Treatment of NSCLC with Rare Mutations

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Disclaimer

There are no conflicts of interest related to this presentation and/or related materials

Disclosures

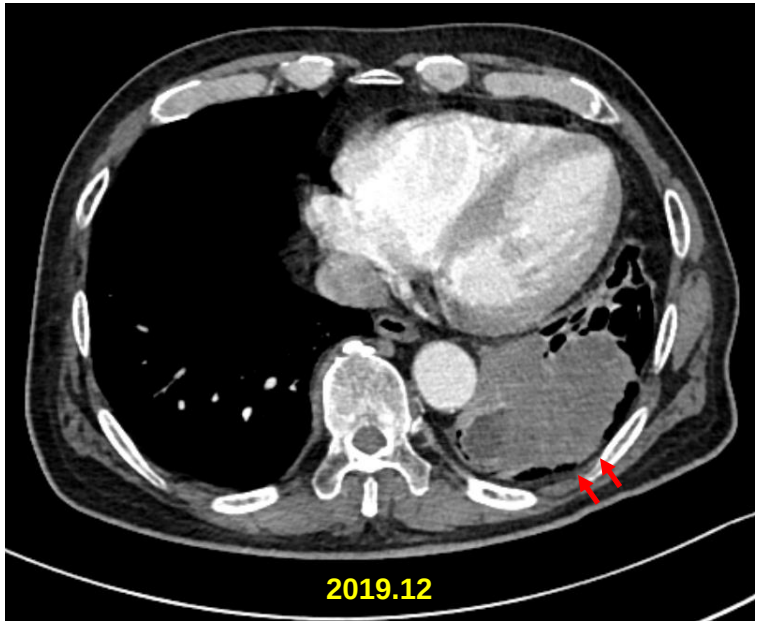
Commercial Interests	Relationships
Boryung, Dakeda, Yuhan, Lilly, Norvatis	Consulting Fees
Boryung, Boehringer Ingelheim, Yuhan, Lilly, MSD, Pfizer, ONO/BMS, AstraZeneca	Honoraria

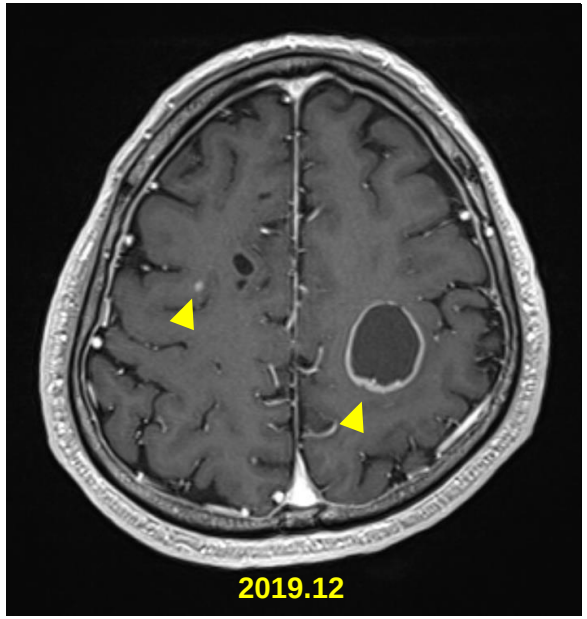
Table of Contents

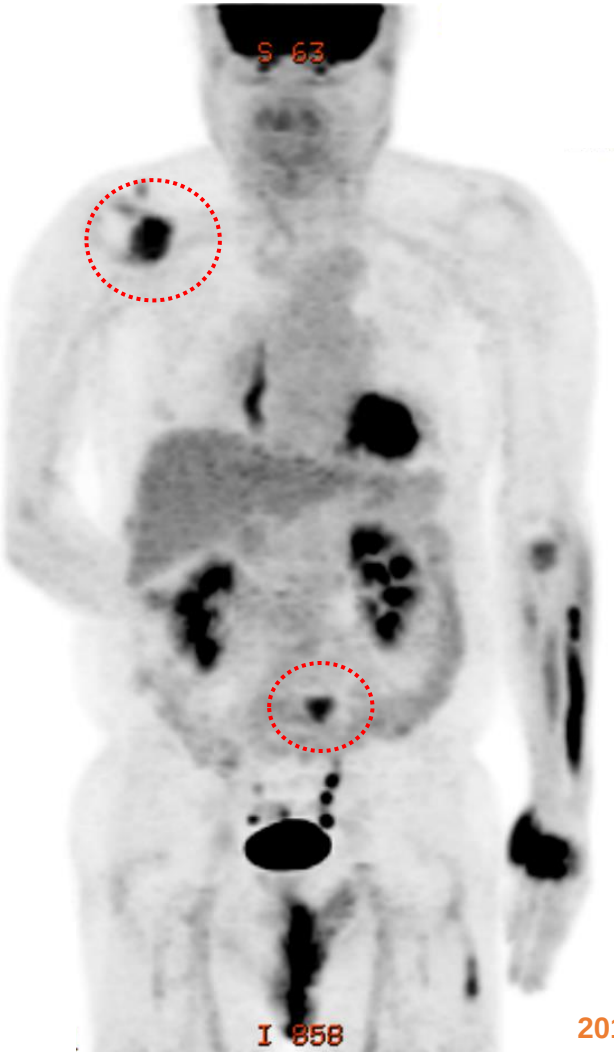
PNUYH CASE 1

M/72

- Ex-smoker (5py, 1990 quit)
- Lung adenocarcinoma (LLL, cIVB)
- EGFR wild/ALK IHC(-)/ROS1 RT-PCR (-)
- PD-L1 negative (SP263)
- Bone/brain mets



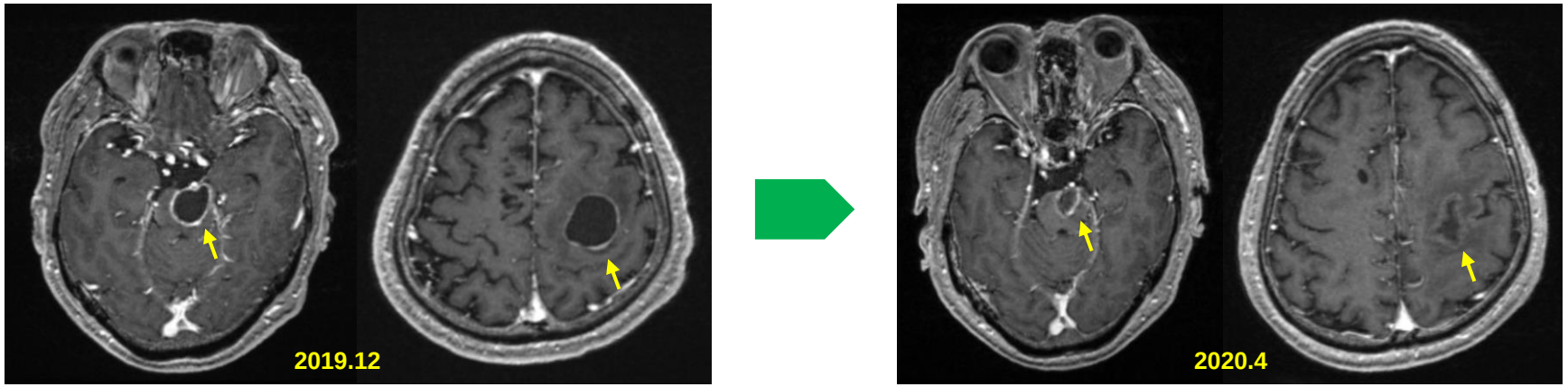




2019.12

PNUYH CASE 1

* Neurologic Sx (visual disturbance/diplopia)-**GKS** (2020.1/2020.7)



* 1L-**pemetrexed/cisplatin** (2020.2~)

