

# The NTRKers: WHO WE ARE

- NTRKers Foundation, Inc. is a non-profit. We are a growing community of patients and care partners, who unite and support people affected by NTRK gene fusion cancer
- Our goal is for every adult and child with NTRK gene fusion cancer to have the best chance of living life to the fullest

# WHAT THE NTRKers ARE DOING TO HELP

- We collaborate with medical experts and other cancer groups
- We host educational webinars and patient summits
- We share experiences and information within our closed Facebook group



**NTRKers**

NEVER ALONE: TESTING. KNOWLEDGE. SUPPORT

# The NTRKers: WHERE TO FIND US

- Find us online: [NTRKers.org](https://NTRKers.org)
- Email us: [Info@NTRKers.org](mailto:Info@NTRKers.org)
- Find us on Twitter: [@NTRKers](https://twitter.com/NTRKers)
- Find us on Facebook: [NTRK Support Group](https://www.facebook.com/NTRKSupportGroup)



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# Understanding Drug Resistance

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December 5, 2024

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# Disclaimer

We will not provide any medical advice or speak to individual cases during this event.

All information shared during this discussion is for general informational and educational purposes only. It is not a substitute for professional medical advice. Always consult with a qualified and licensed physician or other medical care provider and follow their advice without delay.

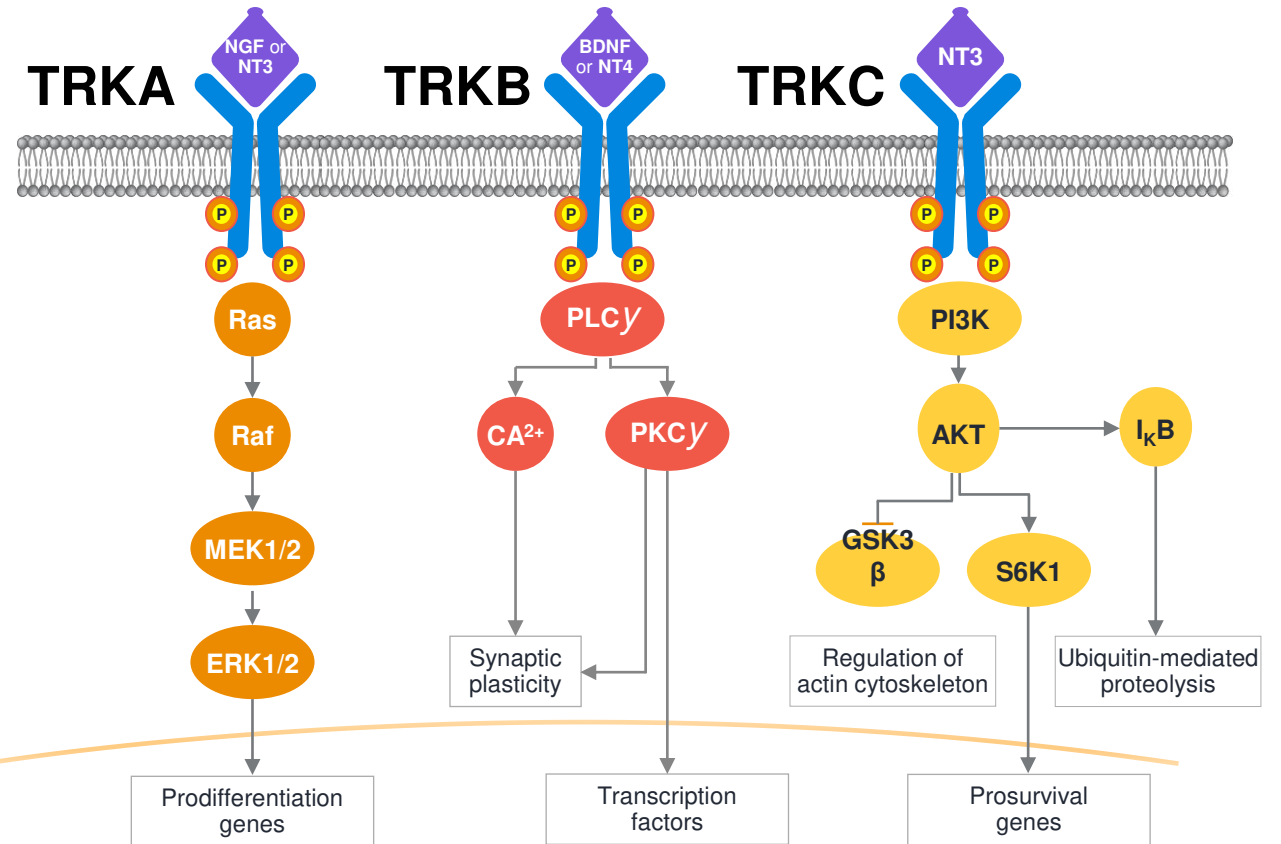
# Trk Receptors in Normal Biology and Cancer

