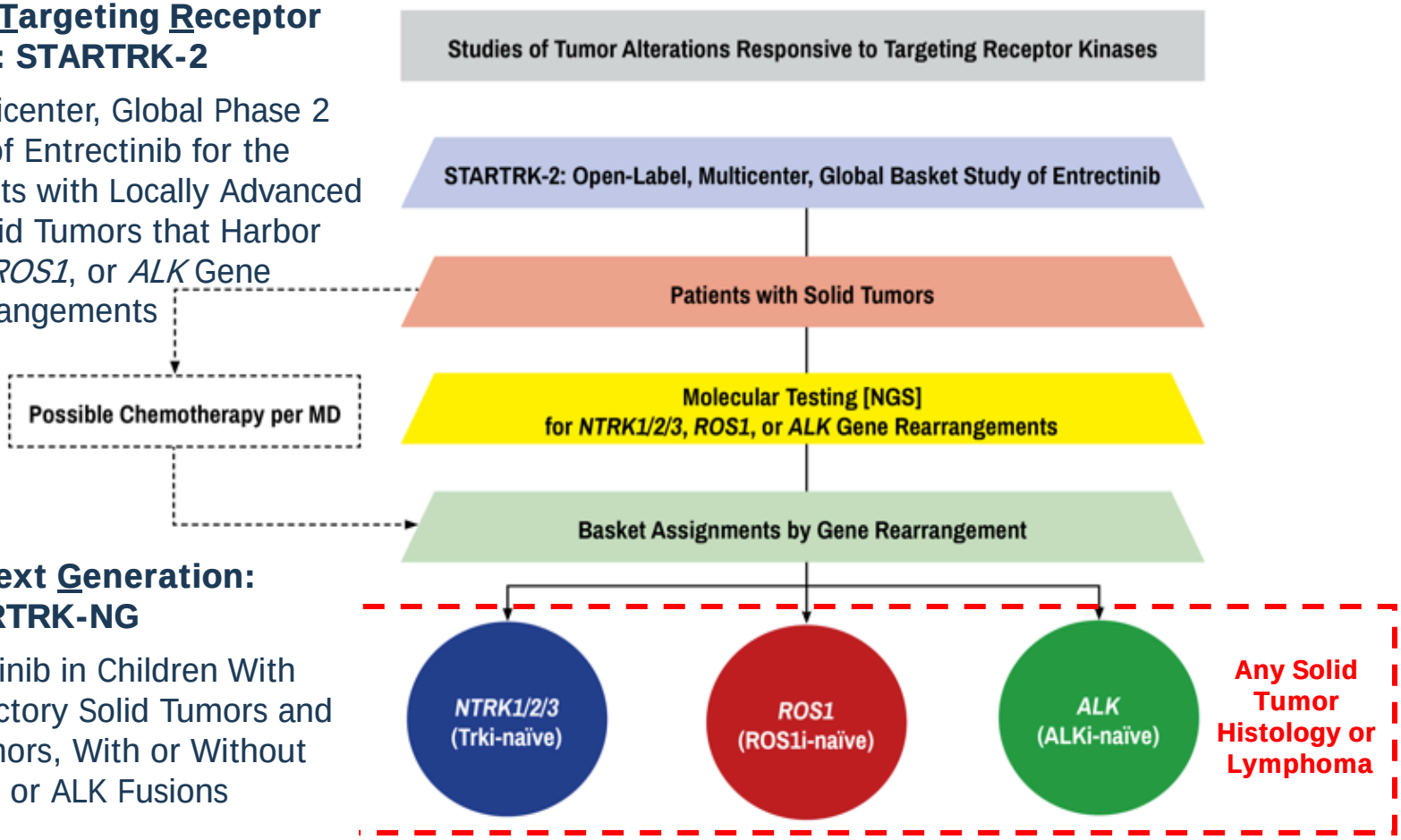
Solution: a flexible trial design and multi-pronged diagnostic workflow

