

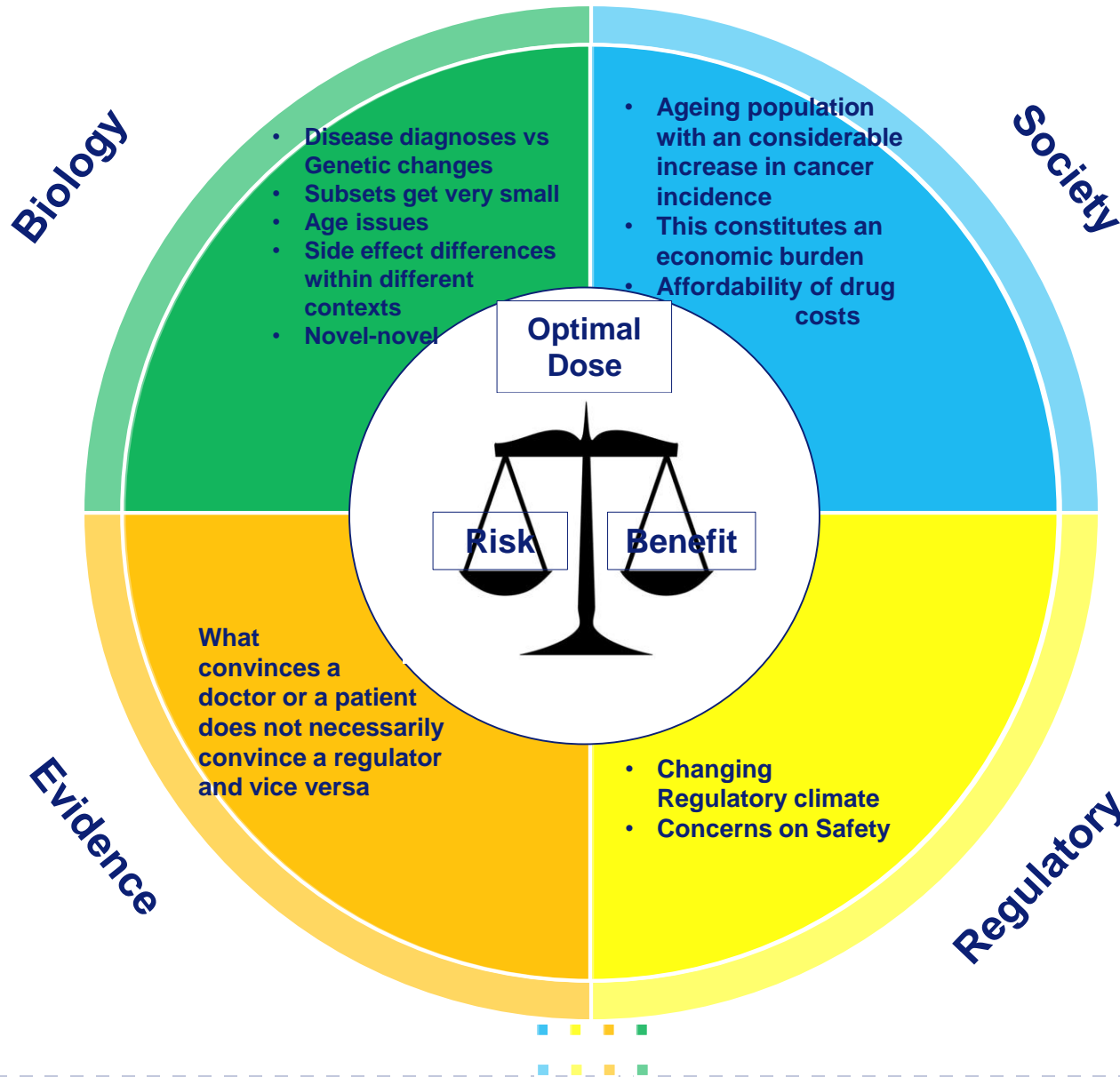
Innovation in Oncology Clinical Trial Design

Introduction

Jaap Verweij
Medical Oncologist
Dean and Vice-chairman Board of Directors
Erasmus MC



