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Drug Resistance in ALK- and ROS1-Rearranged Lung Cancers

Alice T. Shaw, MD PhD
Director, Center for Thoracic Cancers
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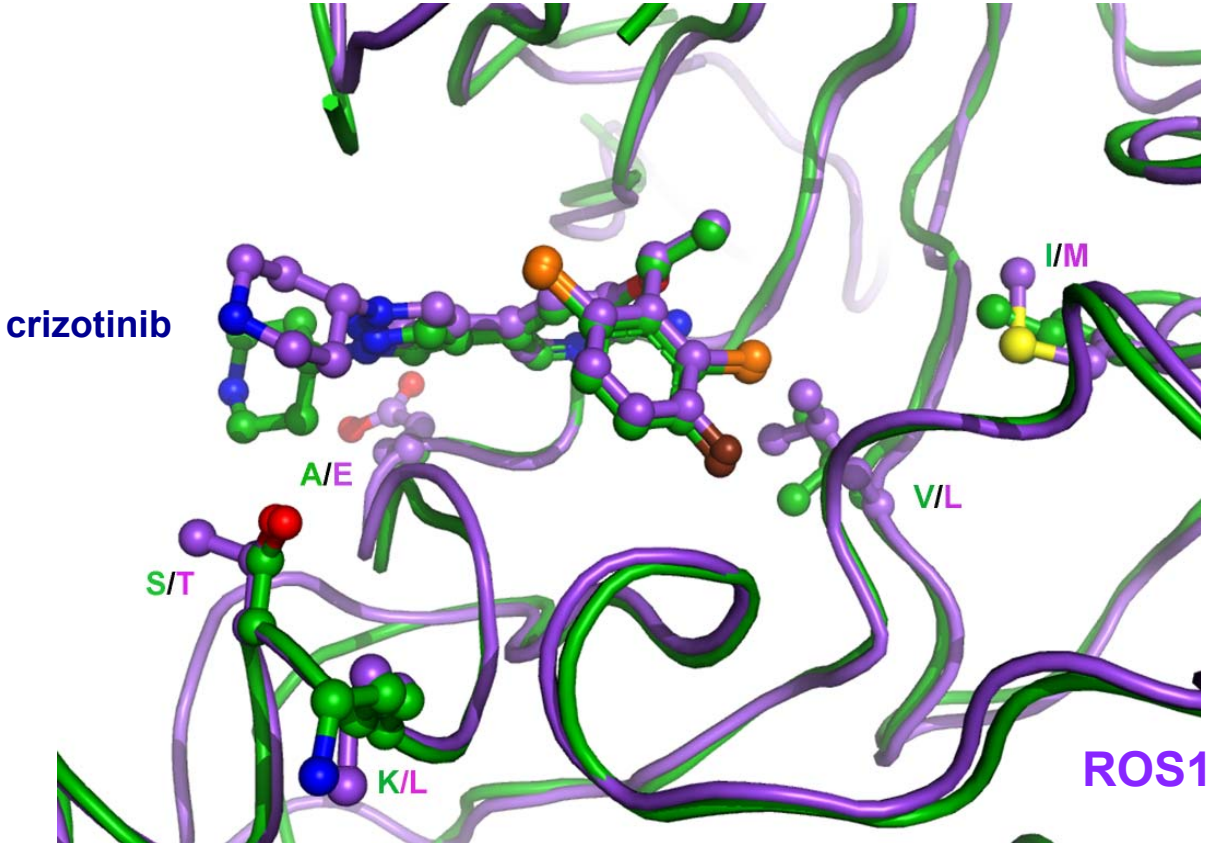
MASSACHUSETTS
GENERAL HOSPITAL
CANCER CENTER

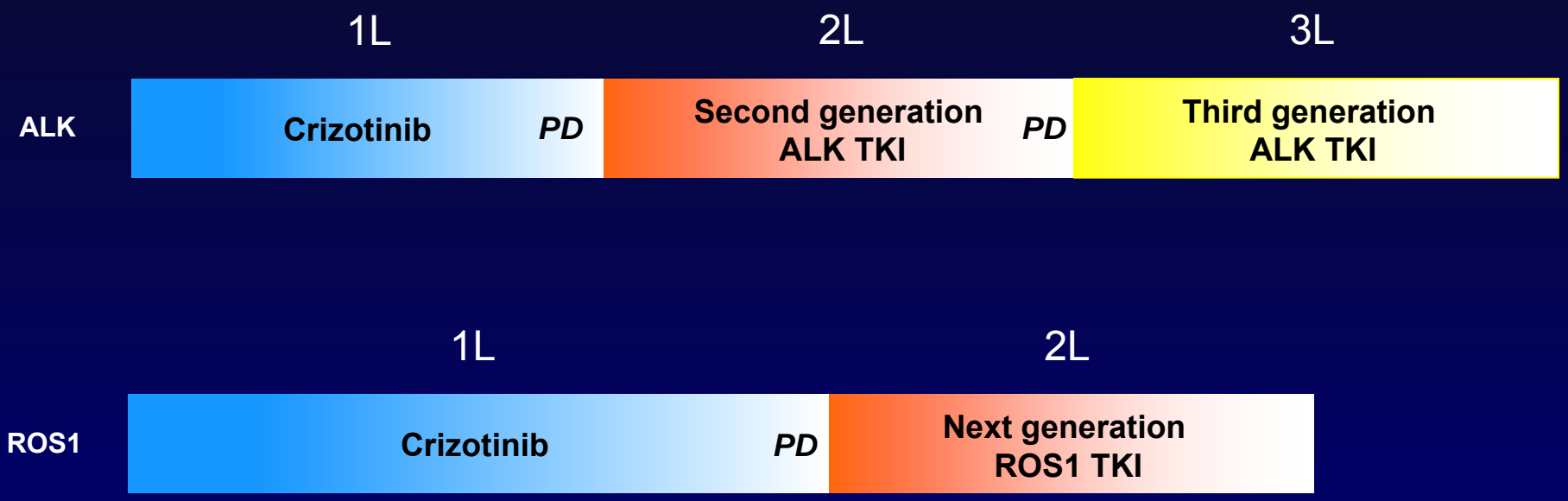
ALK and ROS1 are Related Tyrosine Kinases, and Both are Targeted by Crizotinib



