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# Drug Resistance in ALK- and ROS1-Rearranged Lung Cancers

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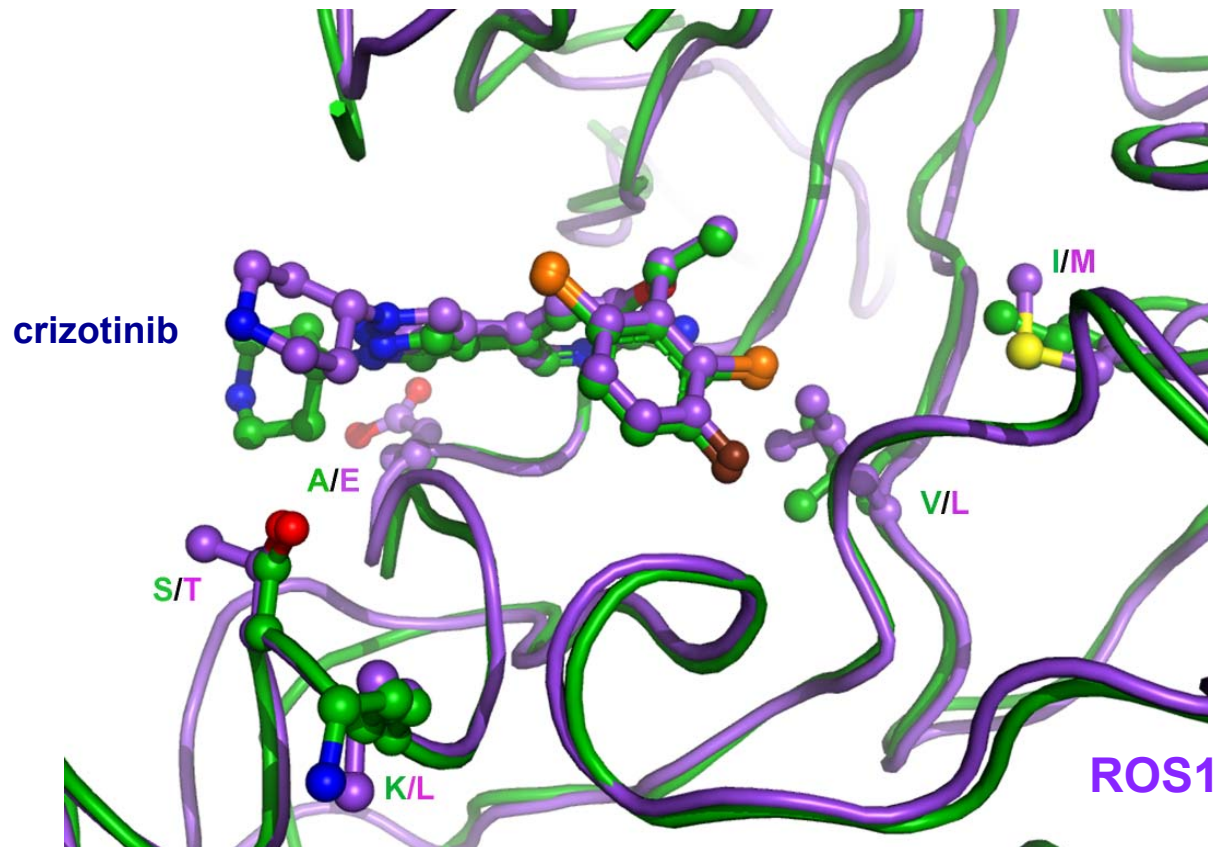


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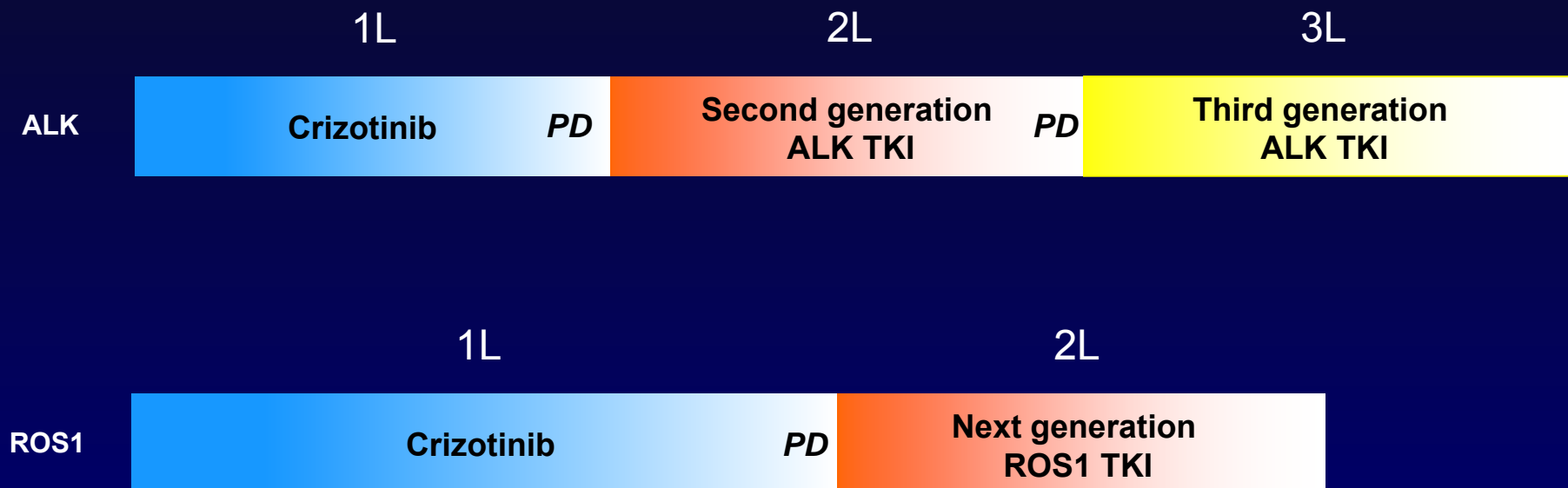
CANCER CENTER