* Tissue NGS → Insufficient for examination

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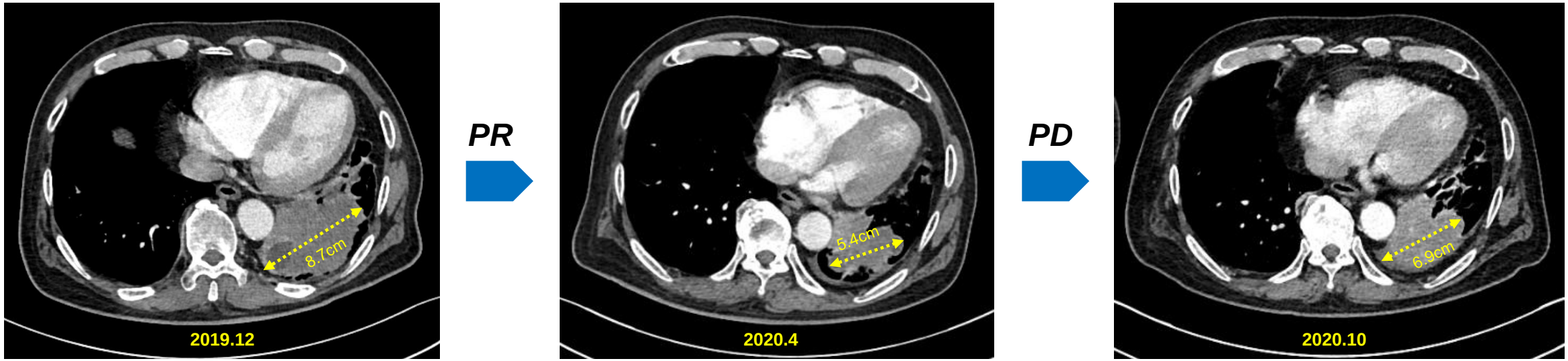
* 1L-**pemetrexed/cisplatin** (2020.2~2020.10, *12)



* Liquid biopsy (Guardant 360, 2020.5)

PNUYH CASE 1

GUARDANT360

Summary of Somatic Alterations & Associated Treatment Options

KEY ✓ Approved in indication ~ Approved in other indication ⊗ Lack of response

Alteration	% cfDNA or Amplification	Associated FDA-approved therapies	Clinical trial availability (see page 3)
CCDC6-RET Fusion	0.1%	✓ Selpercatinib ~ Cabozantinib, Lenvatinib, Nintedanib, Ponatinib, Regorafenib, Sorafenib, Sunitinib, Vandetanib	Yes
PTEN G165*	0.2%	~ Copanlisib, Everolimus, Temsirolimus	Yes
GNAS R201C	0.1%	~ Binimetinib, Cobimetinib, Selumetinib, Trametinib	Yes
TP53 R273C	0.2%	None	No

Variants of Uncertain Significance

ATM K2413Q (4.0%), *DDR2* D678E (0.1%)

The functional consequences and clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

What is the next regimen ??

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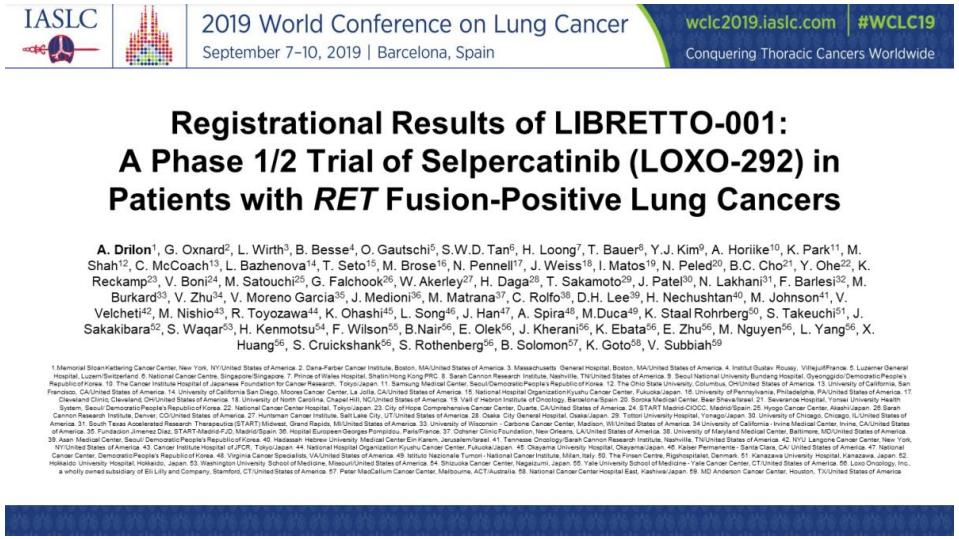
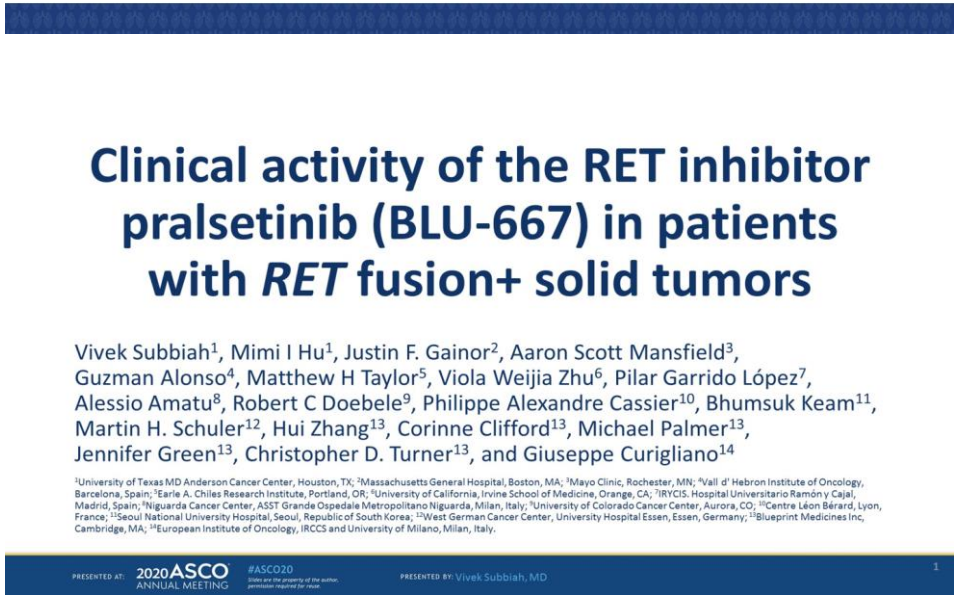


IASLC 2019 World Conference on Lung Cancer
September 7–10, 2019 | Barcelona, Spain
wclc2019.iaslc.com | #WCLC19
Conquering Thoracic Cancers Worldwide

Registrational Results of LIBRETTO-001: A Phase 1/2 Trial of Selpercatinib (LOXO-292) in Patients with *RET* Fusion-Positive Lung Cancers

A. Drilon[1], G. Oxnard[2], L. Wirth[3], B. Besse[4], O. Gautschi[5], S.W.D. Tan[6], H. Loong[7], T. Bauer[8], Y.J. Kim[9], A. Horiike[10], K. Park[11], M. Shah[12], C. McCoach[13], L. Bazhenova[14], T. Seto[15], M. Brose[16], N. Pennell[17], J. Weiss[18], I. Matos[19], N. Peled[20], B.C. Cho[21], Y. Ohe[22], K. Reckamp[23], V. Boni[24], M. Satouchi[25], G. Falchook[26], W. Akerley[27], H. Daga[28], T. Sakamoto[29], J. Patel[30], N. Lakhani[31], F. Barlesi[32], M. Burkard[33], V. Zhu[34], V. Moreno Garcia[35], J. Medioni[36], M. Matrana[37], C. Rolfo[38], D.H. Lee[39], H. Nechushtan[40], M. Johnson[41], V. Velcheti[42], M. Nishio[43], R. Toyozawa[44], K. Ohashi[45], L. Song[46], J. Han[47], A. Spira[48], M.Duca[49], K. Staal Rohrberg[50], S. Takeuchi[51], J. Sakakibara[52], S. Waqar[53], H. Kenmotsu[54], F. Wilson[55], B.Nair[56], E. Olek[56], J. Kherani[56], K. Ebata[56], E. Zhu[56], M. Nguyen[56], L. Yang[56], X. Huang[56], S. Cruickshank[56], S. Rothenberg[56], B. Solomon[57], K. Goto[58], V. Subbiah[59]