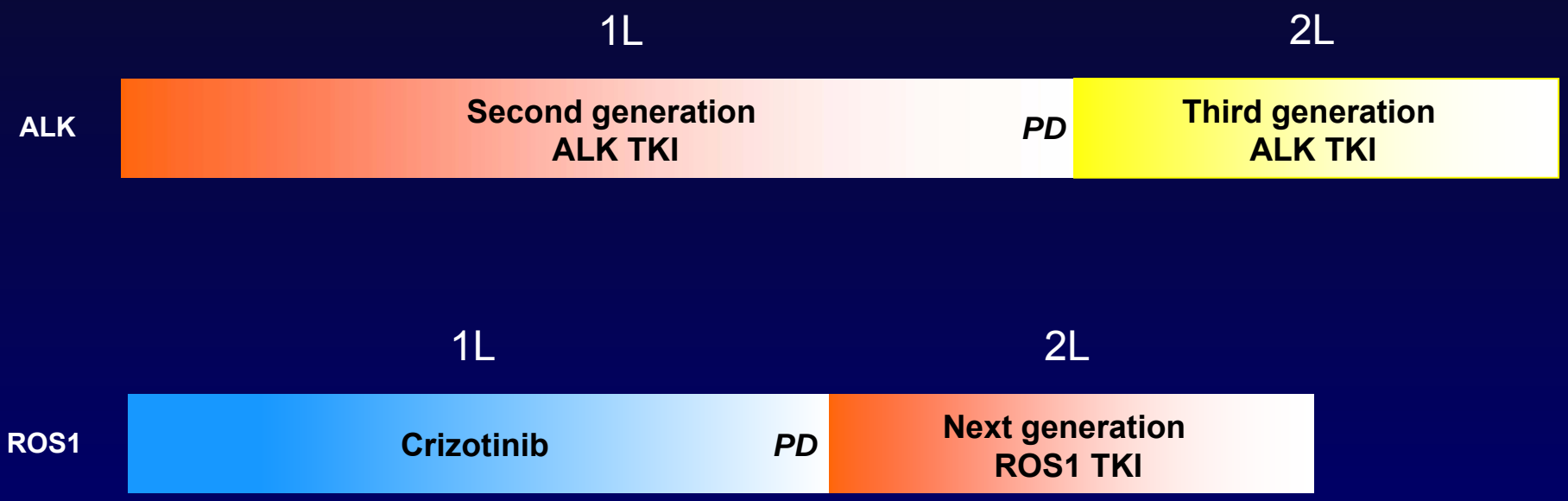
Shaw et al. NEJM 371(21): 1963-71, 2014

ALK+ NSCLC

Current Treatment Strategy for Advanced ALK+ and ROS1+ NSCLC



Current Treatment Strategy for Advanced ALK+ and ROS1+ NSCLC



ALK Inhibitors

ALK TKI		ROS1 activity	Status	Ongoing Studies
Crizotinib	*1st gen*	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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Alectinib	No	FDA Approved (12-11-2015)	Completed
Brigatinib *2nd gen*	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)
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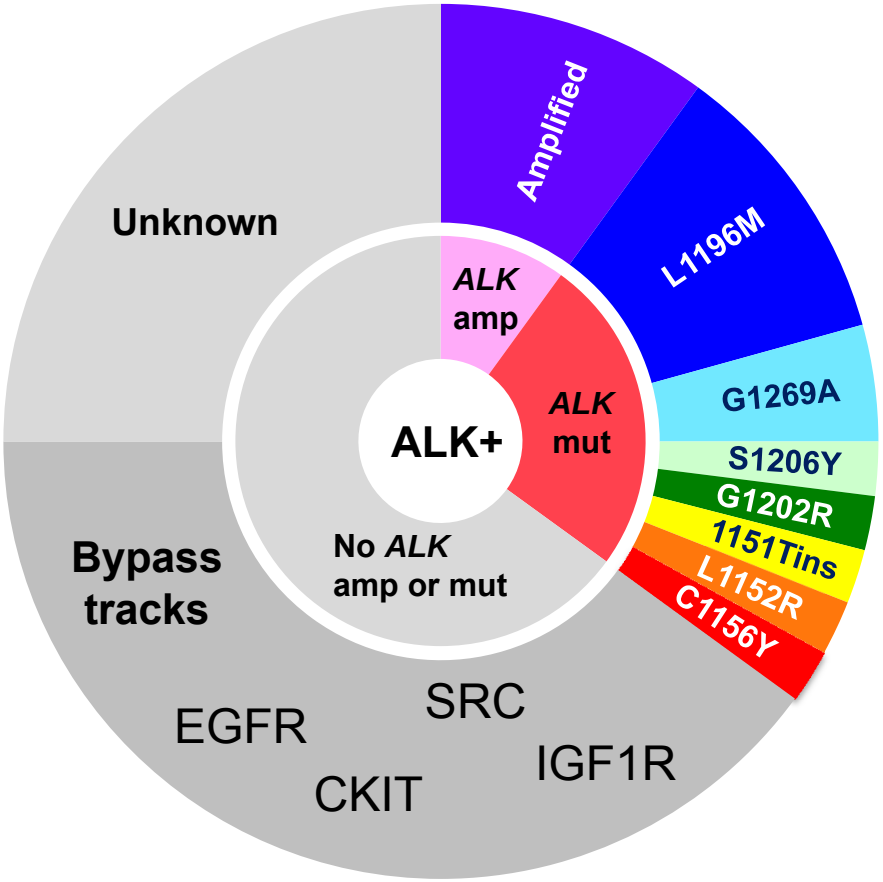
Lorlatinib *3rd gen*	Yes	Investigational FDA Breakthrough Therapy	Phase 3 (vs crizotinib)
TPX-0005	Yes	Investigational	Phase 1