- Basket study: open to all solid tumor patients, and lymphomas, that harbor the requisite biomarker (NTRK, ROS1, or ALK gene fusions)
- Pooled statistical analysis: all baskets contribute to the primary endpoint
- Multiple mechanisms for diagnostic detection: Ignyta central lab, regional commercial labs, local academic labs
- Liberal eligibility criteria for enrollment
- “Just in time” site activation
- Patient advocacy group-driven study awareness

STARTRK-2: Entrectinib Global Phase 2 Pivotal Basket Study

Studies of Tumor Alterations Responsive to Targeting Receptor Kinases: STARTRK-2

Open-Label, Multicenter, Global Phase 2 Basket Study of Entrectinib for the Treatment of Patients with Locally Advanced or Metastatic Solid Tumors that Harbor *NTRK1/2/3*, *ROS1*, or *ALK* Gene Rearrangements

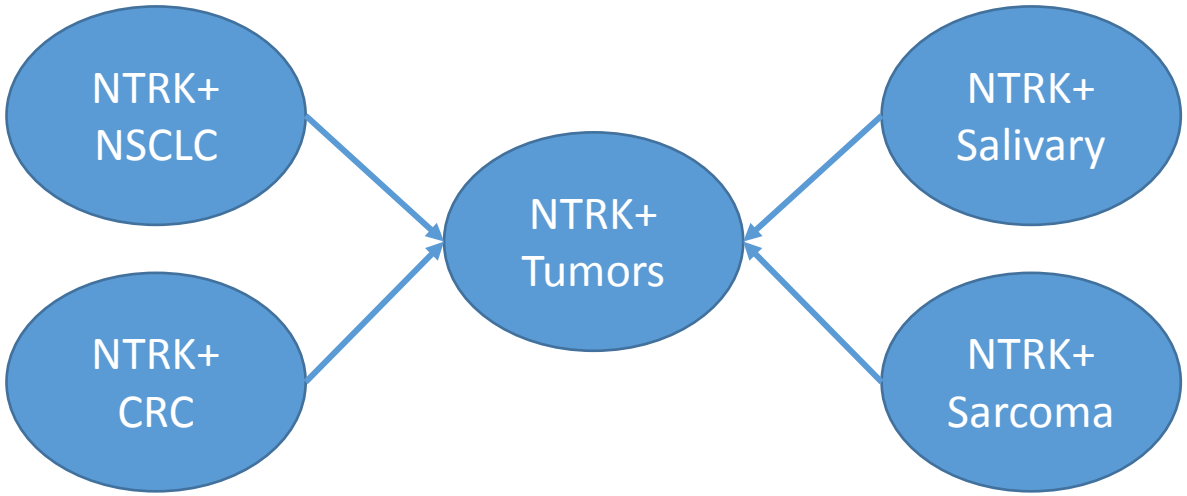


STARTRK Next Generation: STARTRK-NG

Study of Entrectinib in Children With Recurrent or Refractory Solid Tumors and Primary CNS Tumors, With or Without TRK, ROS1, or ALK Fusions

All Baskets Contribute to Primary Endpoint and Registrational Dataset

- Each basket represents a combination of a target gene fusion and a histology
  - E.g., NTRK+ salivary gland cancer; ROS1+ NSCLC
- However, opportunity for pooled analysis
- I.e., combined statistical analysis for primary efficacy endpoint (ORR) across multiple baskets:



- Could lead to an unprecedented “molecular label” where the indication statement is defined by the presence of the genetic aberration (NTRK fusion) rather than where in the body the malignancy is detected

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Ignyta's Trident Strategy for Driving Detection of Rare Patient Populations

Ignyta has taken a three-pronged approach (Trident) to enable broad diagnostic testing to identify rare patients for enrollment into basket studies

1. Established CLIA/CAP lab at Ignyta with no cost, proprietary, highly sensitive fusion testing (*NTRK, ROS1, ALK*)

Central

2. Work with diagnostic consortia & commercial labs throughout US, Europe (e.g., EORTC SPECTA) and Asia (proprietary) to ensure testing of relevant biomarkers and that patients benefit from established infrastructure