1 Memorial Sloan Kettering Cancer Center, New York, NY/United States of America. 2. Dana-Farber Cancer Institute, Boston, MA/United States of America. 3. Massachusetts General Hospital, Boston, MA/United States of America. 4. Institut Gustav Roussy, Villejuif/France. 5. Luzerner General Hospital, Luzern/Switzerland. 6. National Cancer Centre, Singapore/Singapore. 7. Prince of Wales Hospital, Shatin/Hong Kong PRC. 8. Sarah Cannon Research Institute, Nashville, TN/United States of America. 9. Seoul National University Bundang Hospital, Gyeonggido/Democratic People's Republic of Korea. 10. The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo/Japan. 11. Samsung Medical Center, Seoul/Democratic People's Republic of Korea. 12. The Ohio State University, Columbus, OH/United States of America. 13. University of California, San Francisco, CA/United States of America. 14. University of California San Diego, Moores Cancer Center, La Jolla, CA/United States of America. 15. National Hospital Organization Kyushu Cancer Center, Fukuoka/Japan. 16. University of Pennsylvania, Philadelphia, PA/United States of America. 17. Cleveland Clinic, Cleveland, OH/United States of America. 18. University of North Carolina, Chapel Hill, NC/United States of America. 19. Vall d' Hebron Institute of Oncology, Barcelona/Spain. 20. Soroka Medical Center, Beer Sheva/Israel. 21. Severance Hospital, Yonsei University Health System, Seoul/ Democratic People's Republic of Korea. 22. National Cancer Center Hospital, Tokyo/Japan. 23. City of Hope Comprehensive Cancer Center, Duarte, CA/United States of America. 24. START Madrid-CIOCC, Madrid/Spain. 25. Hyogo Cancer Center, Akashi/Japan. 26 Sarah Cannon Research Institute, Denver, CO/United States of America. 27. Huntsman Cancer Institute, Salt Lake City, UT/United States of America. 28. Osaka City General Hospital, Osaka/Japan. 29. Tottori University Hospital, Yonago/Japan. 30. University of Chicago, Chicago, IL/United States of America. 31. South Texas Accelerated Research Therapeutics (START) Midwest, Grand Rapids, MI/United States of America. 33. University of Wisconsin - Carbone Cancer Center, Madison, WI/United States of America. 34 University of California - Irvine Medical Center, Irvine, CA/United States of America. 35. Fundación Jiménez Díaz, START-Madrid-FJD, Madrid/Spain. 36. Hopital European Georges Pompidou, Paris/France. 37. Ochsner Clinic Foundation, New Orleans, LA/United States of America. 38. University of Maryland Medical Center, Baltimore, MD/United States of America. 39. Asan Medical Center, Seoul/ Democratic People's Republic of Korea. 40. Hadassah Hebrew University Medical Center Ein Karem, Jerusalem/Israel. 41. Tennesse Oncology/Sarah Cannon Research Institute, Nashville, TN/United States of America. 42. NYU Langone Cancer Center, New York, NY/United States of America. 43. Cancer Institute Hospital of JFCR, Tokyo/Japan. 44. National Hospital Organization Kyushu Cancer Center, Fukuoka/Japan. 45. Okayama University Hospital, Okayama/Japan. 46. Kaiser Permanente - Santa Clara, CA/ United States of America. 47. National Cancer Center, Democratic People's Republic of Korea. 48. Virginia Cancer Specialists, VA/United States of America. 49. Istituto Nazionale Tumori - National Cancer Institute, Milan, Italy. 50. The Finsen Centre, Rigshospitalet, Denmark. 51. Kanazawa University Hospital, Kanazawa, Japan. 52. Hokkaido University Hospital, Hokkaido, Japan. 53. Washington University School of Medicine, Missouri/United States of America. 54. Shizuoka Cancer Center, Nagaizumi, Japan. 55. Yale University School of Medicine - Yale Cancer Center, CT/United States of America. 56. Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly and Company, Stamford, CT/United States of America. 57. Peter MacCallum Cancer Center, Melbourne, ACT/Australia. 58. National Cancer Center Hospital East, Kashiwa/Japan. 59. MD Anderson Cancer Center, Houston, TX/United States of America



Clinical activity of the RET inhibitor pralsetinib (BLU-667) in patients with *RET* fusion+ solid tumors

Vivek Subbiah[1], Mimi I Hu[1], Justin F. Gainor[2], Aaron Scott Mansfield[3], Guzman Alonso[4], Matthew H Taylor[5], Viola Weijia Zhu[6], Pilar Garrido López[7], Alessio Amatu[8], Robert C Doebele[9], Philippe Alexandre Cassier[10], Bhumsuk Keam[11], Martin H. Schuler[12], Hui Zhang[13], Corinne Clifford[13], Michael Palmer[13], Jennifer Green[13], Christopher D. Turner[13], and Giuseppe Curigliano[14]

[1]University of Texas MD Anderson Cancer Center, Houston, TX; [2]Massachusetts General Hospital, Boston, MA; [3]Mayo Clinic, Rochester, MN; [4]Vall d' Hebron Institute of Oncology, Barcelona, Spain; [5]Earle A. Chiles Research Institute, Portland, OR; [6]University of California, Irvine School of Medicine, Orange, CA; [7]IRYCIS. Hospital Universitario Ramón y Cajal, Madrid, Spain; [8]Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [9]University of Colorado Cancer Center, Aurora, CO; [10]Centre Léon Bérard, Lyon, France; [11]Seoul National University Hospital, Seoul, Republic of South Korea; [12]West German Cancer Center, University Hospital Essen, Essen, Germany; [13]Blueprint Medicines Inc, Cambridge, MA; [14]European Institute of Oncology, IRCCS and University of Milano, Milan, Italy.

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PRESENTED BY: Vivek Subbiah, MD
1

FDA approves selpercatinib for lung and thyroid cancers with RET gene mutations or fusions

On May 8, 2020, the Food and Drug Administration granted accelerated approval to selpercatinib (RETEVMO, Eli Lilly and Company) for the following indications:

- Adult patients with metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC);
- Adult and pediatric patients ≥12 years of age with advanced or metastatic *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy;
- Adult and pediatric patients ≥12 years of age with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

PNUYH CASE 1

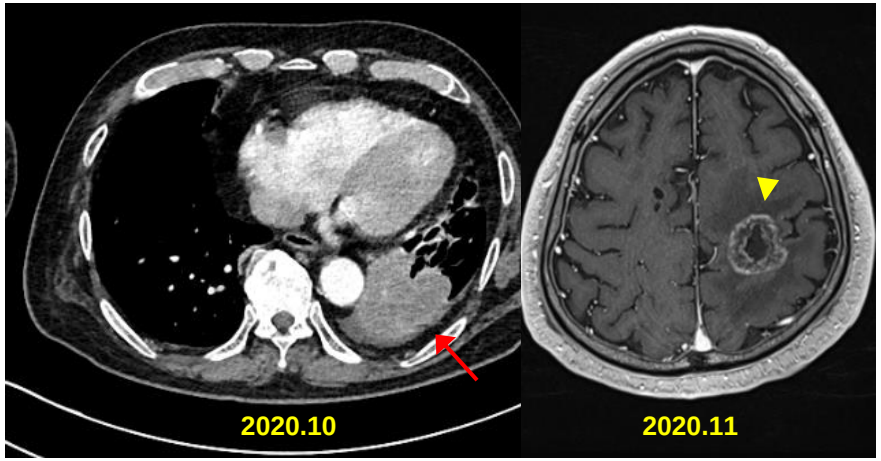
Lilly

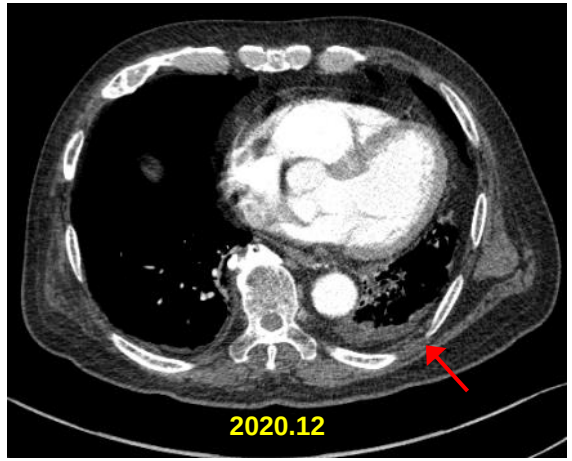
Adult Patient Treatment Plan for Selpercatinib in a Named Patient Program for Locally Advanced or Metastatic Solid Tumors with Rearranged During Transfection (RET) Activation