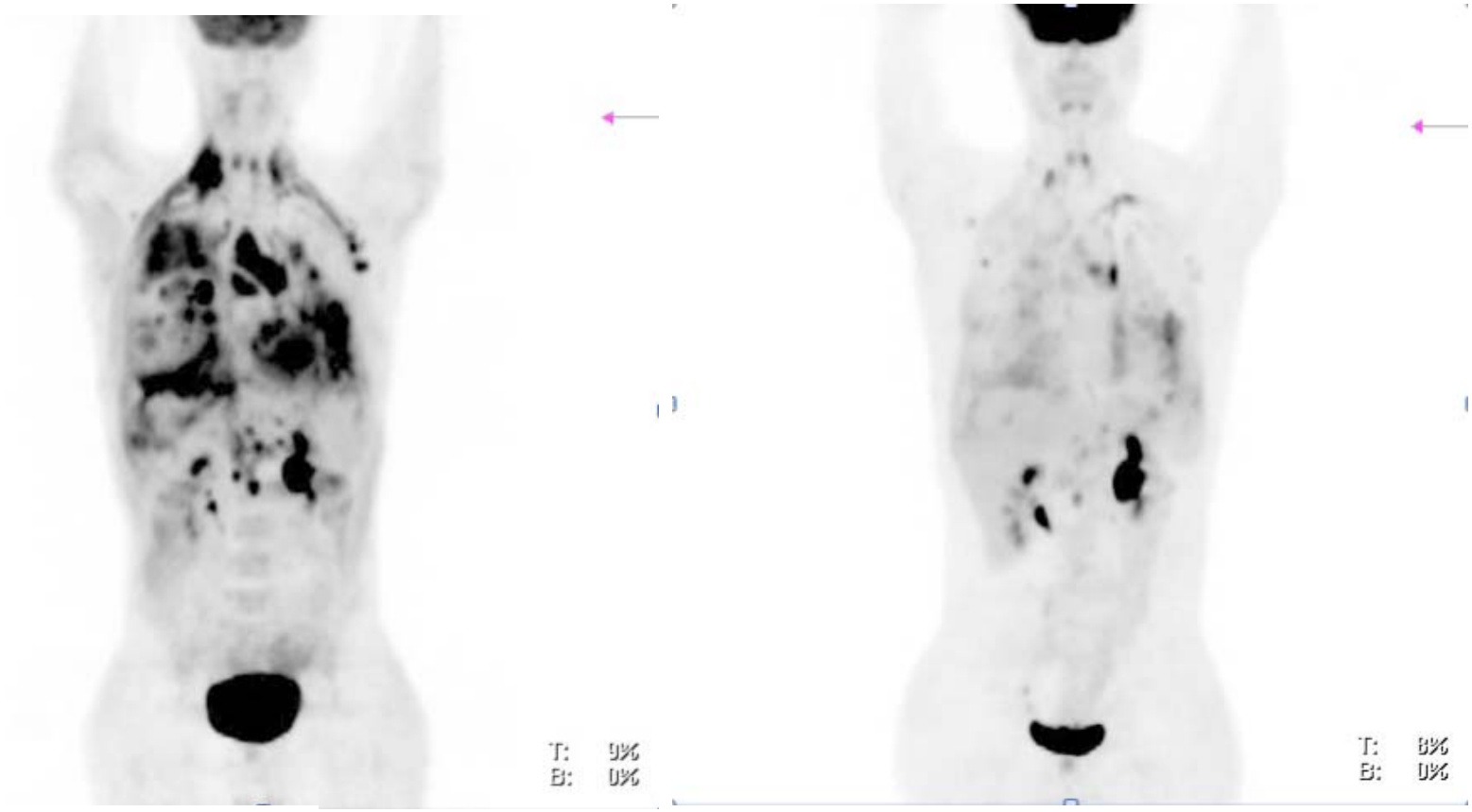
Multiple Different Mechanisms of Resistance to the First Generation ALK TKI Crizotinib