Our challenges are diverse and manifold



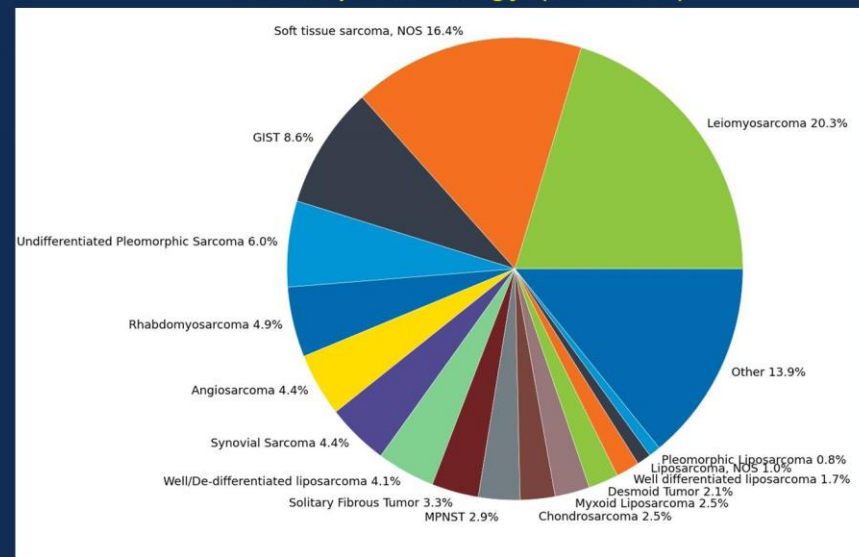
Distribution of Soft tissue versus Bone sarcoma (n = 5749)

Soft tissue 86.6%

Soft Tissue, N = 4900

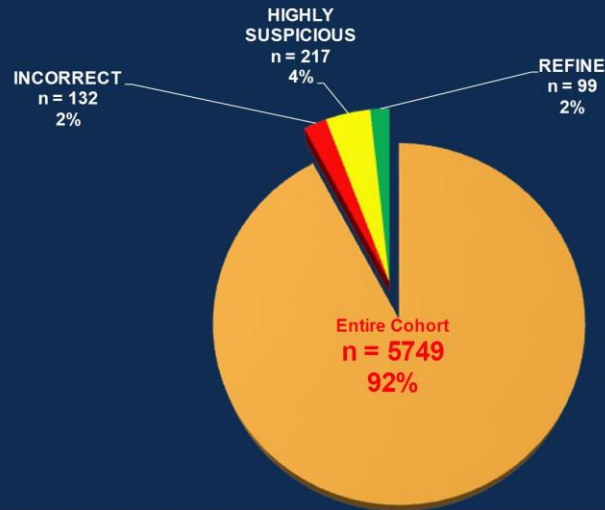
Bone 13.4%

56 unique histology (n = 5749)



Does Genomic profiling aid/refine/modify diagnosis?

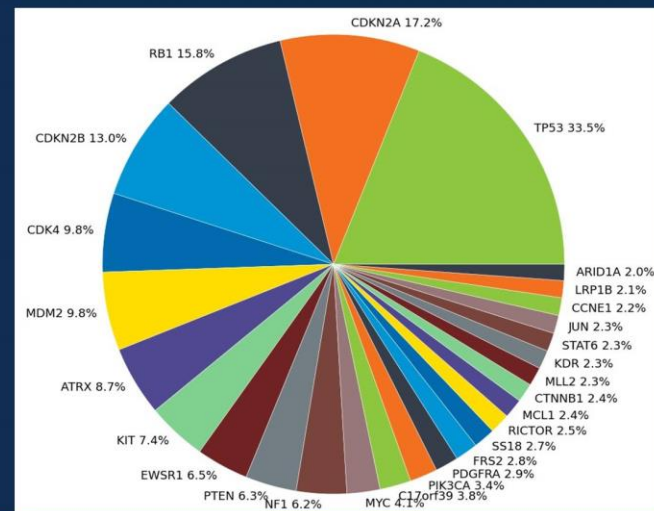
And what about mutations?