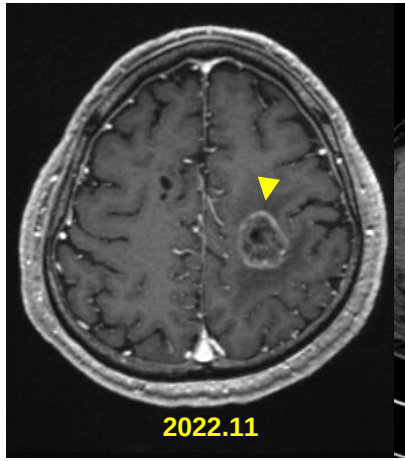
Date: 04 Sep 2020

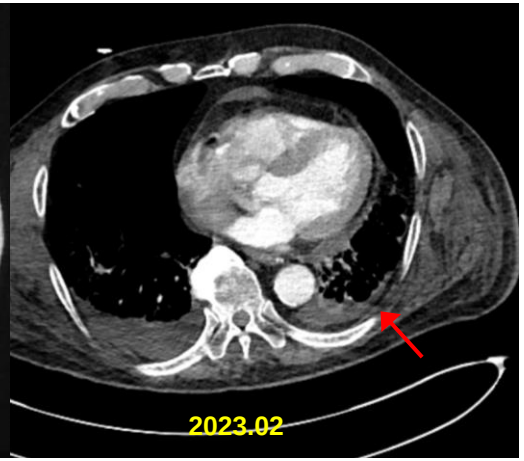
Investigational Product: Selpercatinib (also known as LOXO-292)

* 2L-**selpercatinib** (2020.10~)





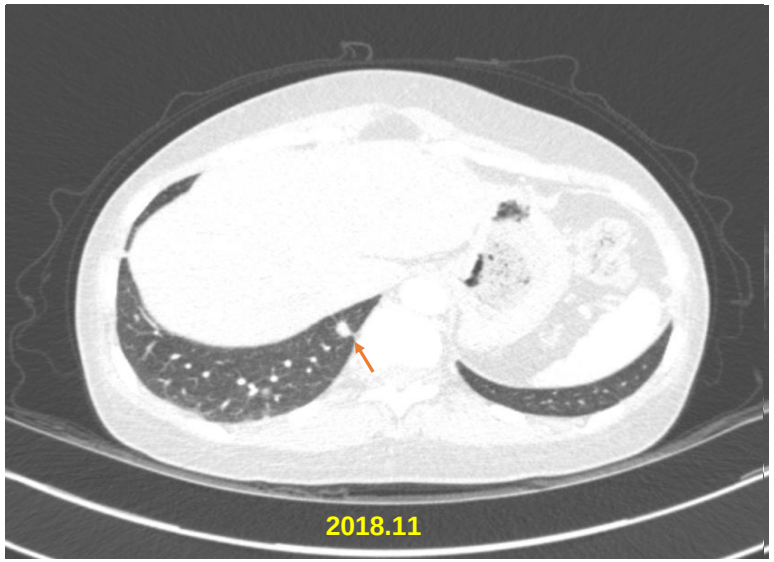


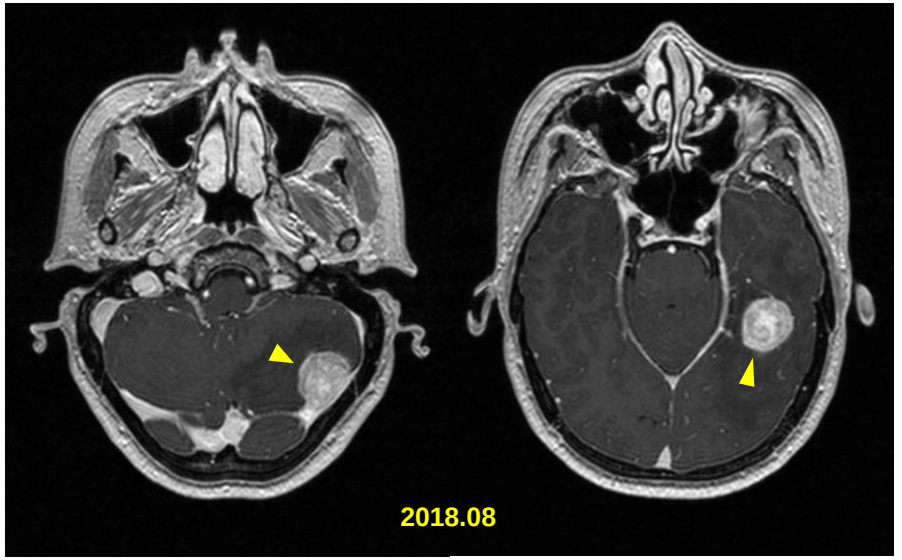


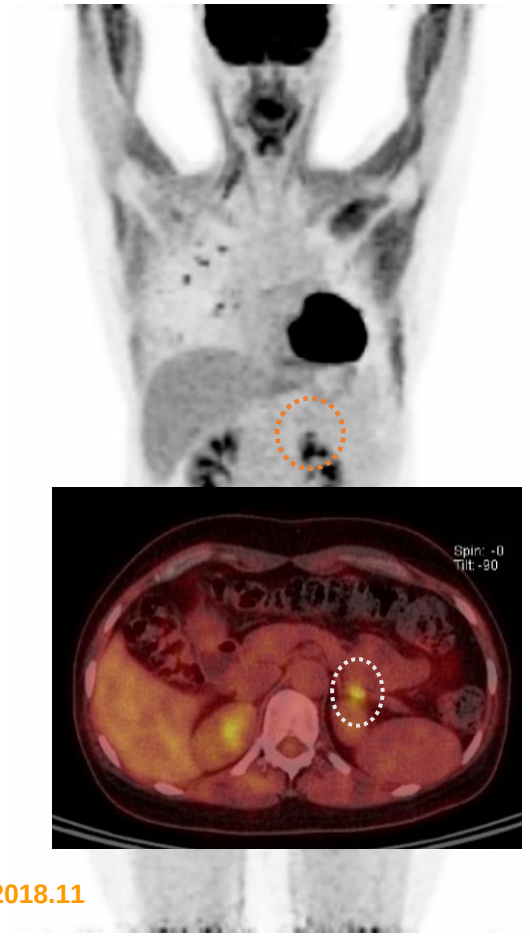
PNUYH CASE 2

F/55

- Non-smoker
- s/p LUL lobectomy vis VATS d/t Lung adenocarcinoma (pT2aN1, pIIB)-2015.4 (SNUBH)
- EGFR wild (PNA clamp)/ALK FISH(-)
- Adjuvant chemotherapy (*4)
- Recurrence (brain/lung to lung/Lt. adrenal gland mets)-2018.8
- s/p GKS /c WBRT (2018.8, SNUBH) => PNUYH (2018.10)







PNUYH CASE 2

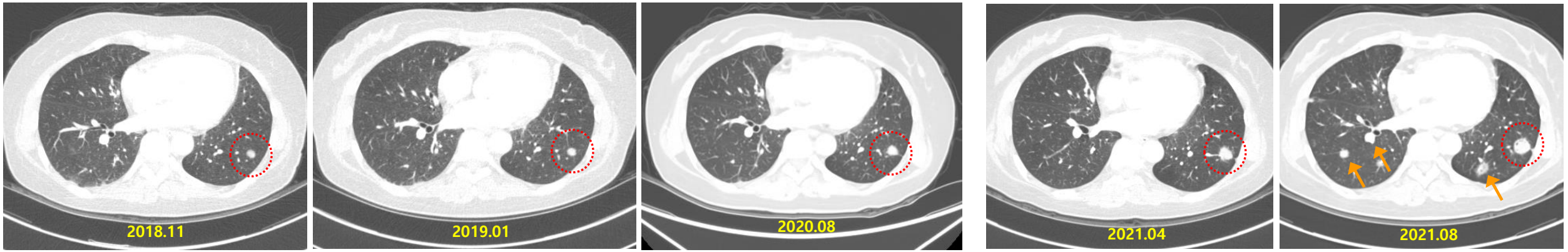
* EGFR Liquid Biopsy (2018.11)-cobas® test

검사항목	검사결과	이전결과	R	P	D
EGFR gene mutation (혈액) (Blood)	Not Detected				
■ Lab. physician's. Report					
[검사방법]					
Real-time PCR					
[검사설명]					
이 검사는 혈액속에 순환하고 있는 종양의 DNA(Circulating tumor DNA, ctDNA)를 이용하여 비소세포성 폐암(NSCLC) 환자의 EGFR					
유전자의 돌연변이 유무를 검사한다. real-time PCR 분석법으로 돌연변이가 흔히 발생하는 부위(hot spot)인 exon 18의 G719X					
치환, exon 19의 결실, exon 20의 T790M 및 S768I 치환, exon 20의 삽입, 그리고 exon 21의 L858R 및 L861Q의 치환 돌연변이를					
확인할 수 있다. 이러한 돌연변이는 NSCLC에서 관찰되는 EGFR 돌연변이의 약 85%로 알려져 있다.					
[검사의 한계]					
이 검사에서 돌연변이가 검출되지 않더라도 EGFR유전자의 돌연변이의 존재를 배제할 수는 없다. 돌연변이의 종류나 추출된 DNA의					
총량 및 돌연변이 유전자의 비율, 검체 상태 등에 영향으로 위음성으로 나올 가능성이 존재한다.					
[검사결과]					
Mutation Not Detected					

PNUYH CASE 2

Pusan National University Yangsan Hospital

* 1L-**pemetrexed/cisplatin** (2018.11~)



SD

1L-Pem/Cis
(2018.11~2020.08, *24)

Watchful Wai
(2020.08~2021.