Shaw et al., ASCO 2013

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

Ceritinib

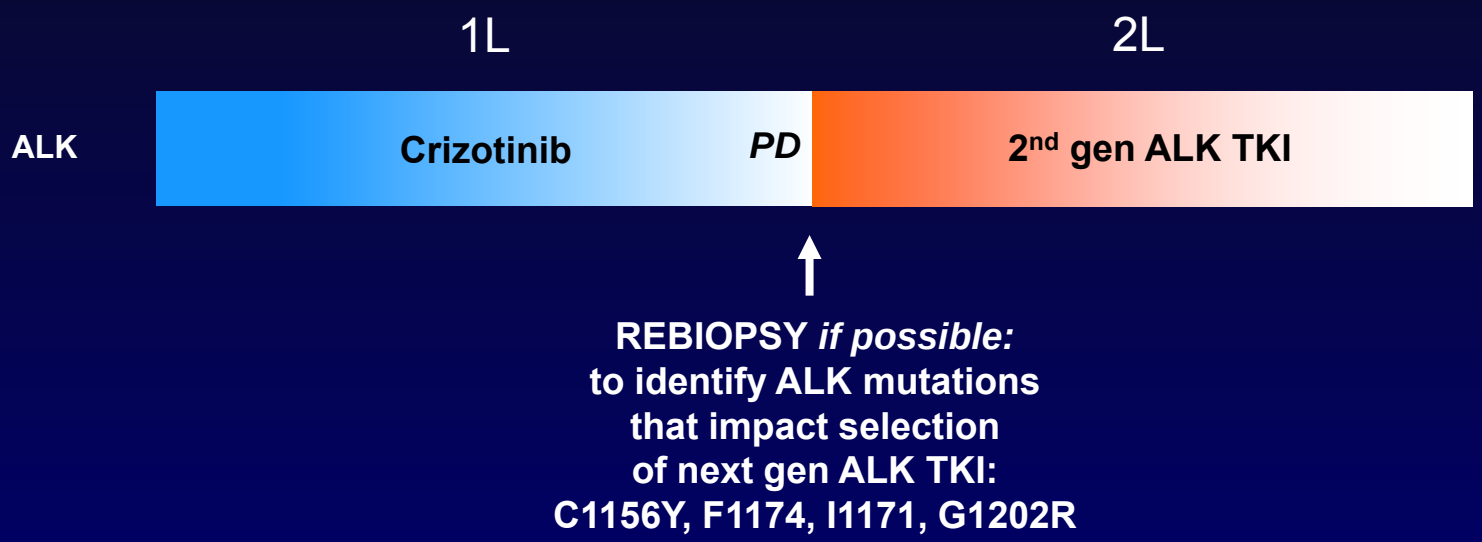


e

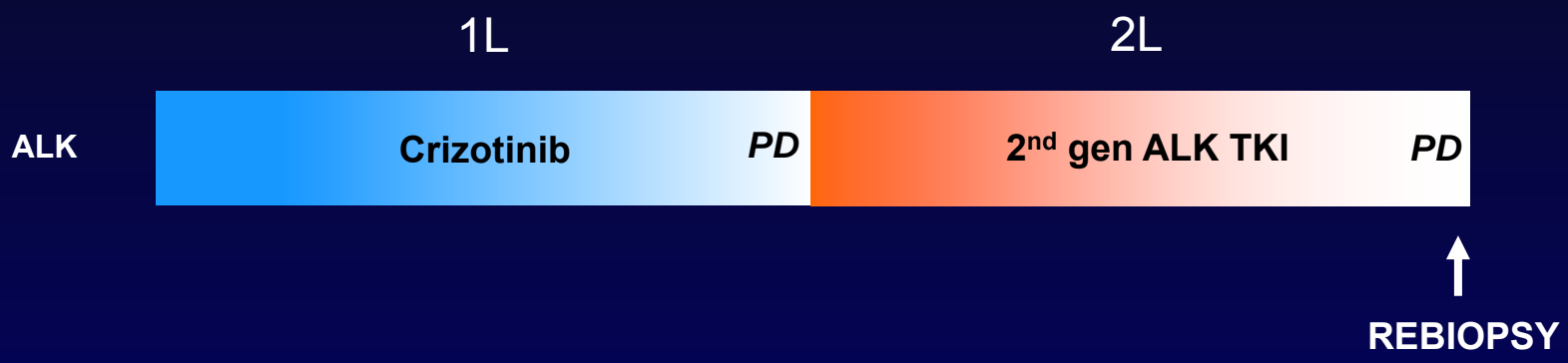
After 3.5 weeks

Shaw et al., NEJM 370(13): 1189-97

Sequential 1st and 2nd Generation ALK TKIs in Advanced ALK+ NSCLC

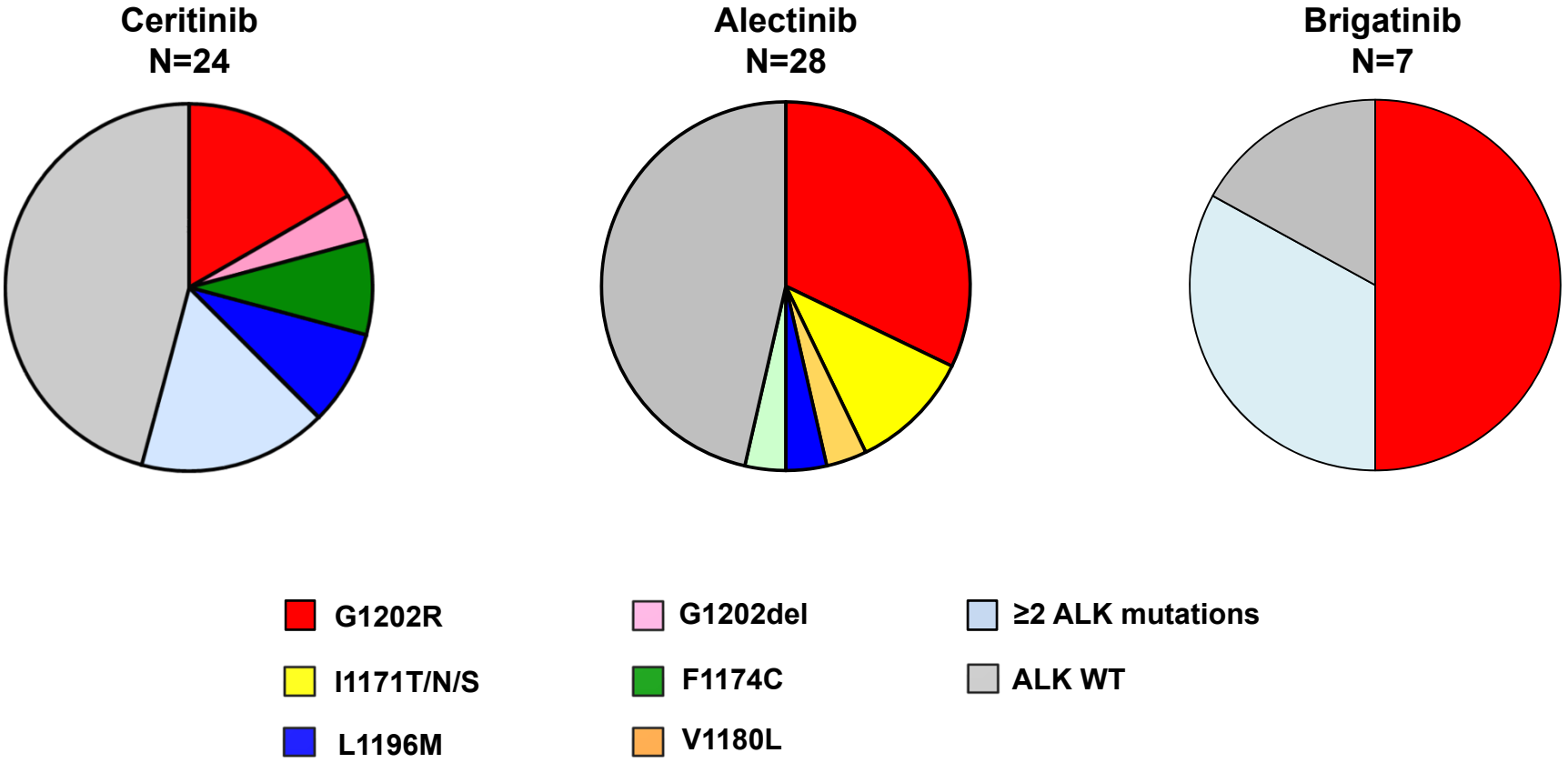


Sequential 1st and 2nd Generation ALK TKIs in Advanced ALK+ NSCLC



Resistance to 2nd Generation ALK TKIs:

ALK Resistance Mutations Identify Tumors That Remain ALK Dependent

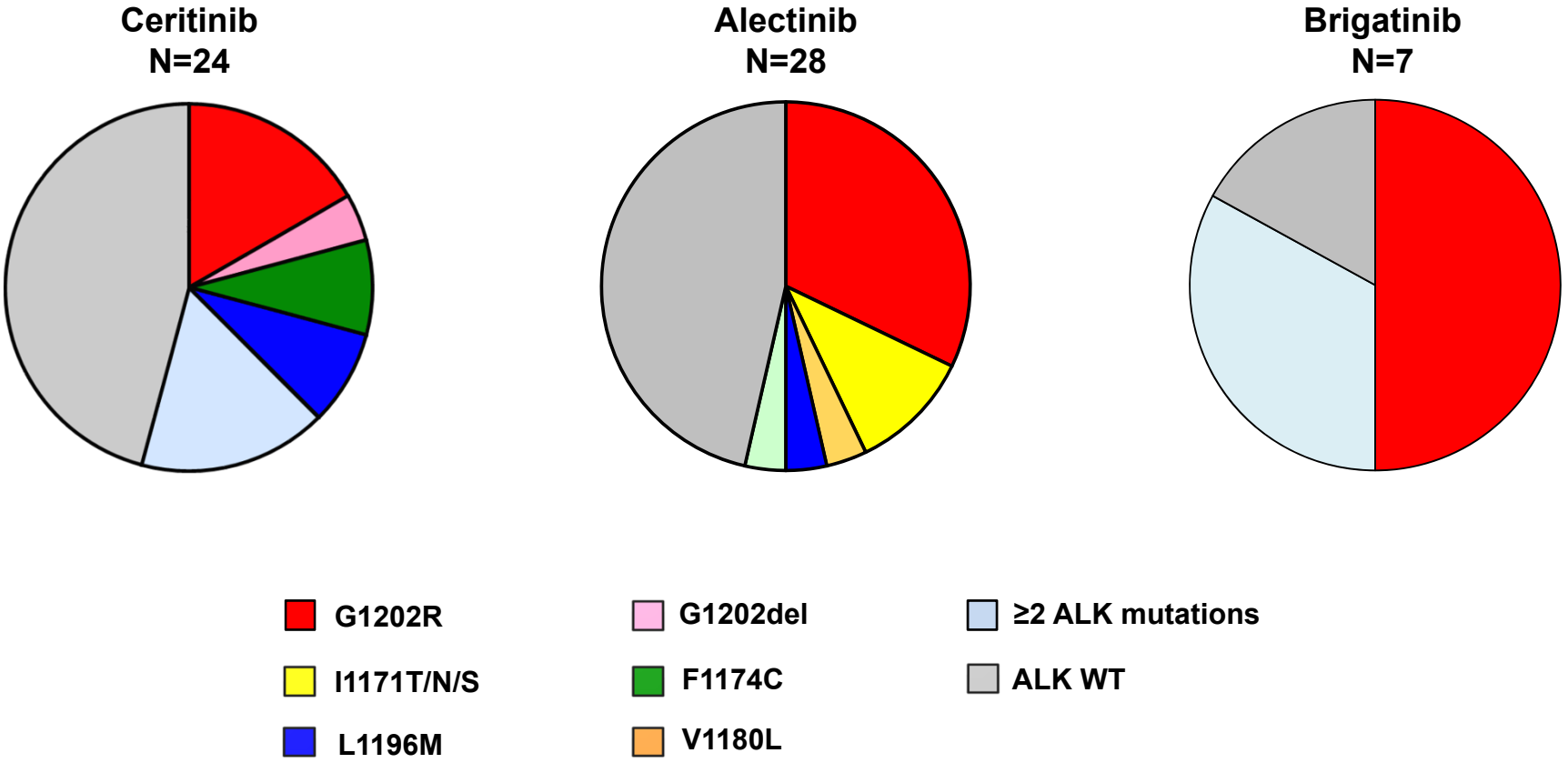


Updated from Gainor et al., Cancer Discov 6(10): 1118-113, 2016

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

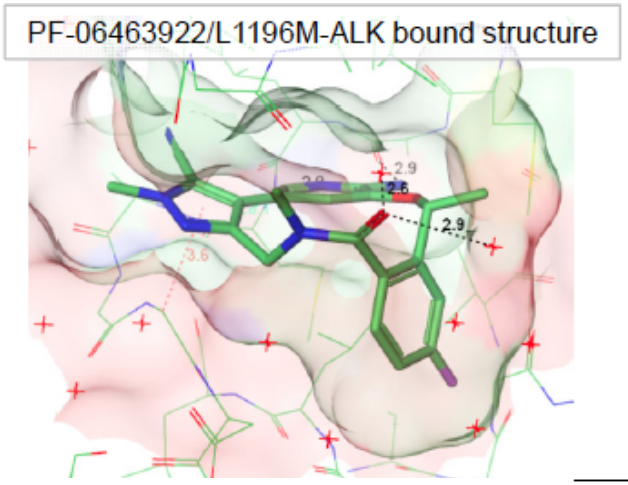
Resistance to 2nd Generation ALK TKIs:

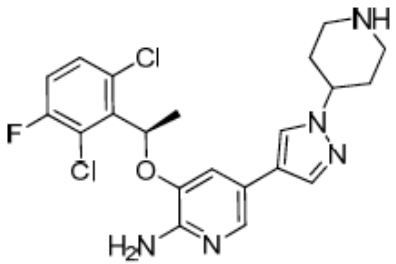
ALK G1202R Commonly Emerges at Resistance