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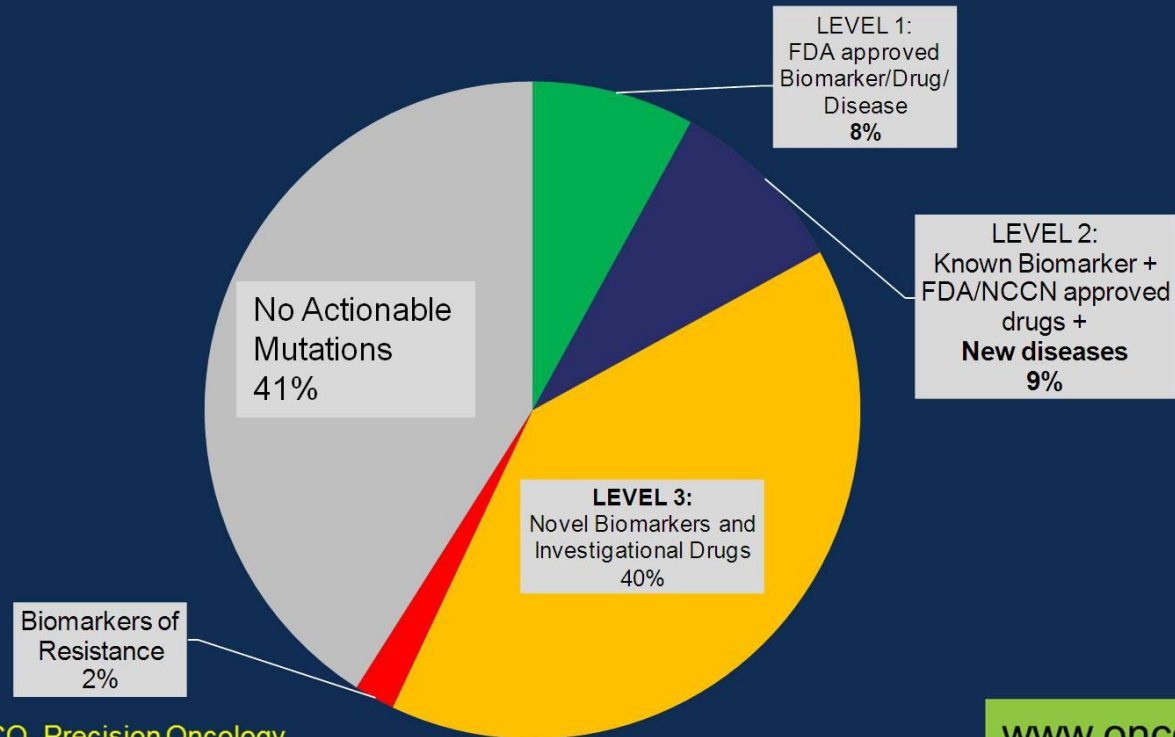
Landscape of Mutations (n = 5749)

634x depth
~62,000 mutations
~1200 fusions



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Landscape of “Actionable” Mutations (n = 5749)