Hold d/t AEs (fatigue/edema, grII)

PNUYH CASE 2

* VATS RLL WR (2021.08)
  - Adenocarcinoma (TTF-1+)
  - EGFR wild/ALK IHC(-)/ROS1 IHC(-)/BRAF IHC(-)
  - PD-L1 negative (SP263/SP142)

< EGFR GENE MUTATION ANALYSIS REPORT >

=[검사결과]==========
EGFR Gene Mutation : Not Detected
==========

-Mutation Type

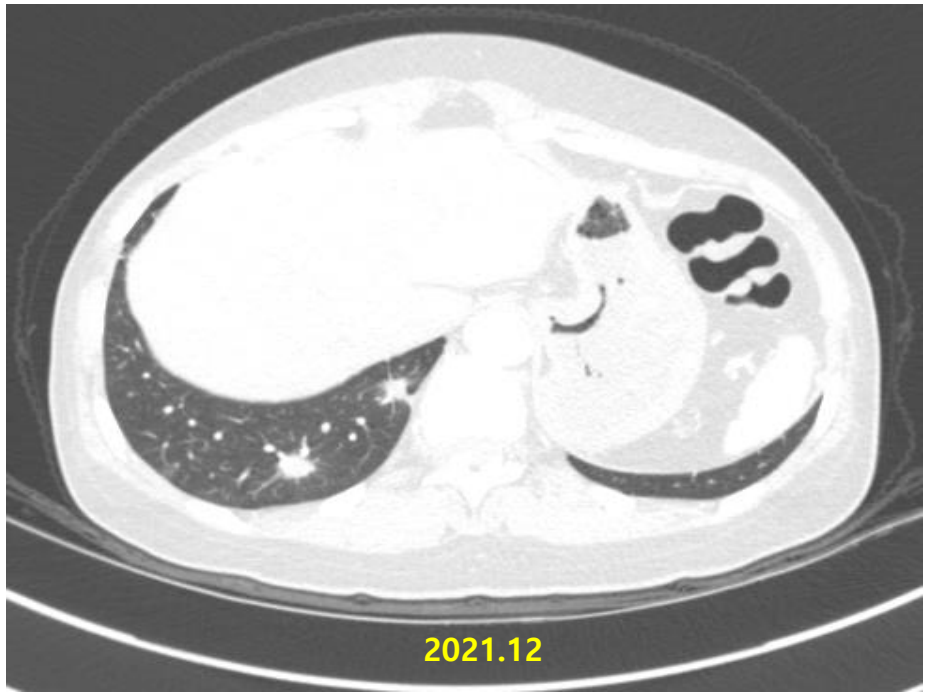
Exon#	Codon#	A.A. Change	Mutation
18	719		Not Detected
19	deletion		Not Detected
20	768		Not Detected
20	790		Not Detected
21	858-861		Not Detected

[검사정보]
SPECIMEN : Genomic DNA isolated from tissue
ANALYZED GENE : EGFR on Chromosome 7p11.2
METHOD : PCR & Direct sequencing (Pyrosequencing)
Reference mRNA sequence : NM_005228.3

PNUYH CASE 2

* 2L-**<u>mobocertinib</u>** (2021.10.1~)

PR !!

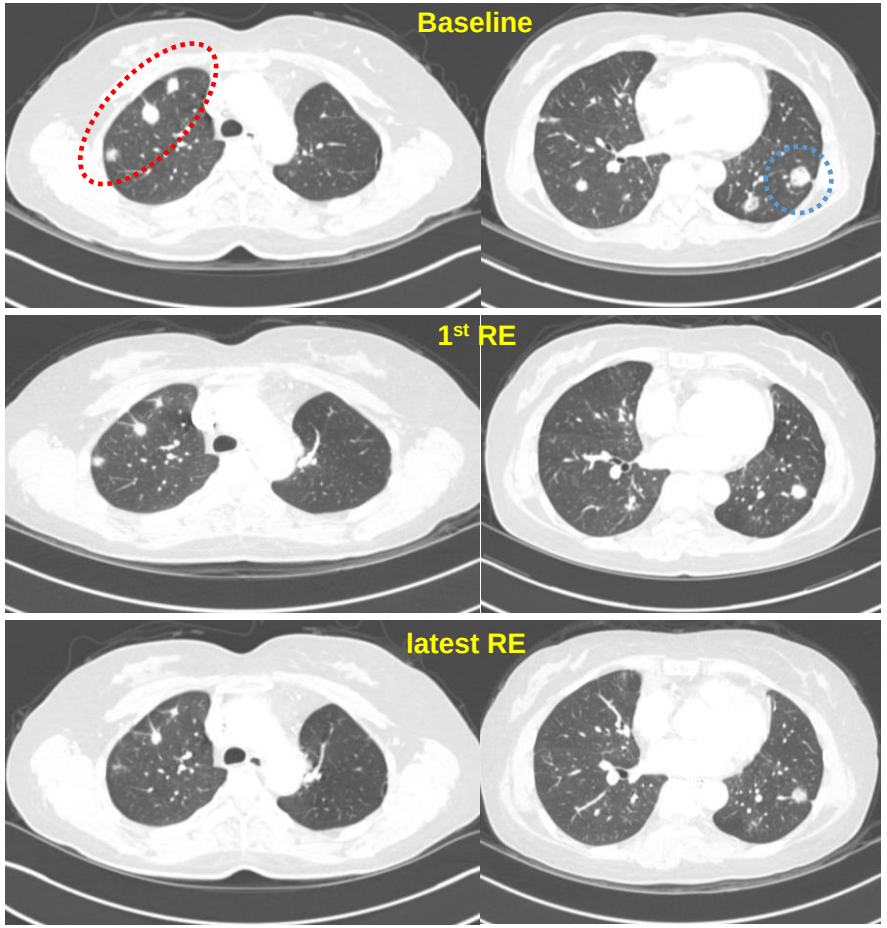


PNUYH CASE 2

Pusan National University Yangsan Hospital

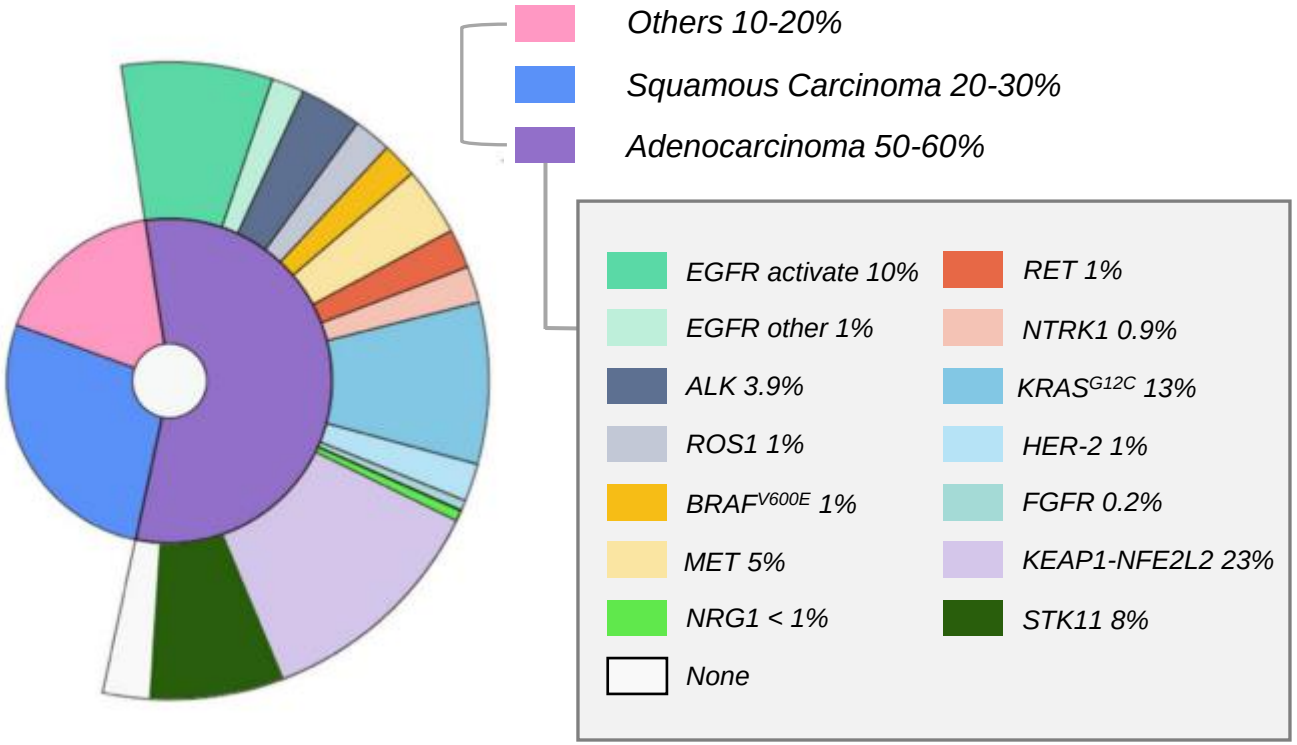
Treatment Course (Mobocertinib)