## Trk receptor normal biology:

- Expressed in neuronal tissue and regulates development and nervous system function
- Rarely expressed in adult nonneuronal tissues

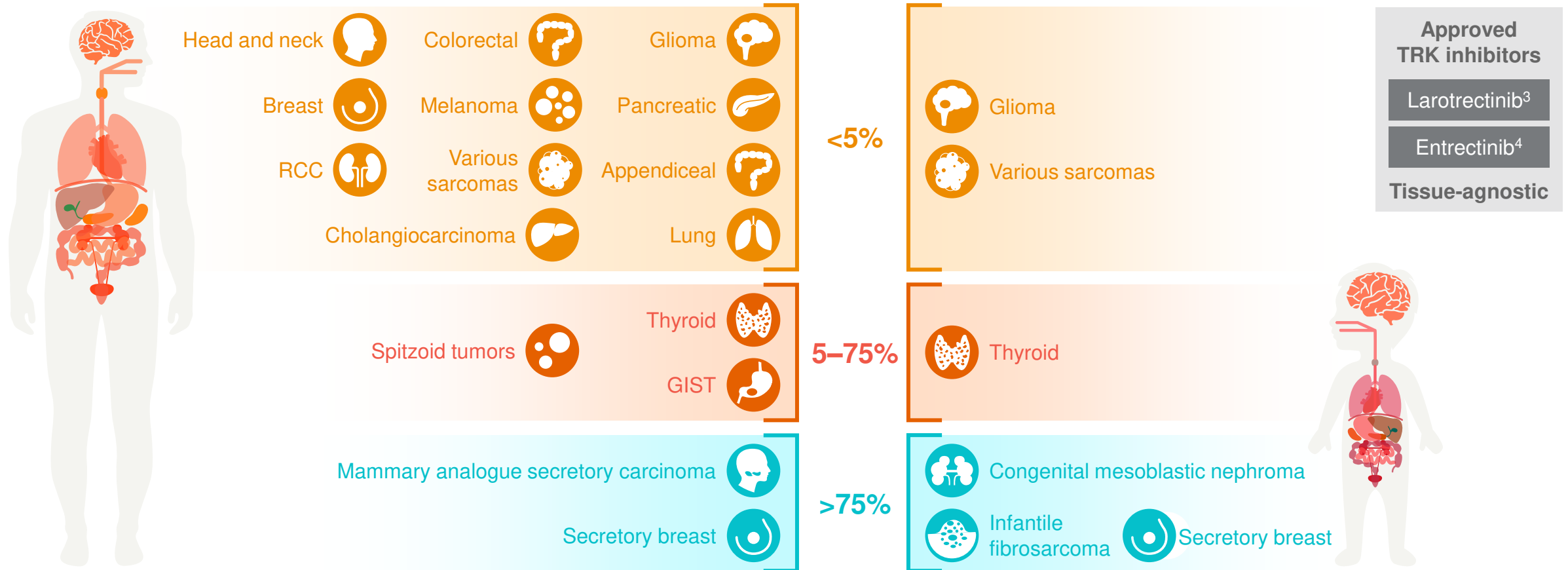
## *NTRK* gene fusions in cancer:

- Oncogenic drivers in various **adult** and **pediatric** cancers
- Causes the TRK protein to always be active, which may contribute to cancer growth



# NTRK Fusion Prevalence in Adult and Pediatric Tumors

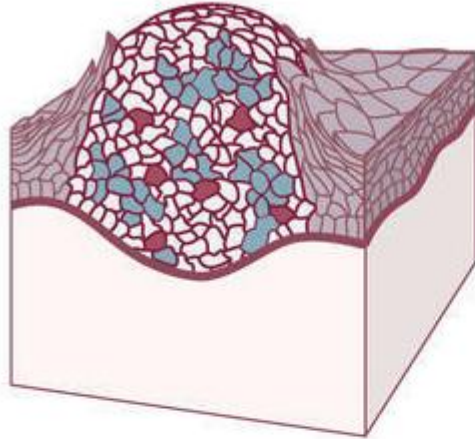
Rare in common tumors, common in rare tumors<sup>1,2</sup>



# Drug Resistance = Molecular Chess

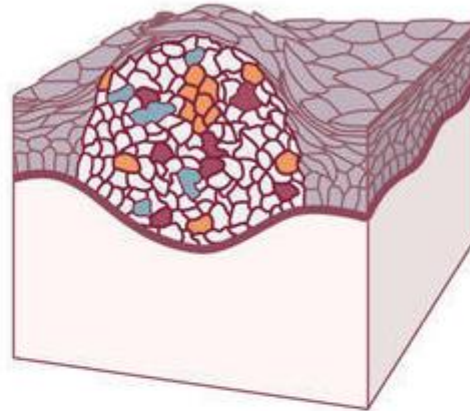


# What is drug resistance?



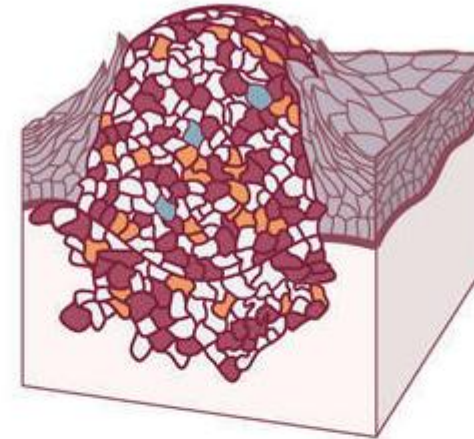
## Before Treatment

Tumors consist of cancer cells with different molecular features, which may make them sensitive or resistant to different types of treatments.



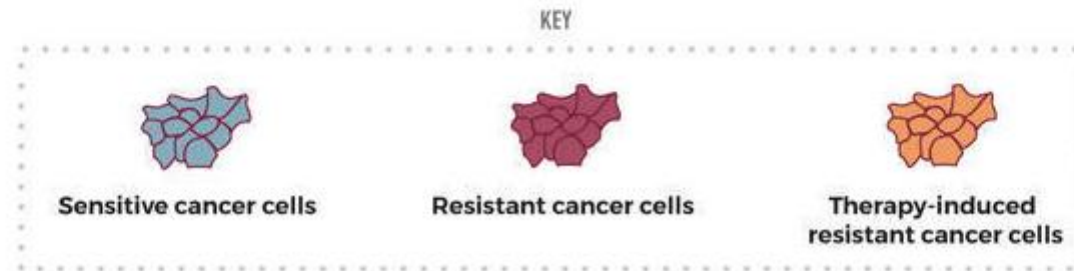
## Responding to Treatment

Although, a drug may kill some cancer cells (the sensitive cells), a subset of them almost invariably survives (the resistant cells).