Chakravarty D, et. al. JCO, Precision Oncology

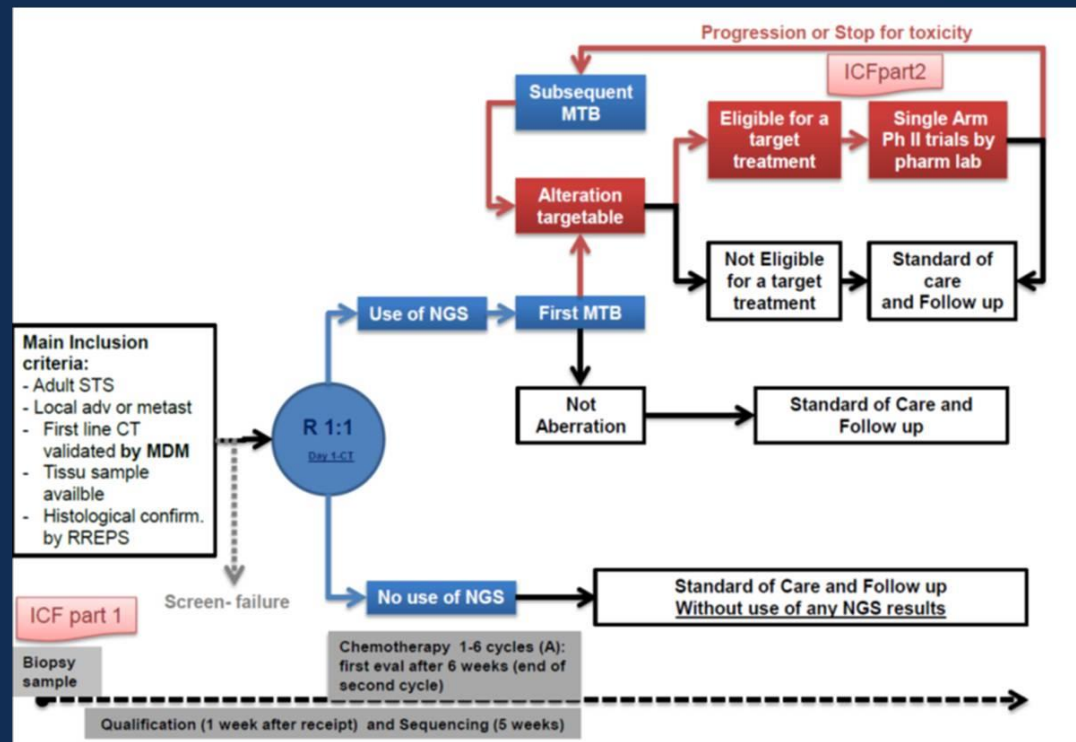
www.oncokb.org

**OncoKB: A Precision Oncology
Knowledge Base**

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MULTISARC Schema



Tropomyosin Receptor Kinase (TRK)

Role of TRK in normal biology and cancer

Neurotrophin family of receptors

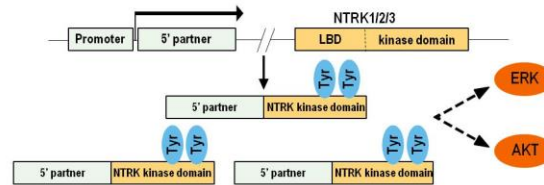
TRKA (*NTRK1*) → Pain, thermoregulation

TRKB (*NTRK2*) → Movement, memory, mood, appetite, body weight

TRKC (*NTRK3*) → Proprioception

TRK fusions

- Ligand binding domain (LBD) replaced by 5' fusion partner
- Drives overexpression and ligand-independent activation



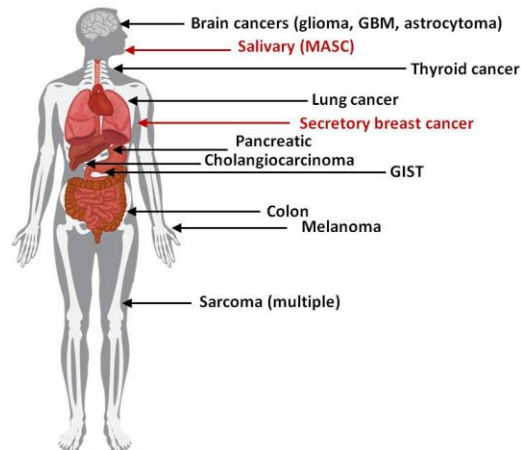
TRK uncommonly expressed in normal tissues or cancer

Fusion drives abnormally high expression and activation of TRK kinase domain

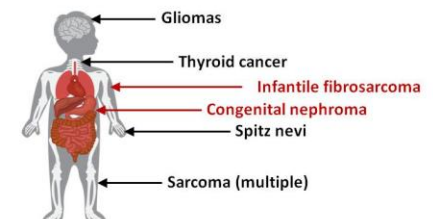
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TRK fusions found in diverse cancer histologies



- Common cancer with low TRK fusion frequency
- Rare cancer with high TRK fusion frequency



Estimated 1,500–5,000 patients harbor TRK fusion-positive cancers in the United States annually

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Larotrectinib (LOXO-101), a selective Tropomyosin Receptor Kinase (TRK) inhibitor