# ALK and ROS1 are Related Tyrosine Kinases, and Both are Targeted by Crizotinib

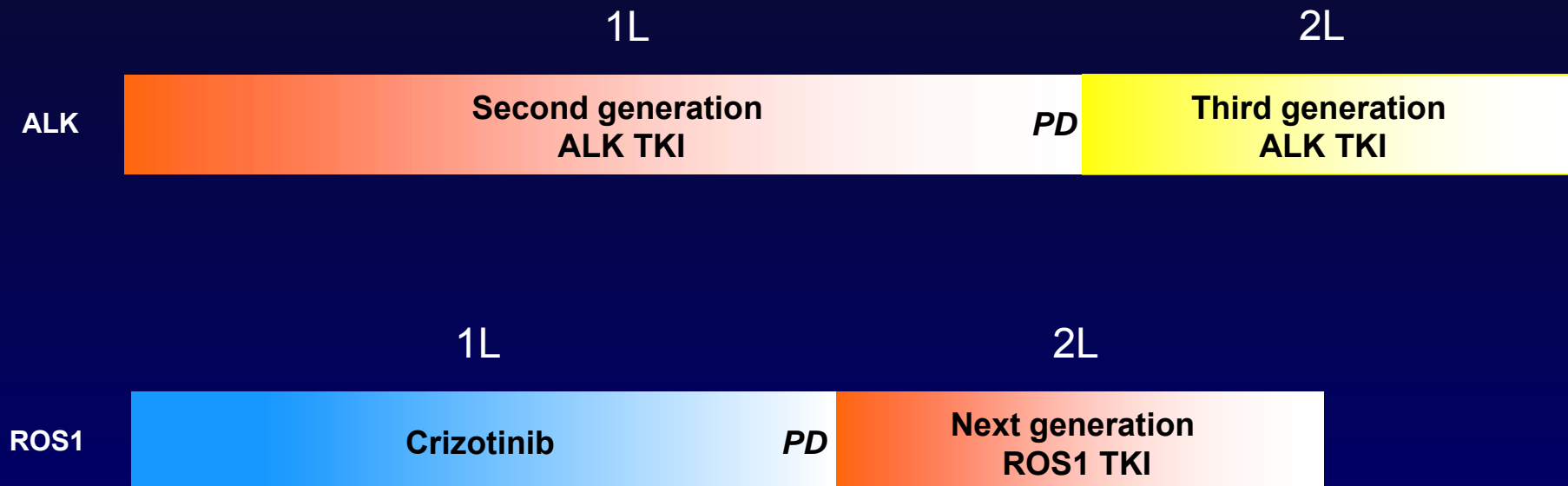


**ALK+ NSCLC**

# Current Treatment Strategy for Advanced ALK+ and ROS1+ NSCLC



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# ALK Inhibitors

ALK TKI	ROS1 activity	Status	Ongoing Studies
Crizotinib	<i>1<sup>st</sup> gen</i> Yes	FDA Approved (8-26-2011)	Completed
Ceritinib	Yes	FDA Approved (4-29-2014)	ASCEND-8 (food effect)
Alectinib	No	FDA Approved (12-11-2015)	Completed
Brigatinib	Yes	FDA Approved (4-28-2017)	Phase 3 (vs crizotinib)
Ensartinib	Yes	Investigational	Phase 3 (vs crizotinib)
Lorlatinib	Yes	Investigational FDA Breakthrough Therapy	Phase 3 (vs crizotinib)
TPX-0005	Yes	Investigational	Phase 1

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Brigatinib	<i>2<sup>nd</sup> gen</i> Yes	FDA Approved (4-28-2017)	Phase 3 (vs crizotinib)
Ensartinib	Yes	Investigational	Phase 3 (vs crizotinib)
Lorlatinib	Yes	Investigational FDA Breakthrough Therapy	Phase 3 (vs crizotinib)
TPX-0005	Yes	Investigational	Phase 1



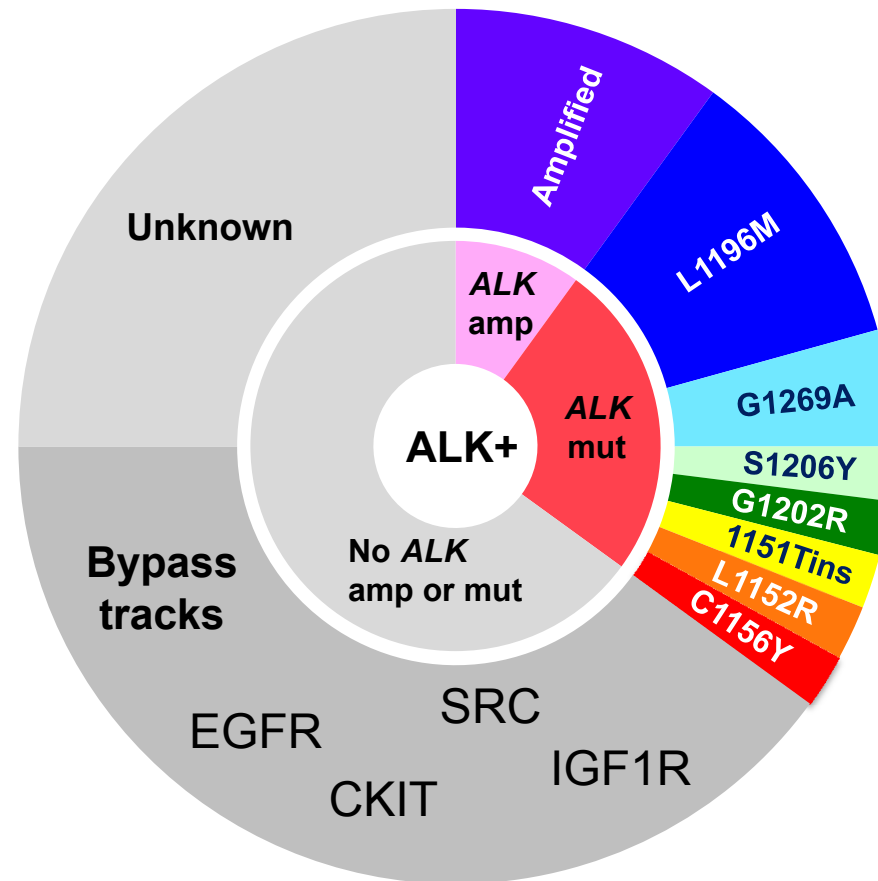
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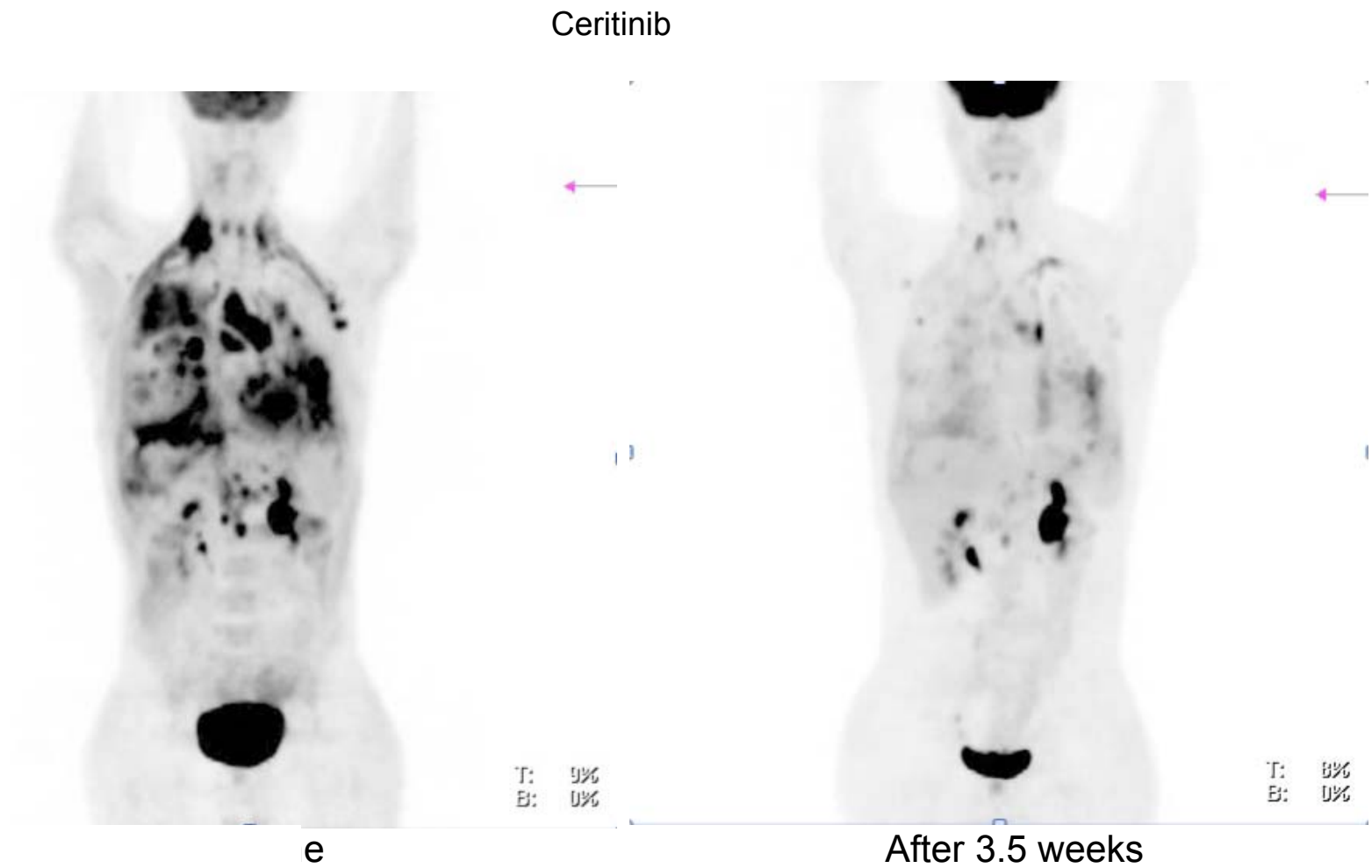
*3rd gen*