2021.10.01	mobocertinib 160mg start
2021.10.29	diarrhea (grI)/skin eruption (grII)
2021.12.06	1st response evaluation => PR
2022.01.21	diarrhea (grII)/skin eruption (grII) => mobocertinib **120**mg DR
2023.01.04	latest response evaluation => PR

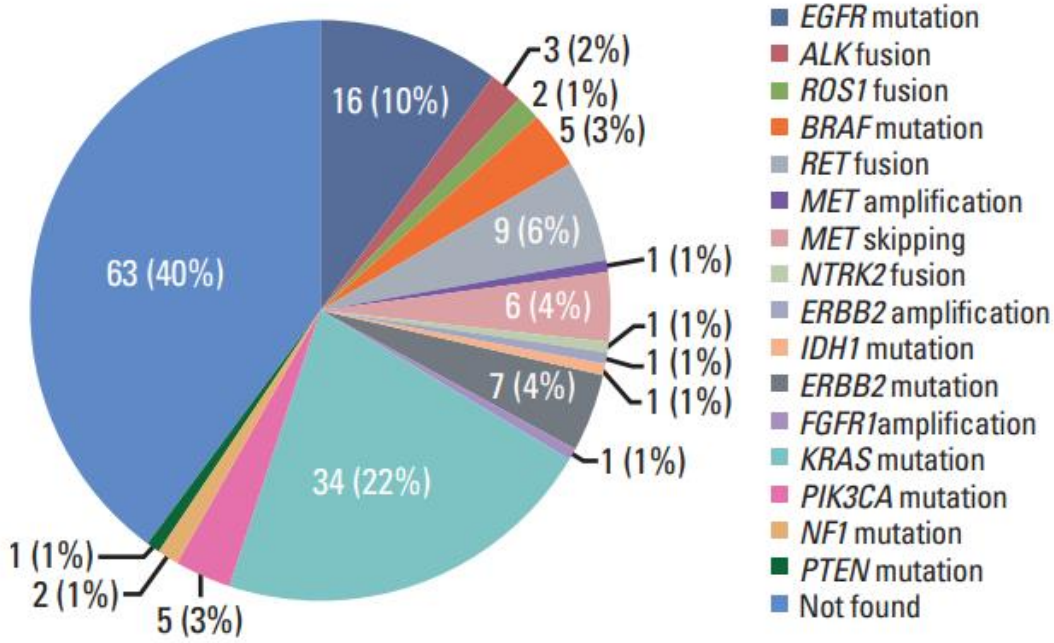


Rare Mutations ??

Incidences of oncogenic driver alterations



From Clinical Trials



From Severance H

Rare, and hard-to-access !!

Guo H, et al. Cells. 2022;11
Park EH, et al. Cancer Res Treat. 2020;52(2):543-551

Driver Mutations

		Detection Methods	TAT	Treatment
♣ *EGFR* mutations (activate) ♣ *ALK* fusions ♣ *ROS1* fusions ♣ *BRAF* mutation (*V600E*)	Reflex	PCR/IHC (NGS)	Short (<7ds)	Reimbursed (1st line)
♣ *KRAS* mutation (*G12C*) ♣ *EGFR* exon 20 insertion ♣ *RET* fusions ♣ *MET* skipping mutations ♣ *HER2* mutations ♣ *NTRK* fusions	Optional	NGS (PCR)	Long (>3wks)	Not-reimbursed (later line)

What do guidelines recommend on biomarker testing in advanced NSCLC ?

Predictive biomarkers	ESMO guidelines (updated 2023)[1]	NCCN guidelines (updated 2023)[2]	CAP/IASLC/AMP guidelines (updated 2018)[3,4]	ASCO guidelines (updated 2018)[5]	Pan-Asian guidelines (updated 2019)[6]
EGFR	●	●	●	●	●
ALK	●	●	●	●	●
ROS1	●	●	●	●	●
BRAF	●	●	●	●	●
PD-L1	●	●	●	●	●
NTRK	●	●	●	●	●
KRAS	●	●	●	●	●
MET	●	●	●	●	●
RET	●	●	●	●	●
HER2	●	●	●	●	●

● Testing recommended

● Expanded panel testing recommended

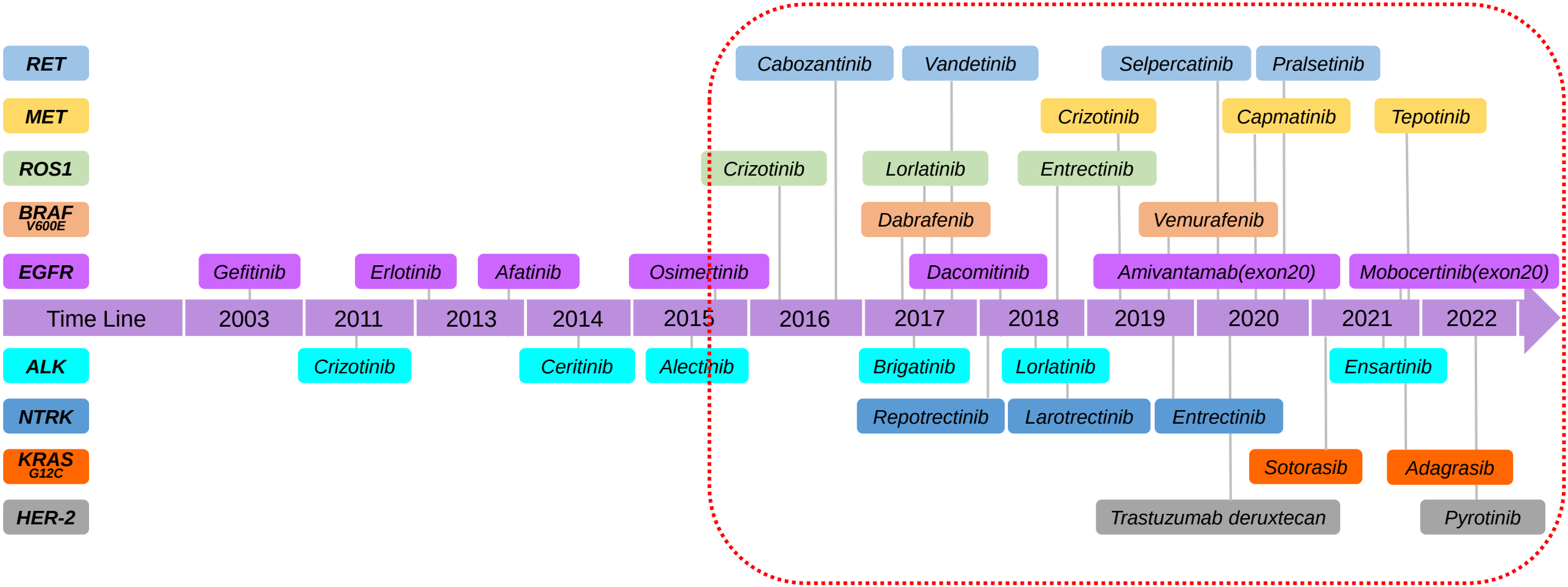
● Single gene or expanded panel testing recommended

● No guideline recommendations to date

AMP, Association for Molecular Pathology; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; ESMO, European Society for Medical Oncology; IASLC, International Association for the Study of Lung Cancer; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death-ligand 1.