Larotrectinib TRK fusion development program

Adult phase I

- Age ≥ 18 years
- Advanced solid tumors

n=8

SCOUT: pediatric phase I/II

- Age ≤ 21 years
- Advanced solid tumors

n=12

NAVIGATE: adult/adolescent phase II 'basket' trial

- Age ≥ 12 years
- Advanced solid tumors
- TRK fusion positive

n=35

**N=55
TRK fusion
patients**

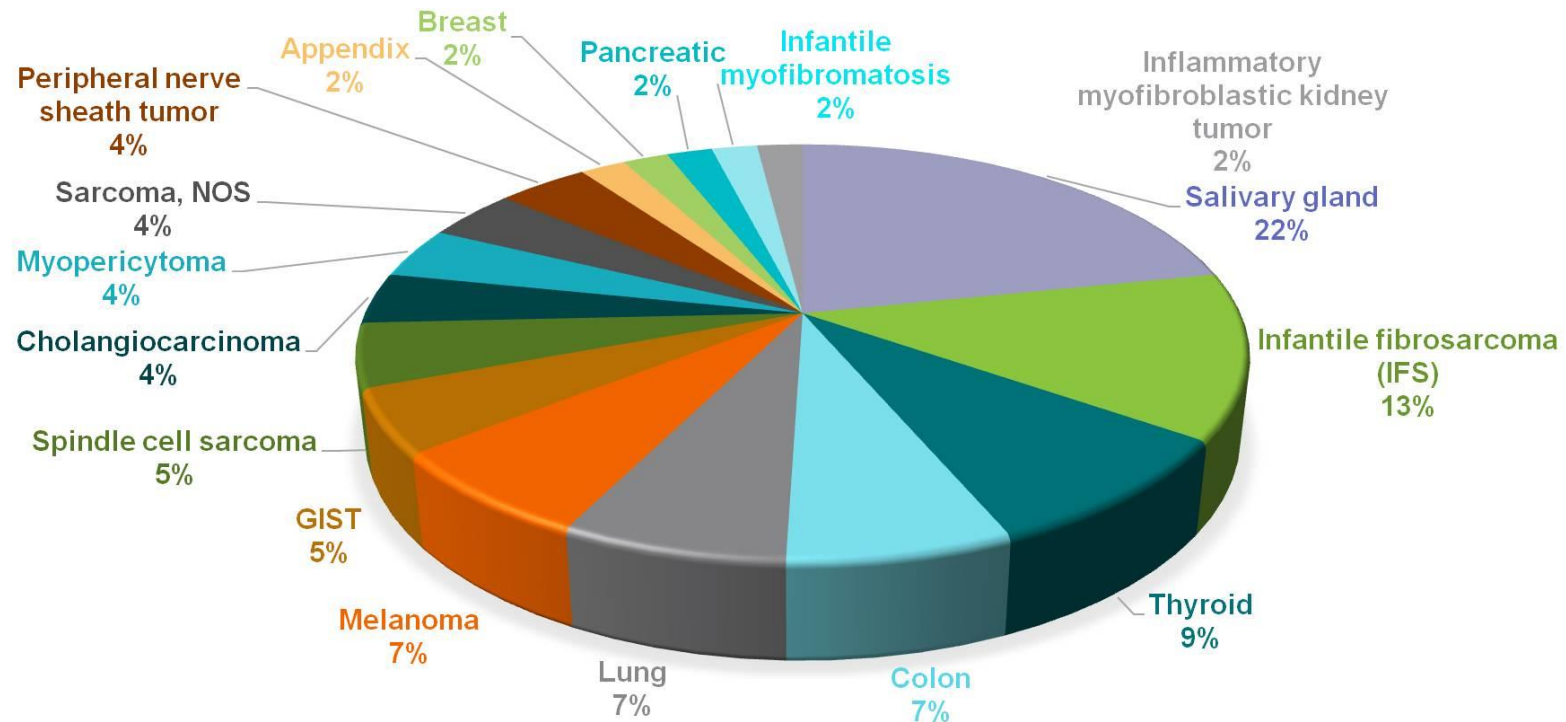
- **TRK fusion status** determined by local CLIA (or similarly accredited) laboratories
- **Primary endpoint**
 - Best objective response rate (ORR)
 - RECIST v1.1 per investigator assessment
- **Secondary endpoints**
 - Duration of response (DOR)
 - Progression-free survival (PFS)
 - Safety
- **Dosing**
 - Single-agent larotrectinib, administered predominantly at 100 mg BID continuously
 - Treatment beyond progression permitted if patient continuing to benefit

Data cut-off: April 14, 2017

N = 55; Age 4 months – 76 years !!!