# Multiple Different Mechanisms of Resistance to the First Generation ALK TKI Crizotinib



# But Most Crizotinib-Resistant Patients Respond to More Potent Next Generation ALK TKIs



# Sequential 1<sup>st</sup> and 2<sup>nd</sup> Generation ALK TKIs in Advanced ALK+ NSCLC



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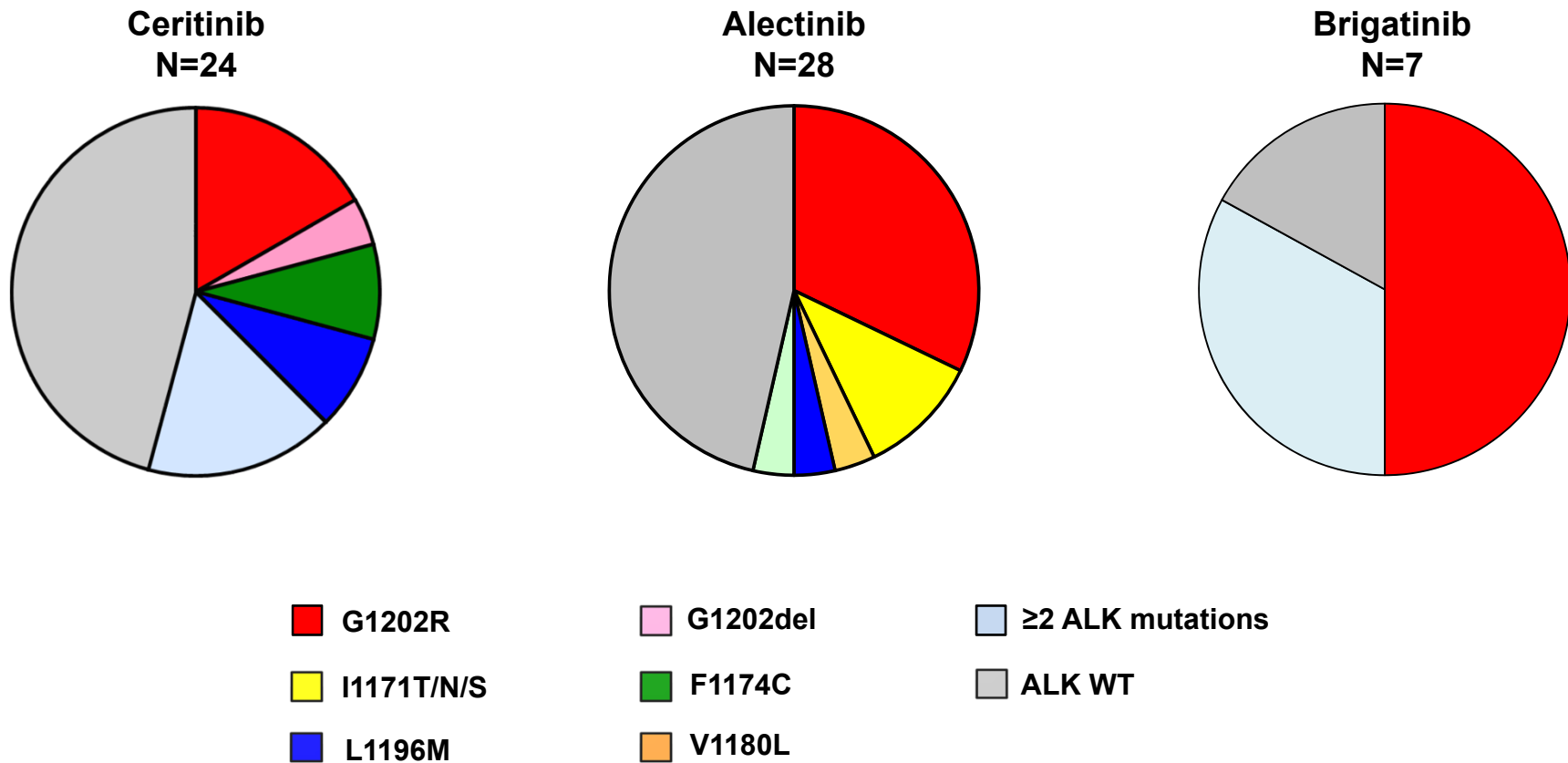
**REBIOPSY *if possible*:**  
to identify ALK mutations  
that impact selection  
of next gen ALK TKI:  
C1156Y, F1174, I1171, G1202R