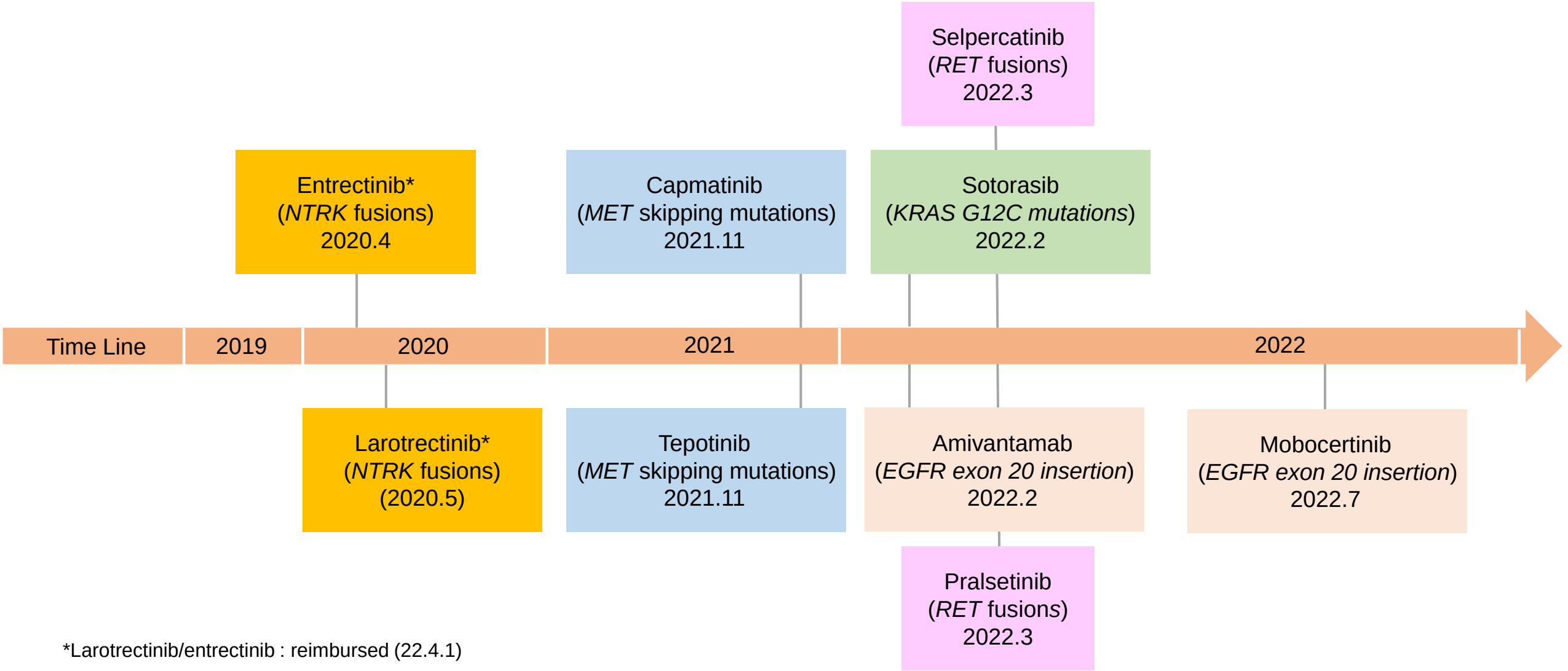
Figure adapted from et al. Lung Cancer 1. Hendriks LE, et al. Ann Oncol. 2023; 2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Version 1.2023; 3. Lindeman NI, et al. J Thorac Oncol 2018;13:323–358; 4. Leighl NB, et al. J Clin Oncol 2014;32:3673–3679; 5. Kalemkerian GP, et al. J Clin Oncol 2018;36:911–919; 6. Wu YL, et al. Ann Oncol 2019;30:171–210.

Timeline of FDA approved targeted therapies



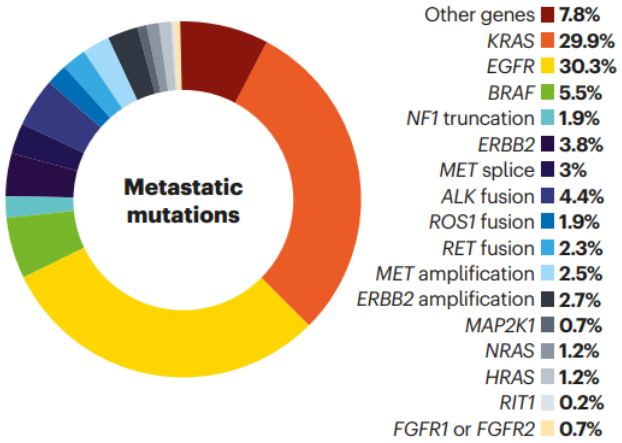
Guo H, et al. Cells. 2022;11

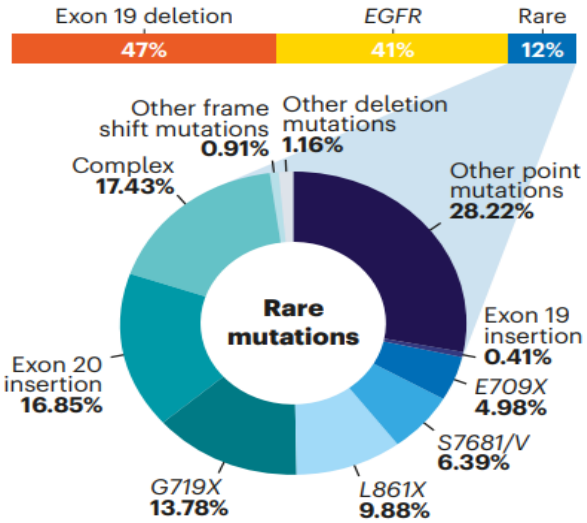
Timeline of MFDS approved rare targeted drugs



*Larotrectinib/entrectinib : reimbursed (22.4.1)

Prevalence of Rare Mutations





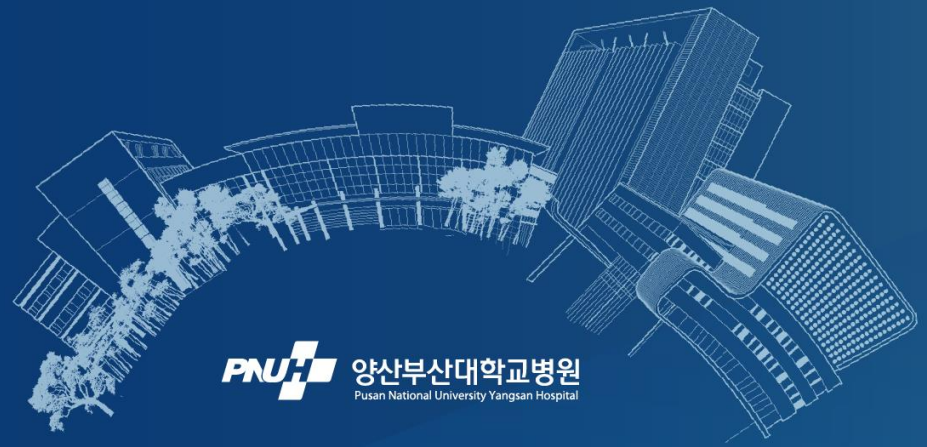
Ferdinandos S, et al. *Nat Rev Cancer.* 2019;19(9):495-509