Lacrotrectinib (LOXO-101), a selective Tropomyosin Receptor Kinase (TRK) inhibitor

Diversity of cancers treated - 17 unique types



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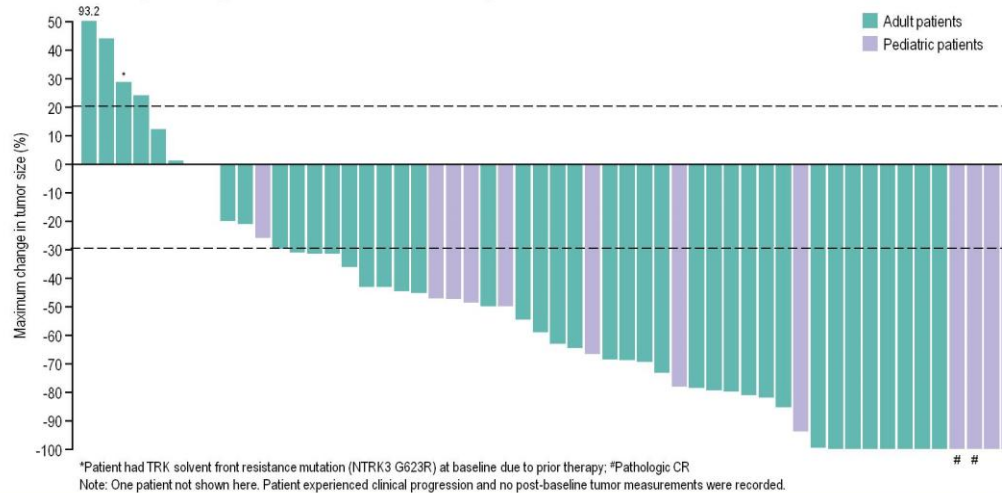
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CR 12%, PR 64%

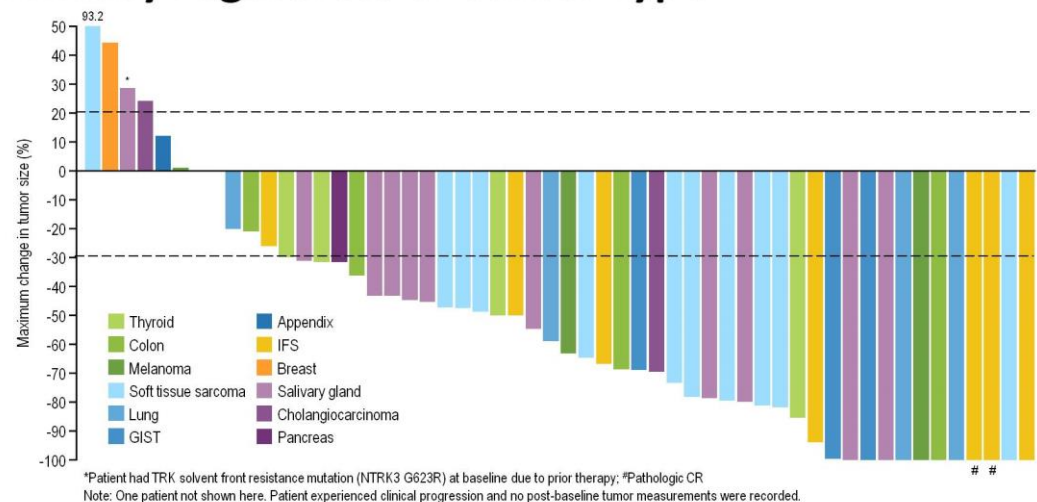
Lacrotrectinib (LOXO-101), a selective Tropomyosin Receptor Kinase (TRK) inhibitor