# Sequential 1<sup>st</sup> and 2<sup>nd</sup> Generation ALK TKIs in Advanced ALK+ NSCLC



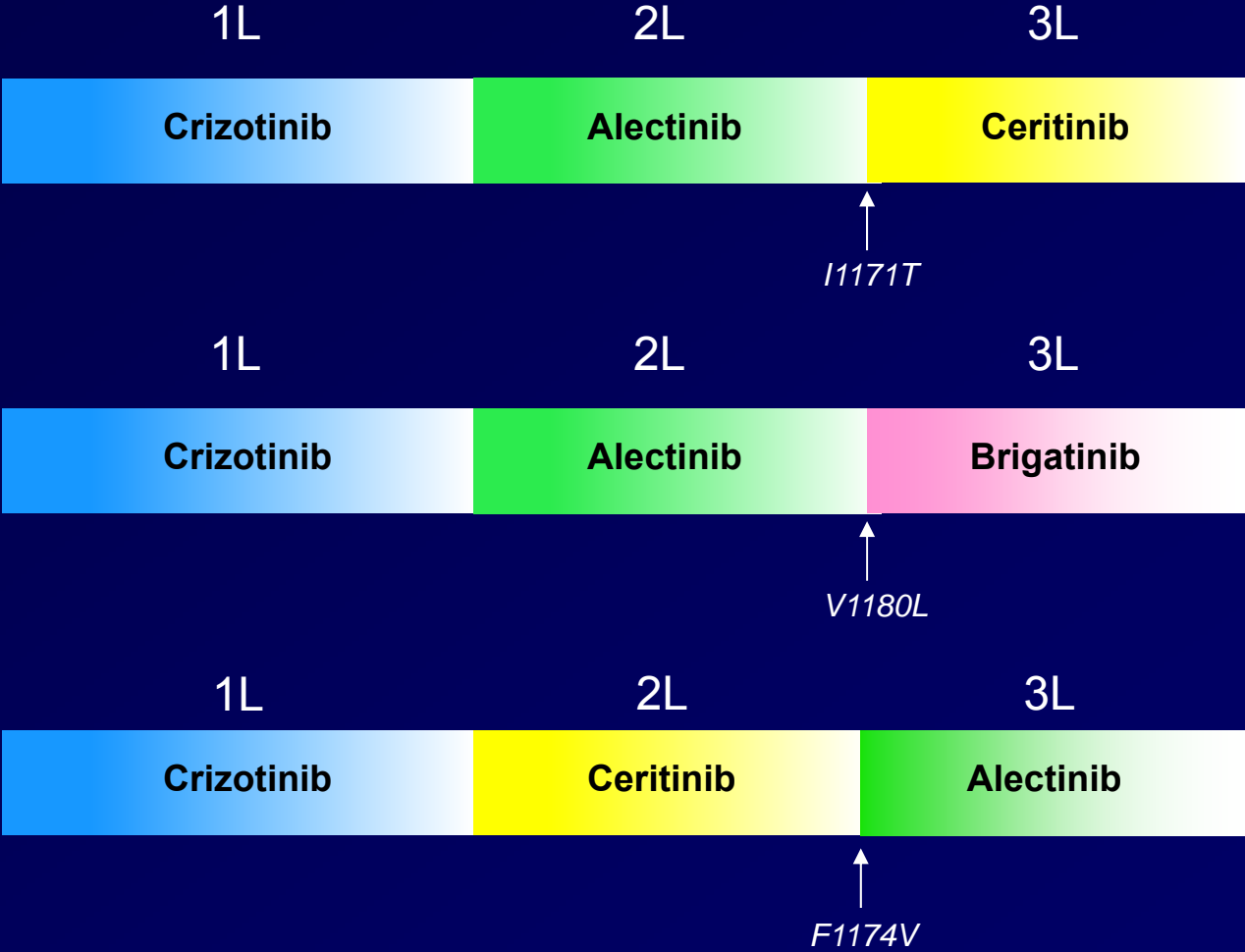
# Resistance to 2<sup>nd</sup> Generation ALK TKIs:

*ALK Resistance Mutations Identify Tumors That Remain ALK Dependent*



Updated from Gainor et al., Cancer Discov 6(10): 1118-113, 2016

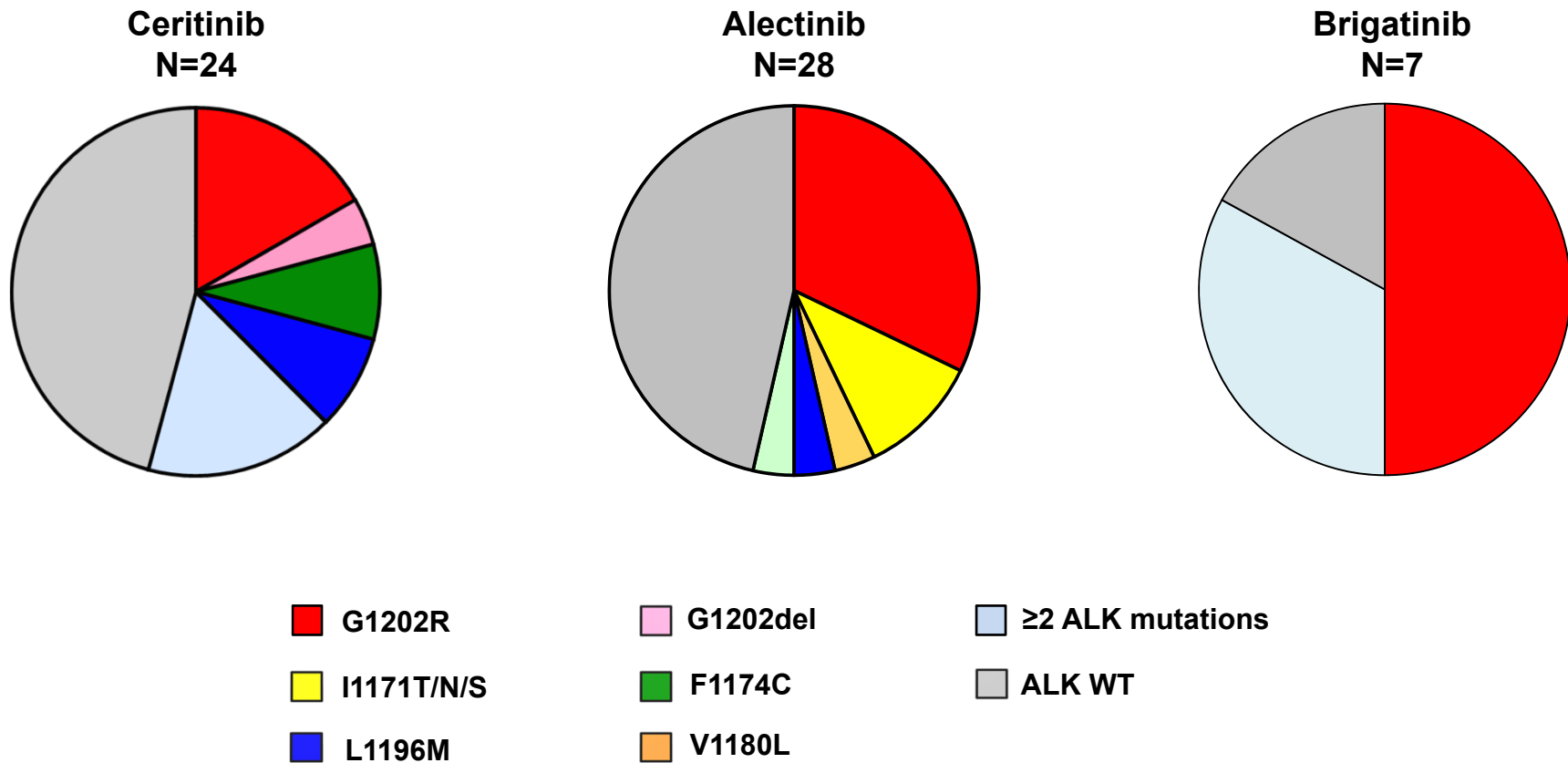
# Real-Life Examples of ALK Mutation-Based Selection of a Third-Line ALK TKI





# Resistance to 2<sup>nd</sup> Generation ALK TKIs:

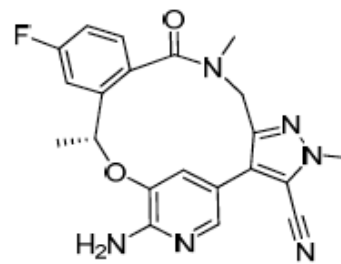
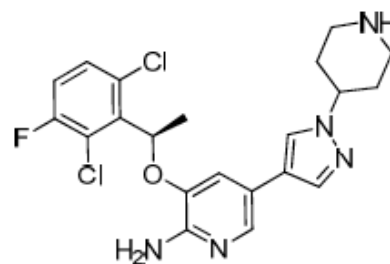
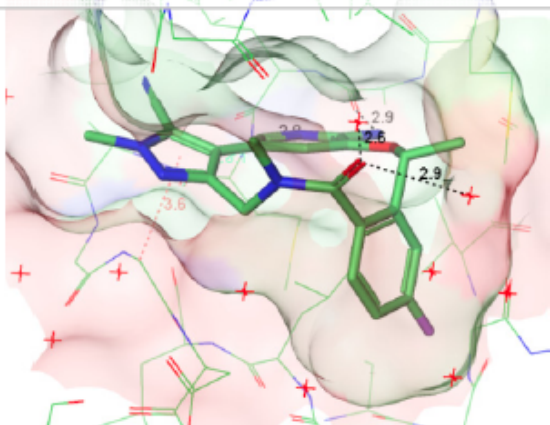
*ALK G1202R Commonly Emerges at Resistance*