## Developing Drug Resistance

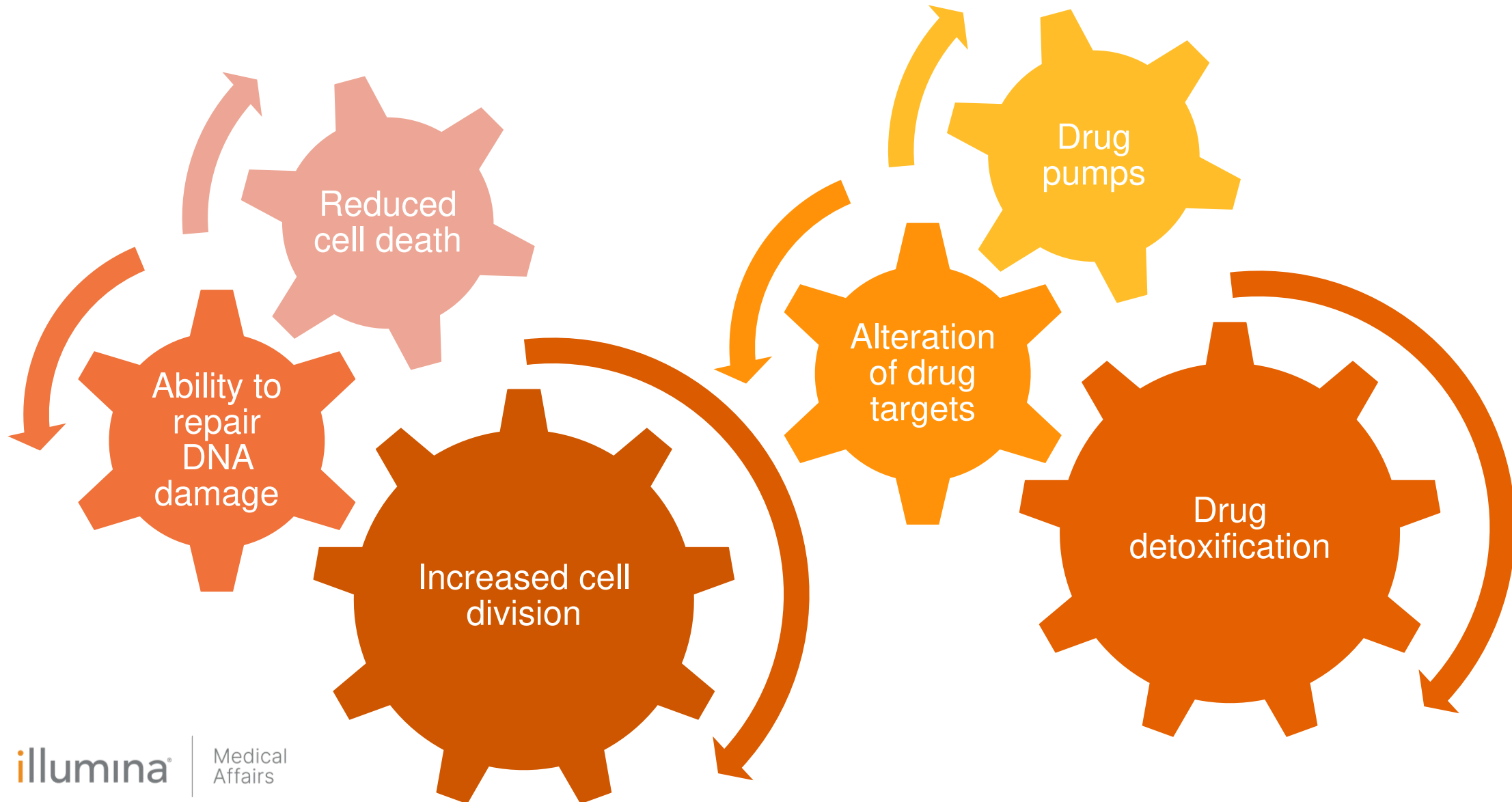
The cancer cells that are resistant will multiply, contributing to the re-growth of the tumor.



cancer.gov



# What causes drug resistance?



# Common Questions

- Can I prevent resistance?
- What does this mean for my treatment plan?
- Characteristics that make resistance more/less likely?
- Differences in pediatric versus adult cancers?