Efficacy regardless of age



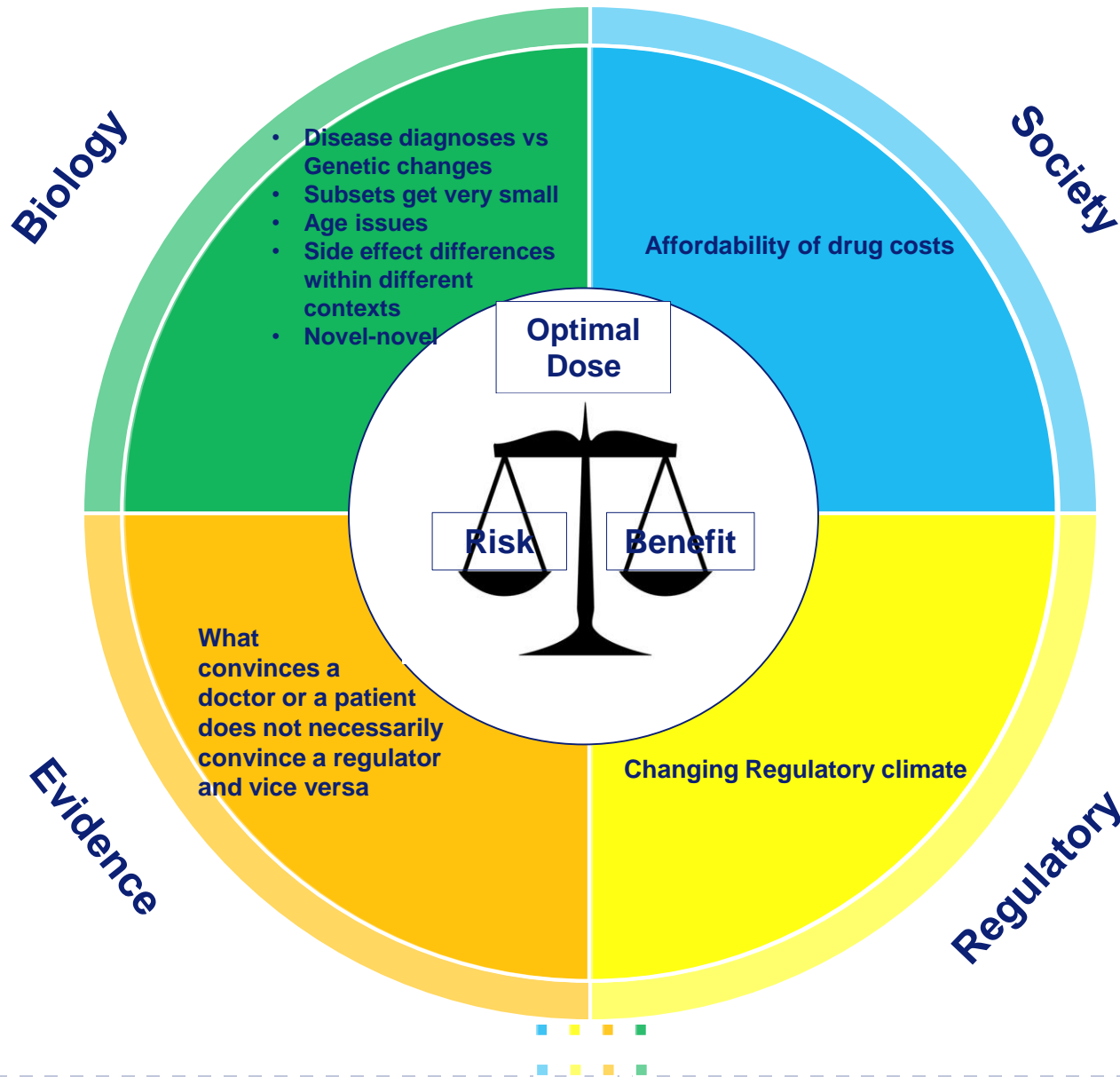
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Efficacy regardless of tumor type



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Our challenges are diverse and manifold



In the end, we all (patients, care-providers, regulators, pharmaceutical industry, and even insurance companies) share the same aim:

**To get a novel and better drug on
the market
as quickly as possible**