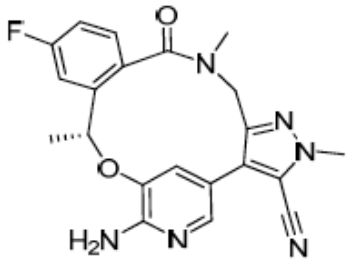


Updated from Gainor et al., Cancer Discov 6(10): 1118-113, 2016

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





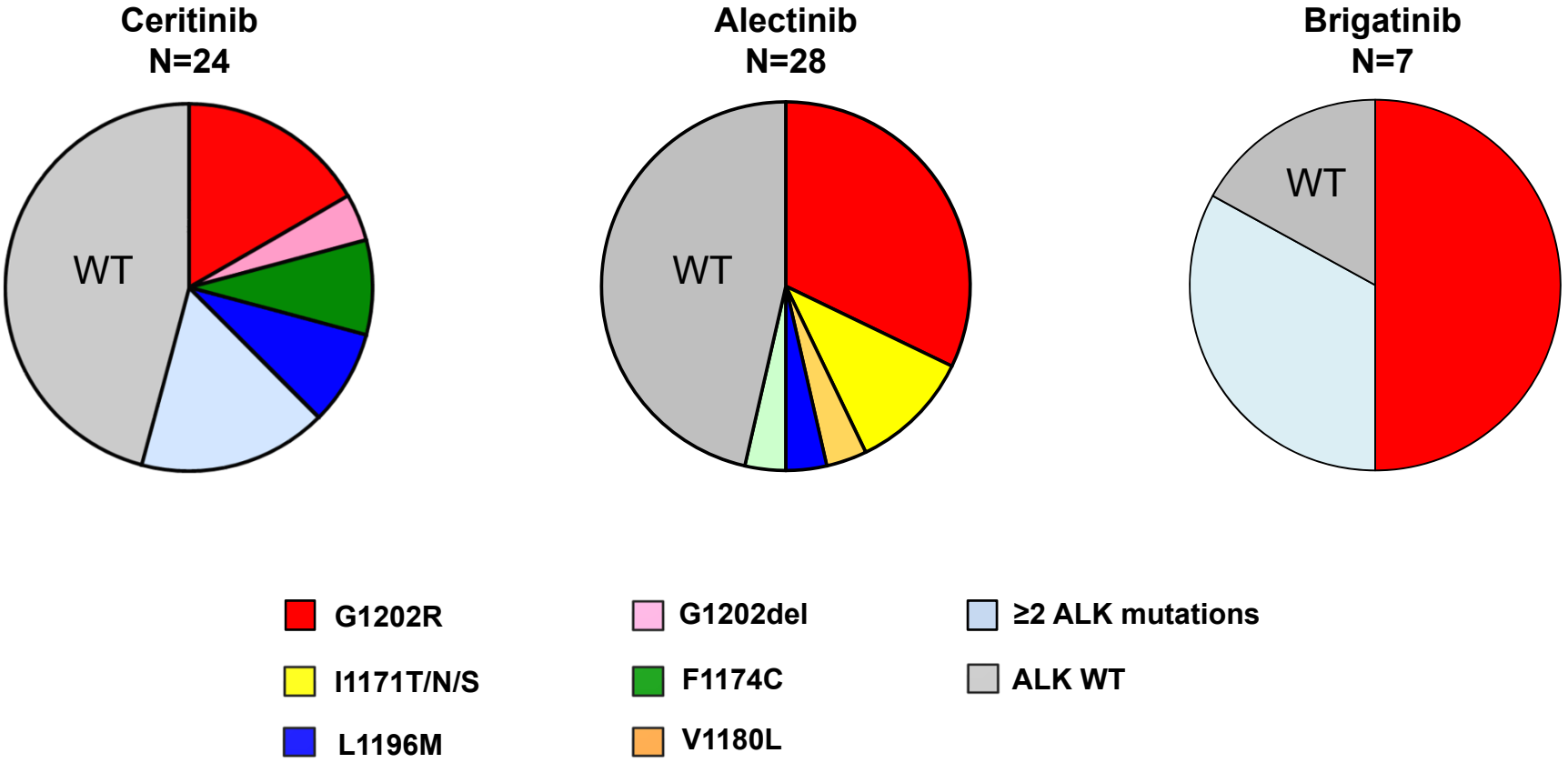


	crizotinib	PF-06463922
ALK WT NIH3T3 IC50 (nM)	80	1.3
ALK L1196M NIH3T3 IC50 (nM)	843	21
ALK G1202R NIH3T3 IC50 (nM)	**1148**	**77**
ROS1-CD74 IC50 (nM)	11	0.24
MDR BA/AB	45	1.5

Johnson et al., J Med Chem 57: 4720-4, 2014

Resistance to 2nd Generation ALK TKIs:

No ALK Resistance Mutations Suggest Tumors May be ALK-Independent

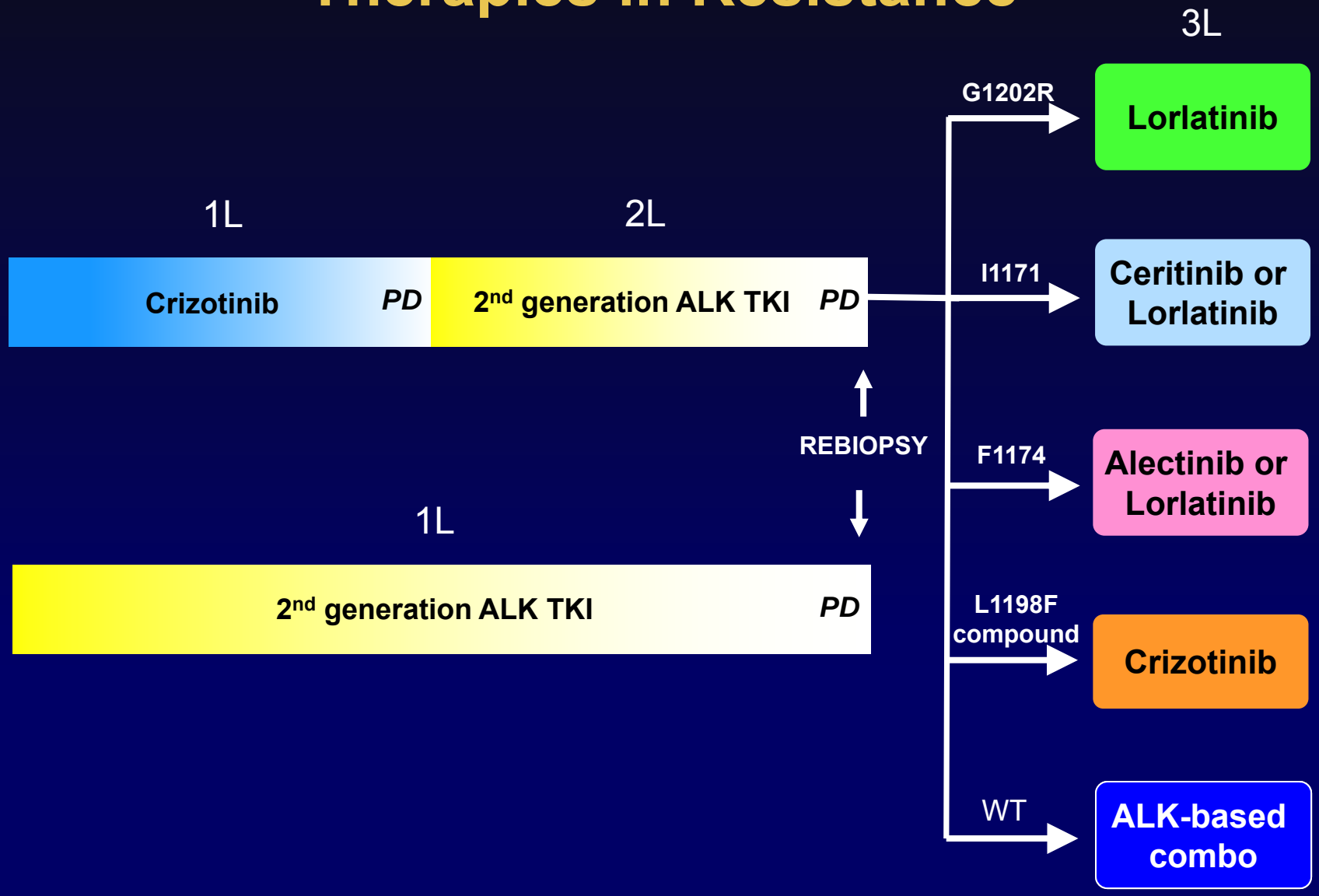


Updated from Gainor et al., Cancer Discov 6(10): 1118-113, 2016

Select Bypass Mechanisms and Therapeutic Combination Strategies in ALK+ NSCLC

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

Tailoring Selection of ALK Targeted Therapies in Resistance

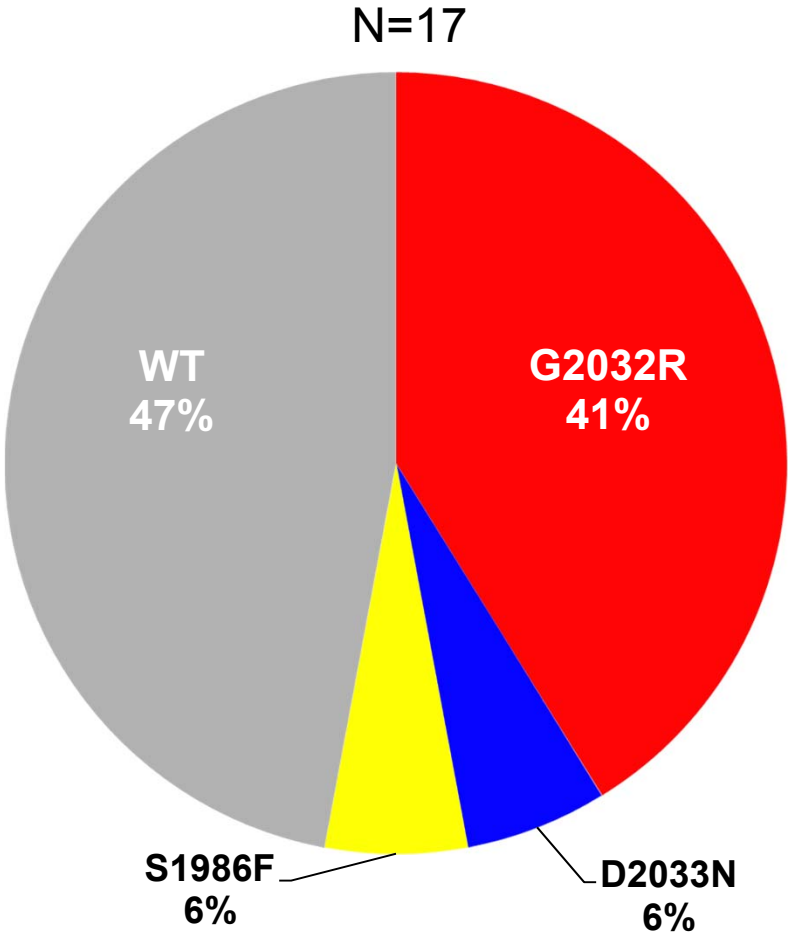


ROS1+ NSCLC

ROS1 Inhibitors

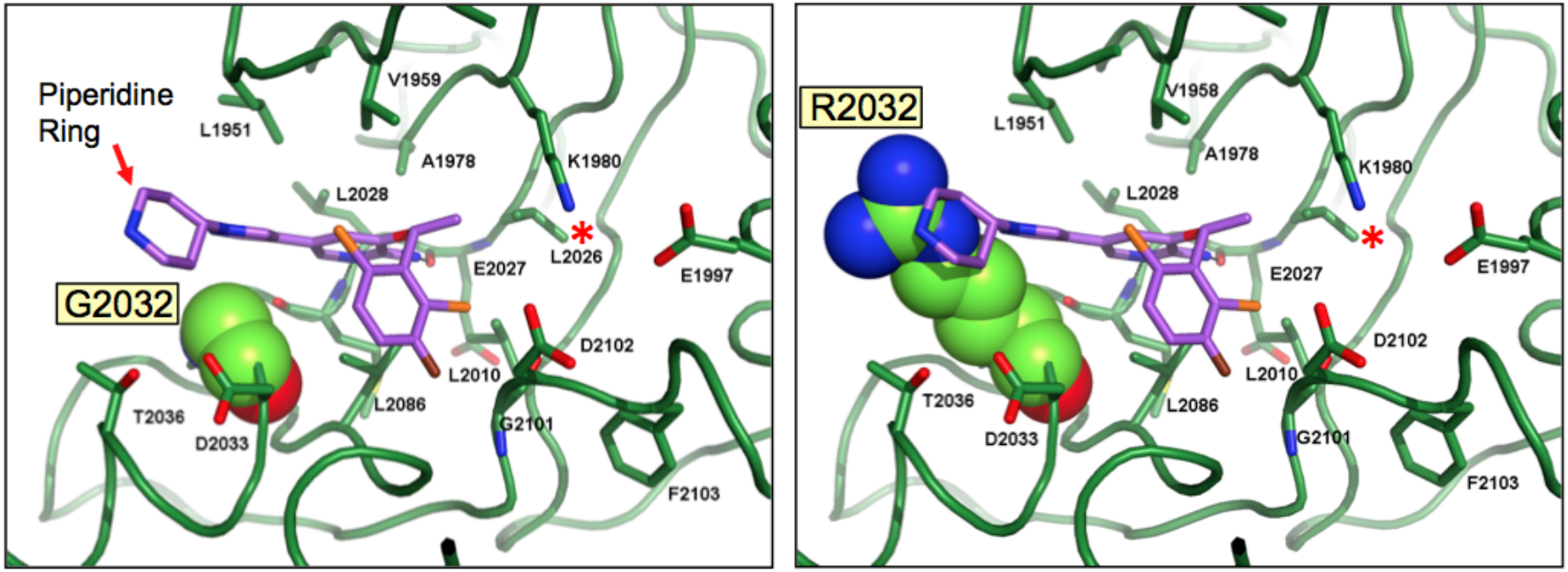
	Major Targets	Status	Ongoing Studies
Crizotinib	ALK, ROS1, MET	FDA Approved (3-11-2016)	Completed
Ceritinib	ALK, ROS1	Investigational	Phase 2 (SIGNATURE)
Brigatinib	ALK, ROS1	Investigational	Investigator initiated trials