Regional

3. Enable local sites throughout Europe, Asia, and US to perform high-sensitivity local fusion testing; IHC, NGS, and/or NanoString®

Local

Ignyta's Proprietary Trailblaze Pharos™ Assay Enables Enrollment into STARTRK-2 Clinical Study

Clinical Sites | **Specimens** | **Ignyta Central Lab** | **Platform** | **Output**

FFPE

TRAILBLAZE PHAROS™

CLIA

CE

CAP

EAP

RNA Prep

ARCHER®

NGS

STARTRK-2
Trial Enrollment

Gene Fusions for
NTRK1, NTRK2, NTRK3, ROS1, ALK

Trailblaze Pharos™ has been granted an Investigational Device Exemption (IDE) and Expedited Access Pathway (EAP) by FDA

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STARTRK-2: Principles of Study Eligibility

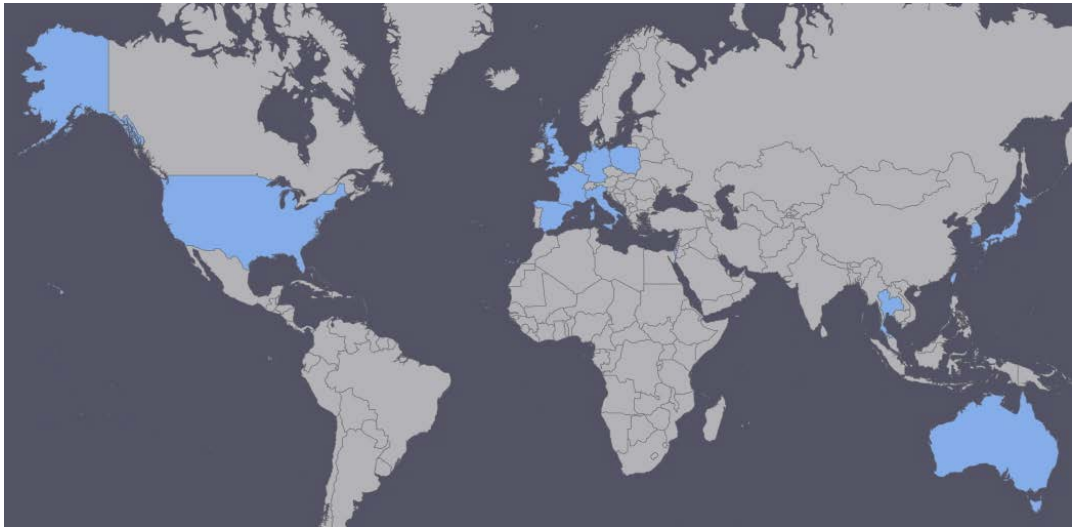
Draft Issue Brief on Eligibility

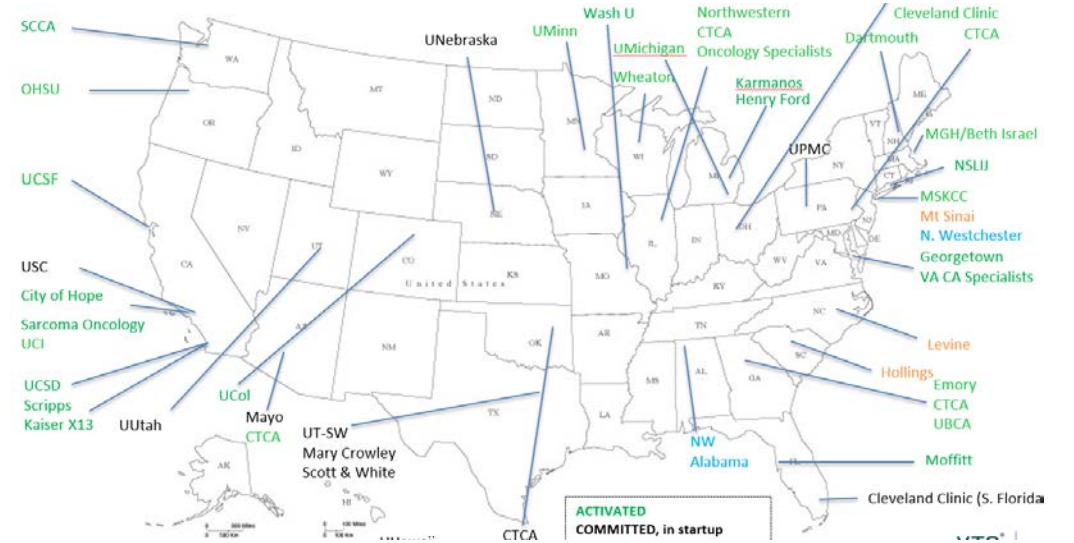
- *Allow broad enrollment while restricting primary analysis to defined patient population*
  - *Protect integrity of trial while enabling data collection in broader populations*
  - *Data may be helpful to inform safe clinical use in "real-world" patients*