Updated from Gainor et al., Cancer Discov 6(10): 1118-113, 2016

# Lorlatinib (PF-06463922) is a Potent, Pan-Inhibitory, CNS Penetrant ALK/ROS1 TKI

PF-06463922/L1196M-ALK bound structure



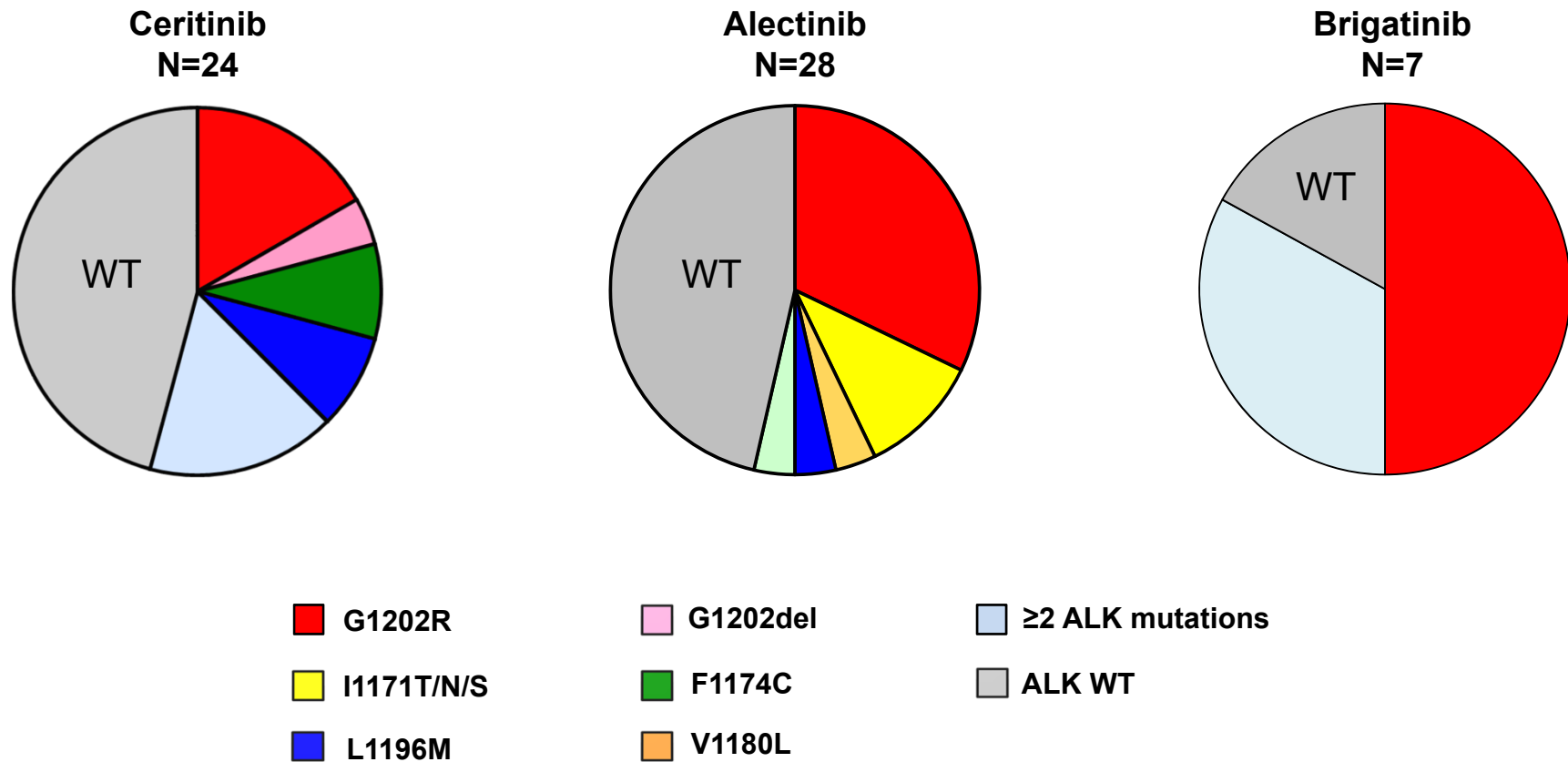
**crizotinib**

**PF-06463922**

ALK WT NIH3T3 IC50 (nM)	80	1.3
ALK L1196M NIH3T3 IC50 (nM)	843	21
<b>ALK G1202R NIH3T3 IC50 (nM)</b>	<b>1148</b>	<b>77</b>
ROS1-CD74 IC50 (nM)	11	0.24
MDR BA/AB	45	1.5

# Resistance to 2<sup>nd</sup> Generation ALK TKIs:

*No ALK Resistance Mutations Suggest Tumors May be ALK-Independent*

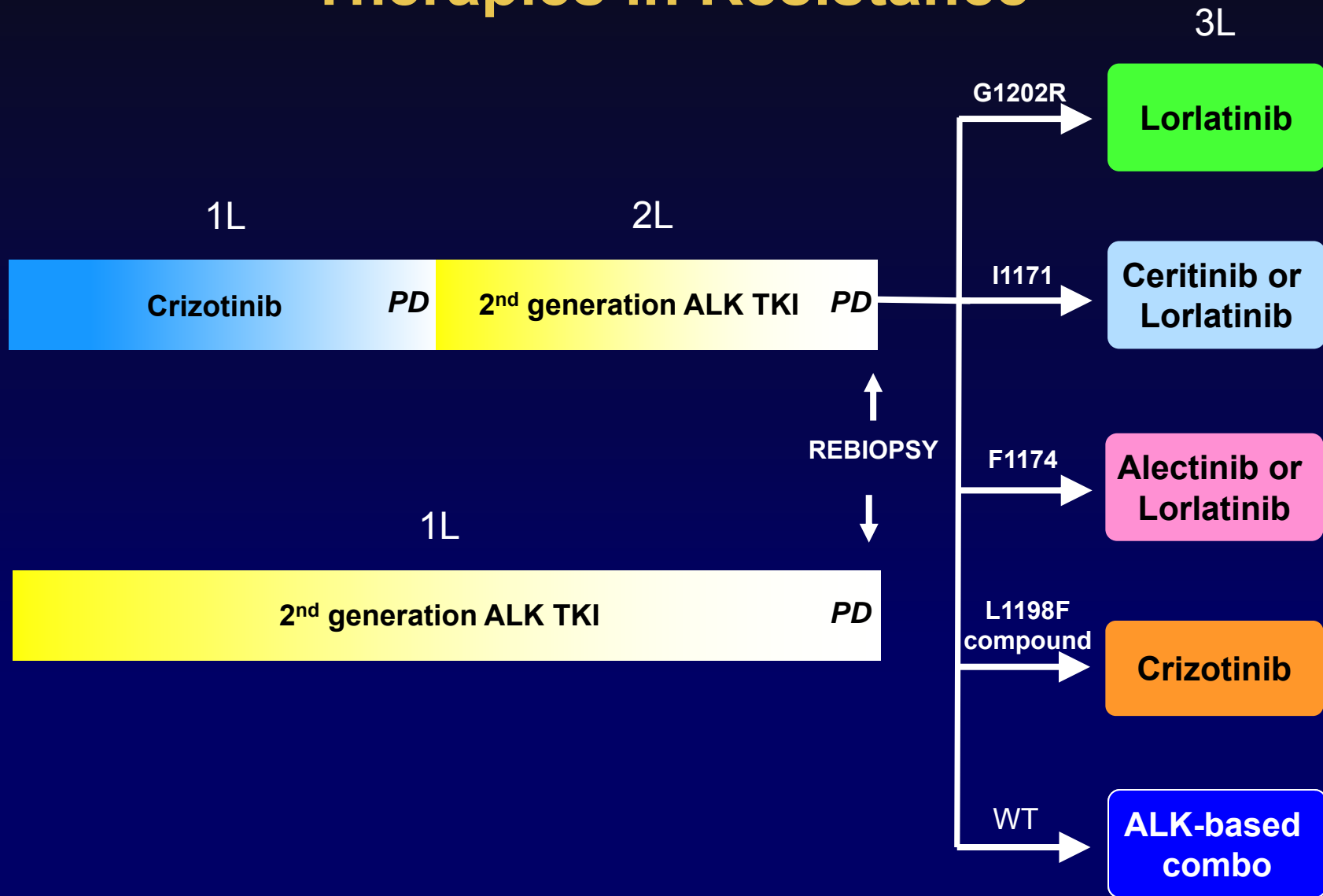


Updated from Gainor et al., Cancer Discov 6(10): 1118-1113, 2016

# Select Bypass Mechanisms and Therapeutic Combination Strategies in ALK+ NSCLC

Pathway	Mechanism of activation	Potential Rx
EGFR	Ligand secretion (EGF, amphiregulin, neuregulin)	<i>Ceritinib + cetuximab</i> <i>Brigatinib + panitumumab</i>
CKIT	Amplification, ligand secretion (SCF)	
MET	Gene amplification	<i>Crizotinib + lorlatinib</i> <i>Ceritinib + capmatinib</i>
IGF-1R	Ligand secretion (IGF-1)	
HER2/HER3	Ligand secretion (EGF, neuregulin)	
SRC	Unknown	<i>TPX-0005</i>
MAPK	WT KRAS copy number gain, DUSP6 downregul'n	<i>Ceritinib + trametinib</i> <i>Alectinib + cobimetinib</i>
RTK(s)	Diverse mechanisms	<i>Ceritinib + SHP099</i>