Lorlatinib	ALK, ROS1	Investigational	Phase 2 (closed)
Entrectinib	ALK, ROS1, TRK	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



Gainor et al., JCO precision oncol, Aug 2017

Structural Basis for ROS1 G2032R-Mediated Resistance to Crizotinib



Awad et al., NEJM 368(25): 2395-2401, 2013

Next-Generation ROS1 Inhibitors

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

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

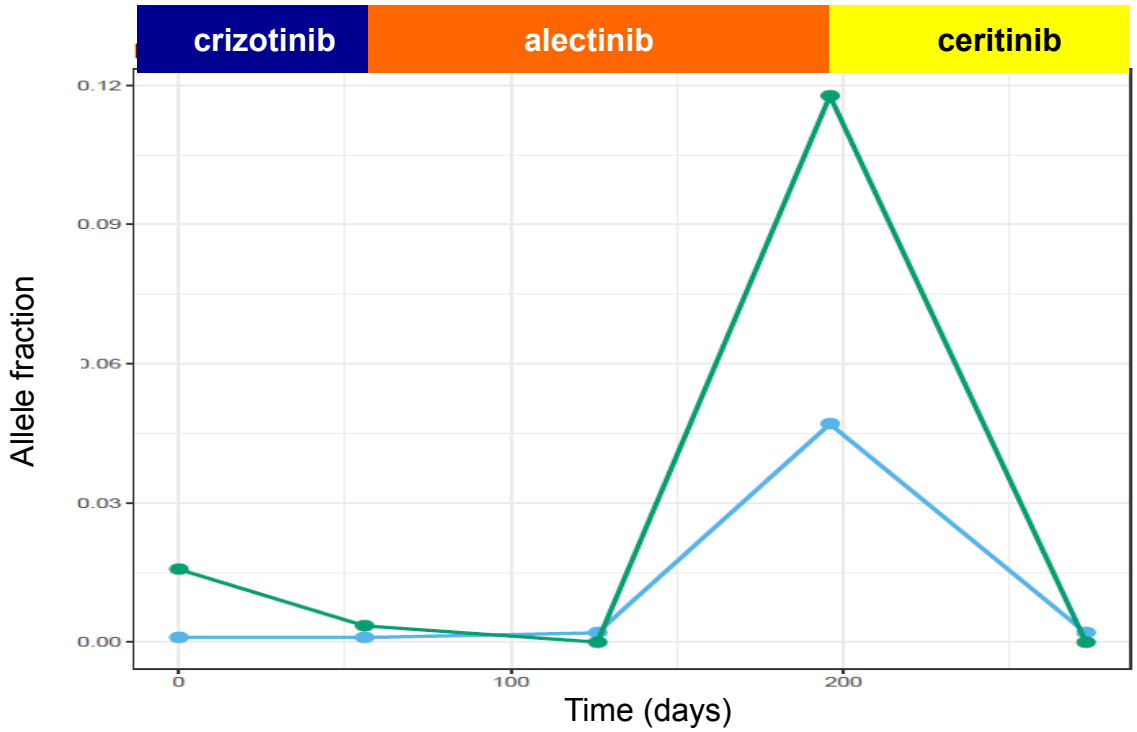
Summary

- 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



EML4-ALK

ALK I1171N

(resistant to alectinib, sensitive to ceritinib)

Ibiayi Dagogo-Jack, in press

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!