STARTRK-2 Approach

- Broad Inclusion/Exclusion criteria
  - Consider tumor type, age, minimal organ function, prior treatment history, CNS involvement, etc.
  - Restrict to only what is absolutely necessary to interpret efficacy and safety
  - No requirements for minimal renal function or hematological function
- Allow patients with CNS disease (primary or metastatic)
- Acknowledge that certain patients may contribute only to a subset of endpoints
  - E.g., non-measurable but evaluable disease: PFS, OS, safety, PK

Global Study Increases Catchment Area
"Just in Time" Network Brings the Study to the Patient





- 14 Countries on four continents
- >150 sites worldwide
- >70 sites in the US
- "Just in time" site activation at 150 additional US sites via site management organization (SMO) when patients are detected at non-current sites
  - Central IRB
  - Central contract
- Travel concierge, including internationally, for any patients not near a STARTRK-2 site

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Patient and Provider Awareness Initiatives

- Patient Advocacy Group initiatives
  - Conference presentations
  - Newsletters
  - Banner ads
  - E-Blasts
- Search Engine Optimization & Management
- Clinical trial website for each of patients and providers

sarcoma alliance

American Head & Neck Society

Inspire™ 1,000,000+ members are better together!

NTRK Fusion - Now Recruiting for Trial - startrktrials.com
Ad www.startrktrials.com/ (844) 782-7875
For **NTRK**/ALK/ROS1 Positive Cancers. See if You Qualify Today.
Now Enrolling Patients · Precision Cancer Medicine · Investigational Medicine
For Providers | Latest Scientific Data
About the Trial | Refer a Patient