# Tailoring Selection of ALK Targeted Therapies in Resistance



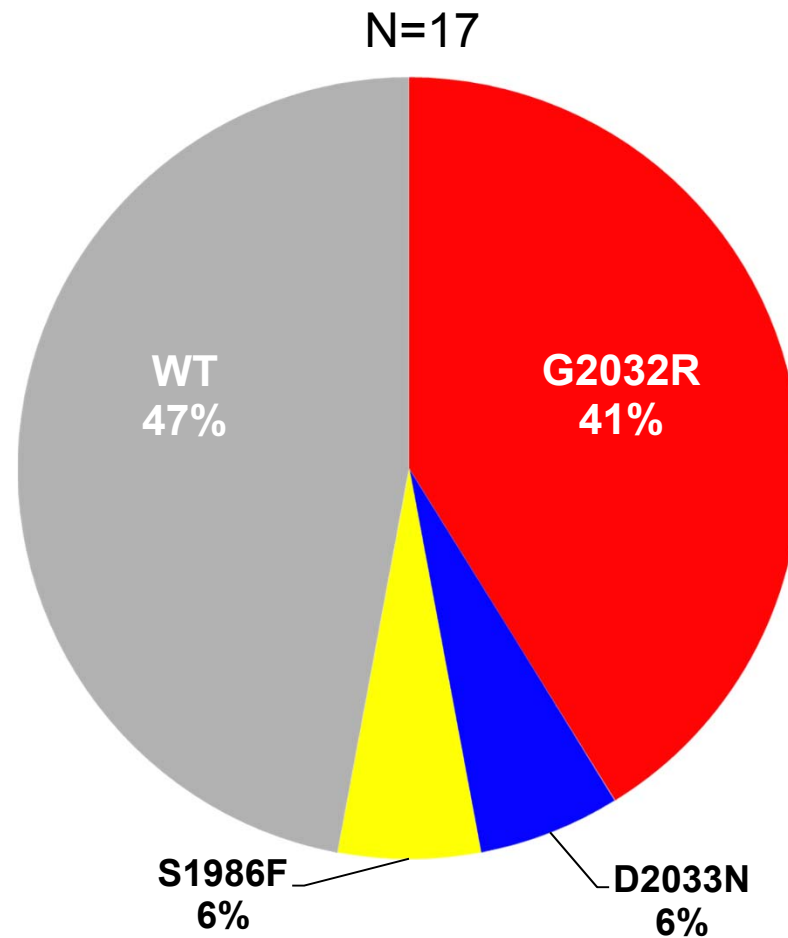
**ROS1+ NSCLC**



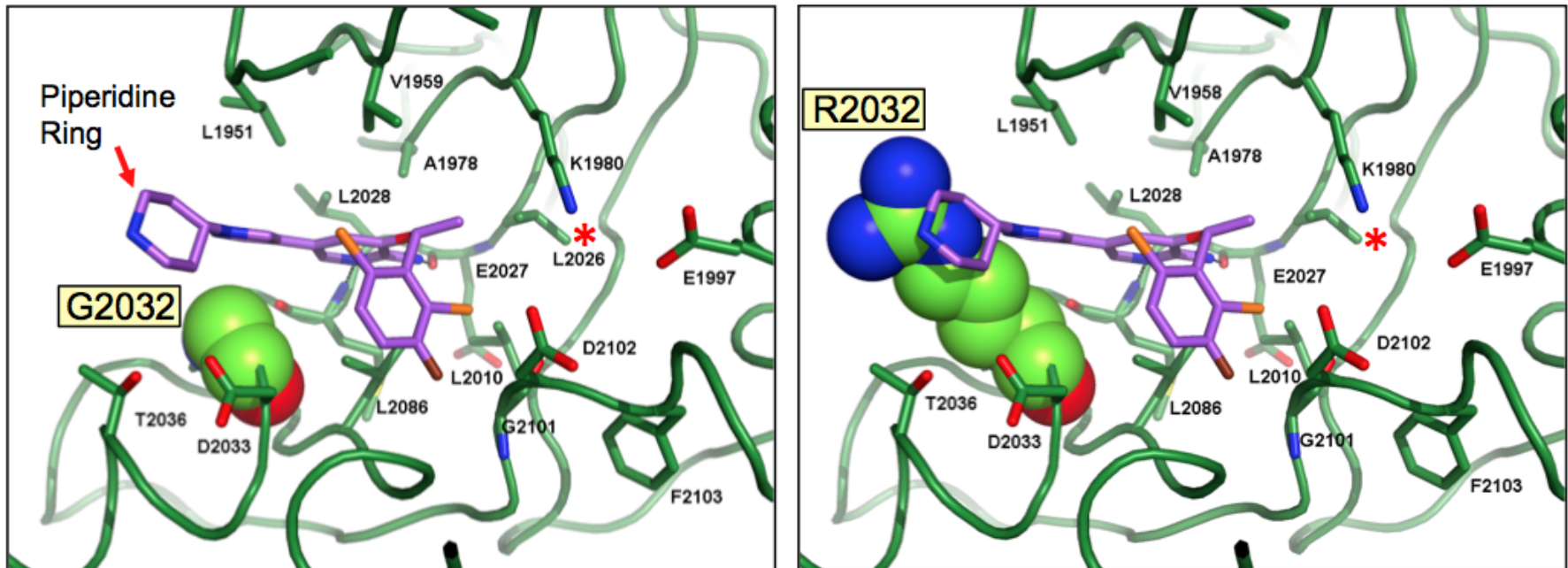
# ROS1 Inhibitors

	<b>Major Targets</b>	<b>Status</b>	<b>Ongoing Studies</b>
Crizotinib	ALK, ROS1, MET	FDA Approved (3-11-2016)	Completed
Ceritinib	ALK, ROS1	Investigational	Phase 2 (SIGNATURE)
Brigatinib	ALK, ROS1	Investigational	Investigator initiated trials
Lorlatinib	ALK, ROS1	Investigational	Phase 2 (closed)
Entrectinib	ALK, ROS1, TRK	Investigational	Phase 2 (CNS only)
DS-6051b	ALK, ROS1, TRK	Investigational	Phase 1
Cabozantinib	VEGFR, MET, RET, ROS1	Investigational (FDA Approved for Thyroid CA)	Phase 2 (MSKCC)
TPX-0005	ALK, ROS1, TRK, SRC	Investigational	Phase 1