# Acquired Resistance to TRK Inhibitors

## On-Target Resistance

Secondary Mutations in the <i>NTRK</i> gene		
G595R	G693R	G623R
F589L	F633L	F617L
G667C	G709C	G696A
A608D		

## Mutations in other genes/pathways

- *KRAS* mutation
- *MET* amplification
- *BRAF* mutation
- *IGF1R* activation

## Off-Target Resistance

Progression on  
1<sup>st</sup> generation  
TRK inhibitors

Entrectinib  
Larotrectinib

Repotrectinib  
Selitrectinib

2<sup>nd</sup> generation TRK  
inhibitors

SoC or clinical trial  
when available

# Acquired Resistance to TRK Inhibitors

18\* *NTRK*<sup>+</sup> patients who progressed

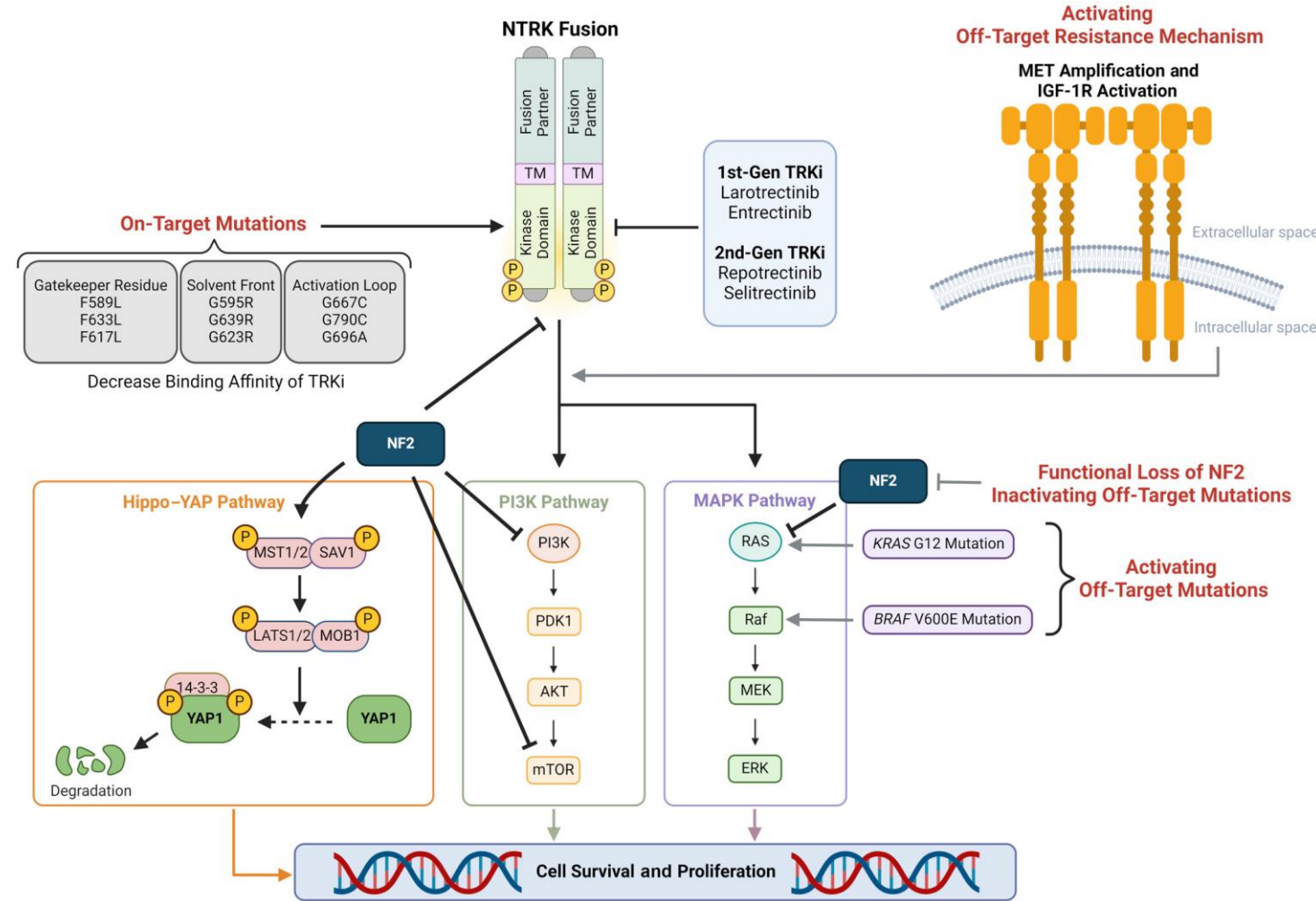


15/18 on-target resistance

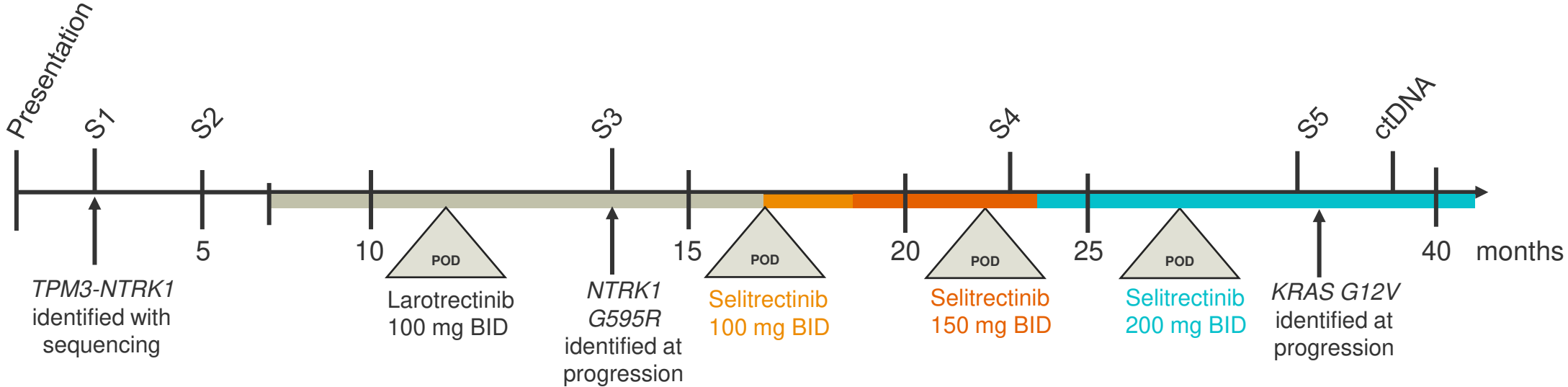
2/18 off-target resistance

1/18 no identifiable mechanism

Abstract 3104, ASCO 2022 Annual meeting  
\*only looked for patients who had progressed on first generation therapy



# Case Example: Resistance to Larotrectinib in a *TPM3-NTRK1*-Driven Sarcoma



47-year-old woman diagnosed with unclassified sarcoma

Patient was enrolled on a phase 2 trial of larotrectinib with an initial PR

- An expanded-access, single-patient protocol was initiated using selitrectinib and a PR was achieved at 3 months
- After 5 months, isolated progression and the selitrectinib dose was increased, and **the patient remained free of disease progression for >1 year**

# Thank you!

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