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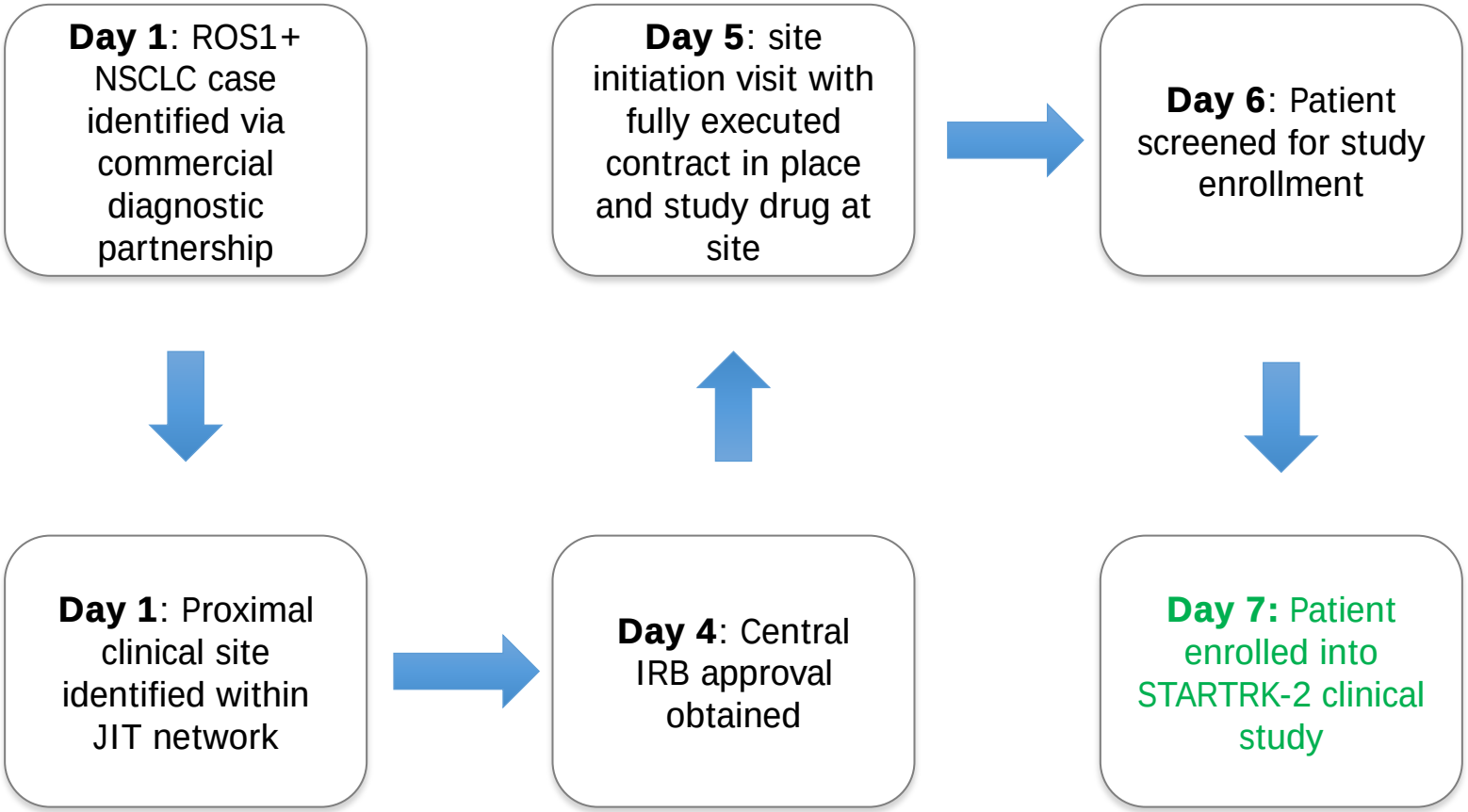
Rapid Execution of Just In Time (JIT) Process with Commercial Diagnostic Partner and Site Management Organization (SMO)



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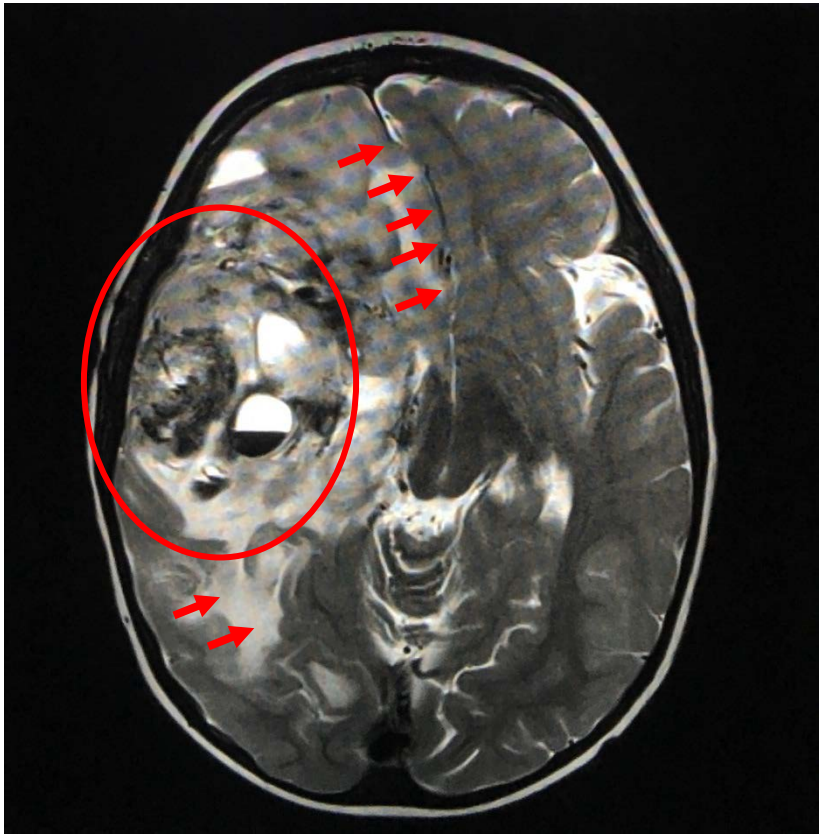
Sometimes All of the Preparations Are Insufficient; and Compassionate Use Is Required