# Crizotinib Resistance in ROS1+ NSCLC is Often Mediated by Secondary ROS1 Resistance Mutations



# Structural Basis for ROS1 G2032R-Mediated Resistance to Crizotinib



# Next-Generation ROS1 Inhibitors

	Major Targets	Predicted G2032R activity?	Trials
Ceritinib	ALK, ROS1	No <sup>1</sup>	Phase 2 (SIGNATURE)
Brigatinib	ALK, ROS1	No <sup>1</sup>	Investigator initiated trials
Lorlatinib	ALK, ROS1	Yes/No <sup>2,3</sup>	Phase 2 (closed)
Entrectinib	ALK, ROS1, TRK	No <sup>4</sup>	Phase 2 (CNS only)
DS-6051b	ALK, ROS1, TRK	Yes <sup>5</sup>	Phase 1
Cabozantinib	VEGFR, MET, RET, ROS1	Yes <sup>1,6</sup>	Phase 2 (MSKCC)
TPX-0005	ALK, ROS1, TRK, SRC	Yes <sup>7</sup>	Phase 1

<sup>1</sup>Katayama et al., Clin Cancer Res 21(1): 166-74, 2015; <sup>2</sup>Zou et al., PNAS 112: 3493-8, 2015; <sup>3</sup>Facchinetti et al., Clin Cancer Res 22: 5983-91, 2016; <sup>4</sup>Drilon et al., Cancer Discov, Feb 9 2017; <sup>5</sup>Papadopoulos et al., AACR 2016; <sup>6</sup>Davare et al., PNAS 110(48): 19519-24, 2015; <sup>7</sup>Zhai et al., AACR 2016

## Summary

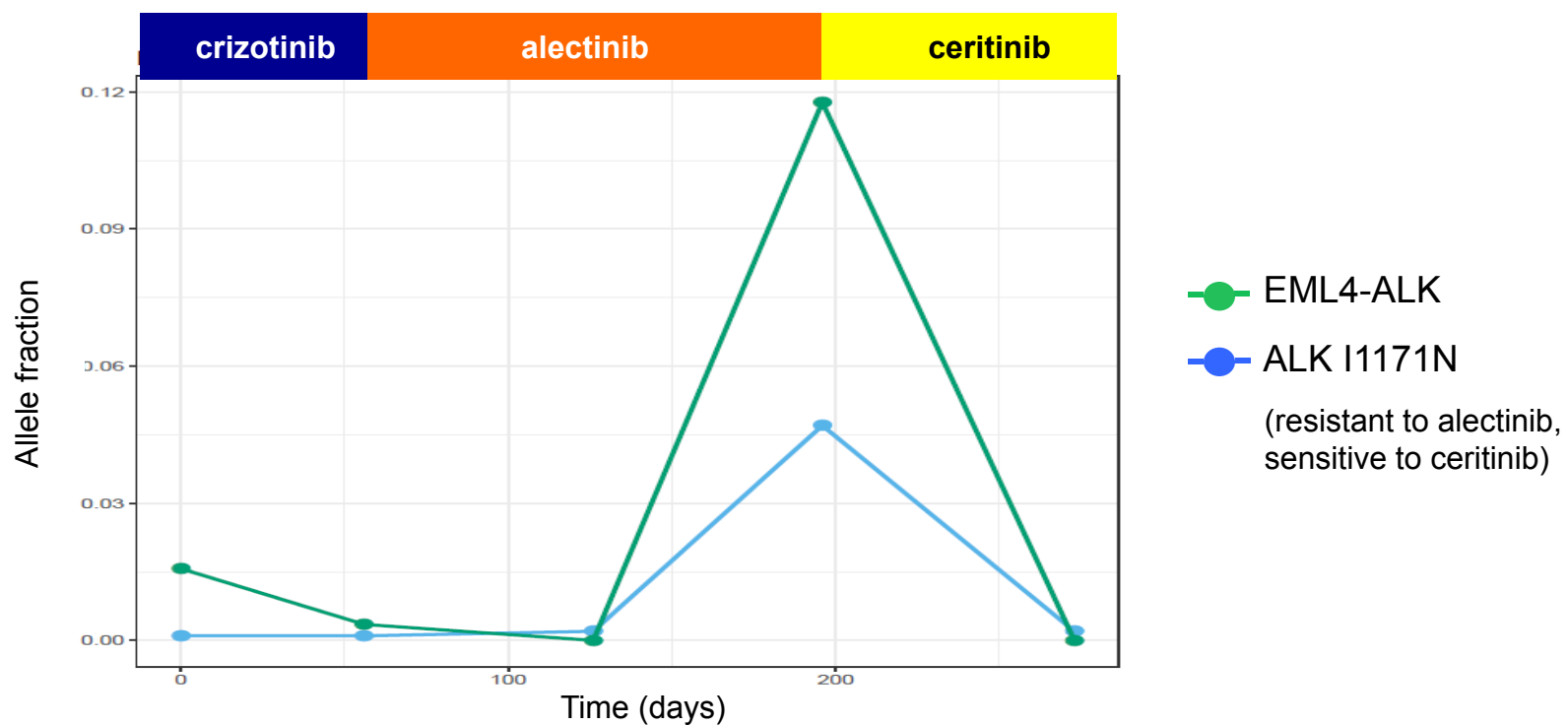
- **ALK+ and ROS1+ lung cancers are distinct molecular subsets of lung cancer and are highly oncogene-addicted**
- **A significant proportion of ALK+ lung cancers evolve multiple sequential on-target mechanisms of resistance, many of which are targetable**
- **Approximately one-half of ROS1+ lung cancers develop on-target mechanisms of resistance to crizotinib, particularly ROS1 G2032R**
- **Rebiopsies at the time of resistance can help guide the selection of subsequent targeted agents**

## Future Directions

- **Liquid biopsies may be useful for detecting resistance mutations in ALK+ and ROS1+ NSCLC**



# Plasma-Based Detection of Actionable ALK Resistance Mutations



## Future Directions

- **Liquid biopsies may be useful for detecting resistance mutations in ALK+ and ROS1+ NSCLC**
- **At some point, all ALK+ and ROS1+ cancers will develop off target mechanisms of resistance and lose their oncogene dependence**
- **Novel combinations and multimodality regimens are needed to improve outcomes for resistant patients**
- **Pan-inhibitory and CNS penetrant molecules like lorlatinib will have the greatest impact in the front-line setting**

**Thank you!**