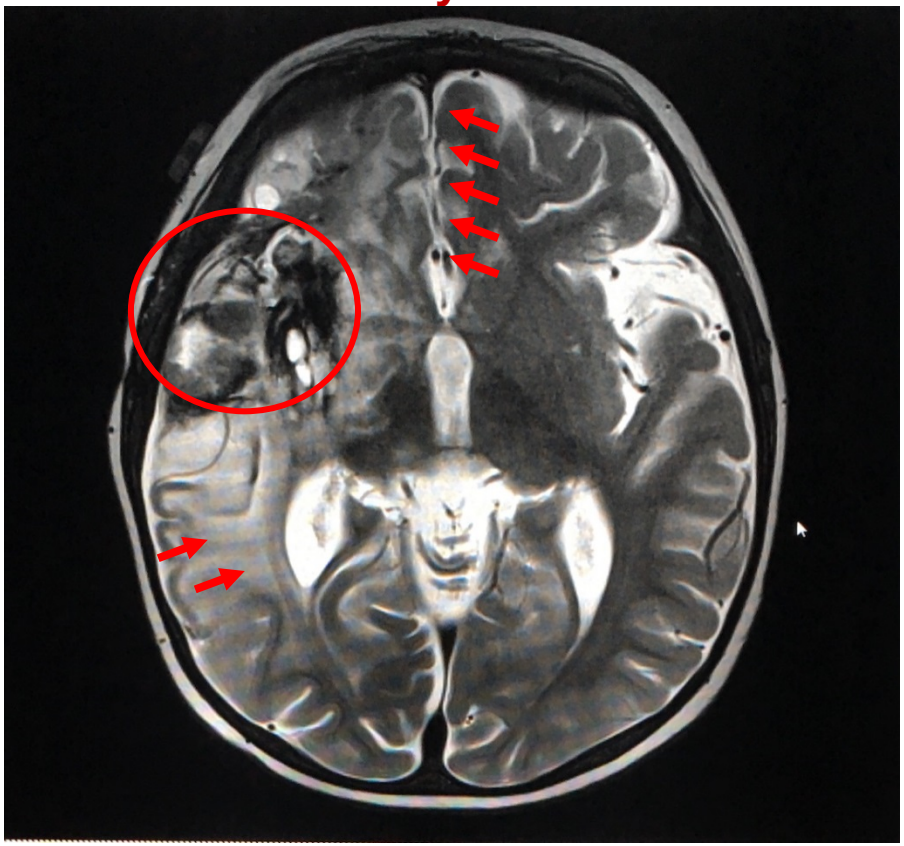
20-month old boy with recurrent, metastatic infantile fibrosarcoma harboring *ETV6-NTRK3* gene rearrangement (first detected in Ignyta Dx lab)

Baseline



Patient not eating, progressively less active and more sleepy

Day 35



Patient eating, mobile (crawling), more alert

Images: Heym, Cook Children's

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Lessons Learned

- Rare patient populations that are highly actionable are worth pursuing
- Design your clinical trial enrollment to match the biology of the patients; in this case, across multiple tumors
- Engage the regulatory agencies early; they are often more flexible than you might think
- Be open to building rather than buying (e.g., diagnostics); but as the landscape evolves, adapt with it
- Compassionate use cases may not drive the primary endpoint; but they sure invigorate the team

Thank You