Issues in rare mutations

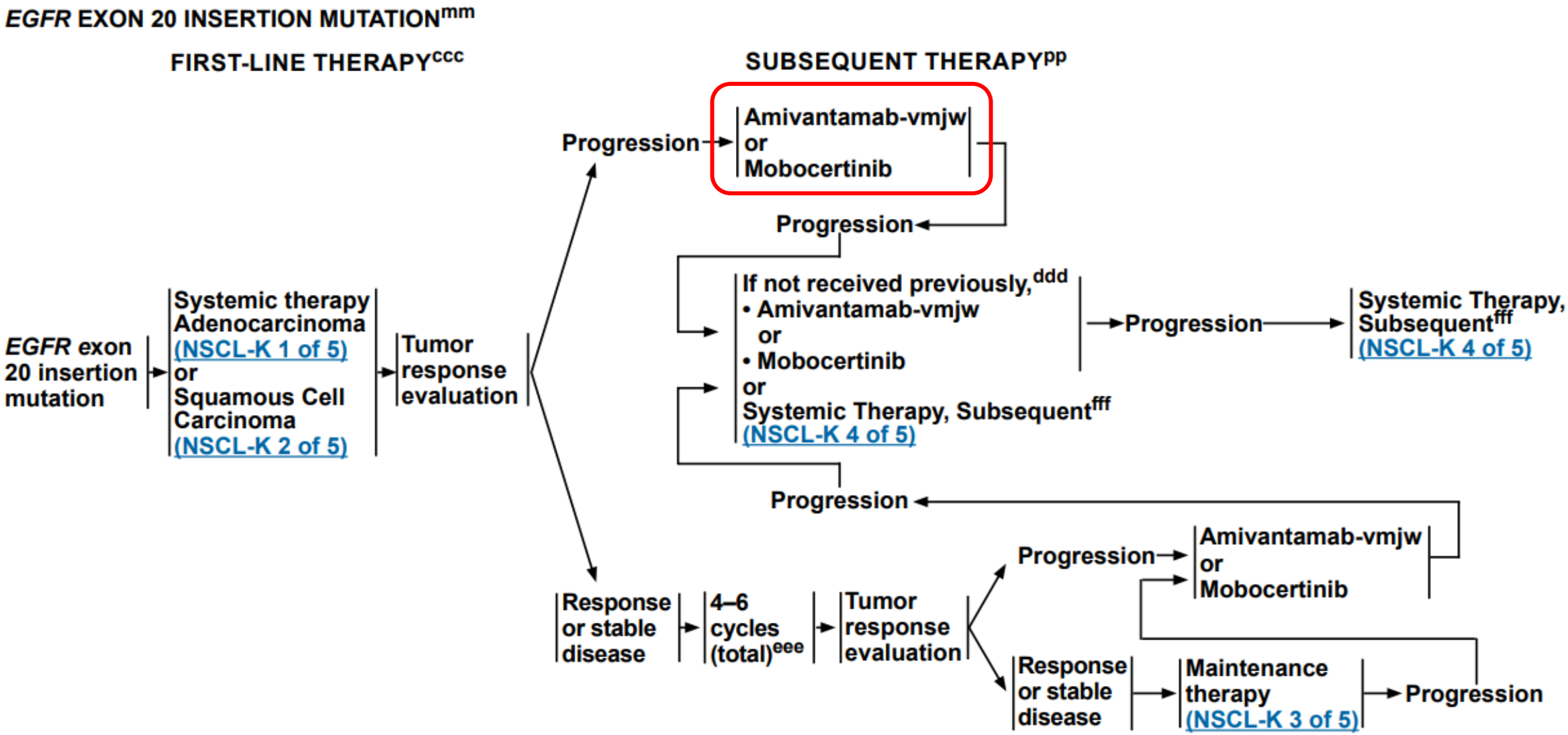
Actionable Rare mutations

- *EGFR* exon 20 insertions
- *KRAS* G12C mutations
- *RET* fusions
- *MET* 14 skipping mutations
- *NTRK* fusions

EGFR exon 20 insertion

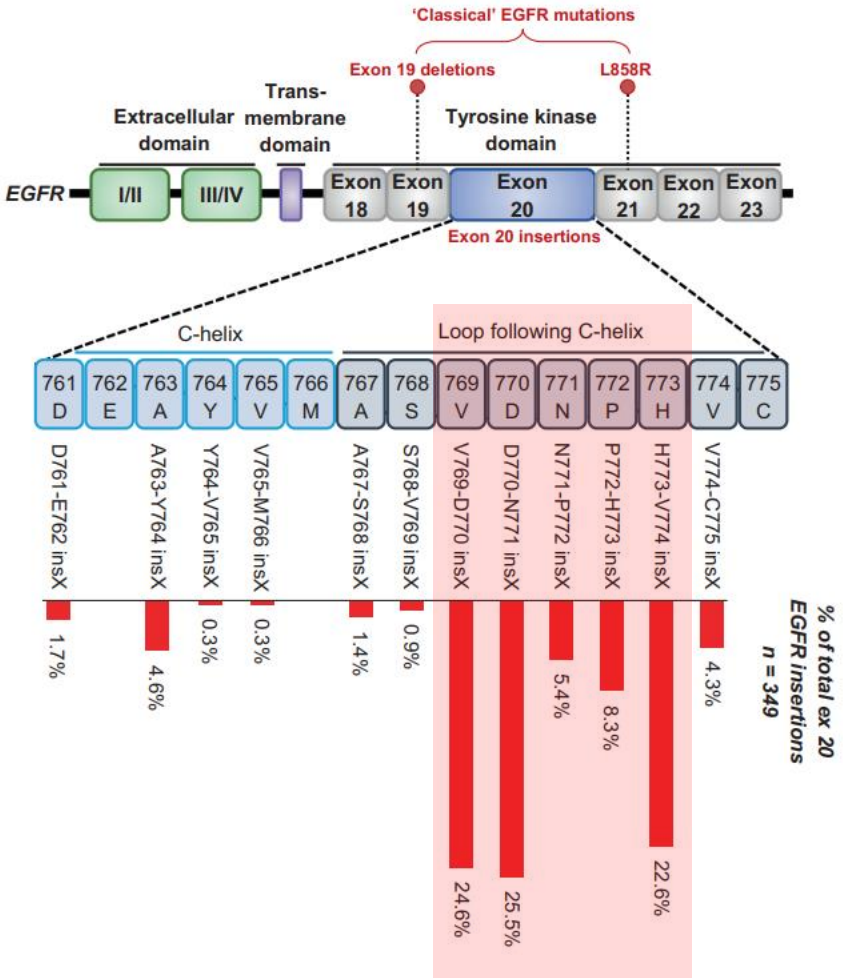


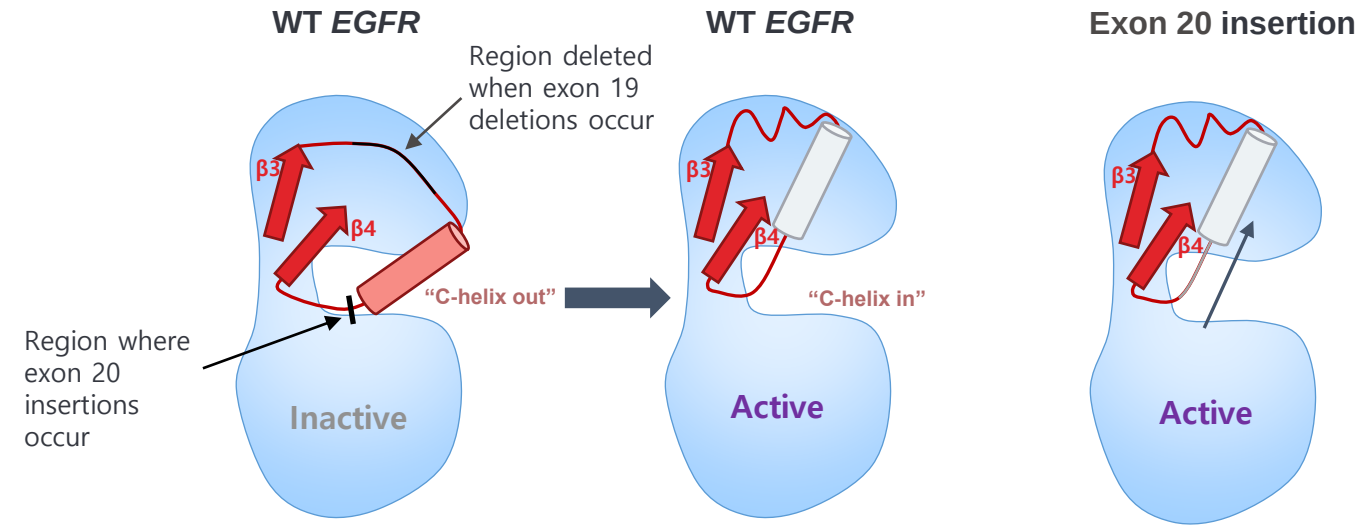
NCCN Guidelines: Ver2. 2023



Version 2 2023, National Comprehensive Cancer Network

EGFR exon 20 insertions in NSCLC

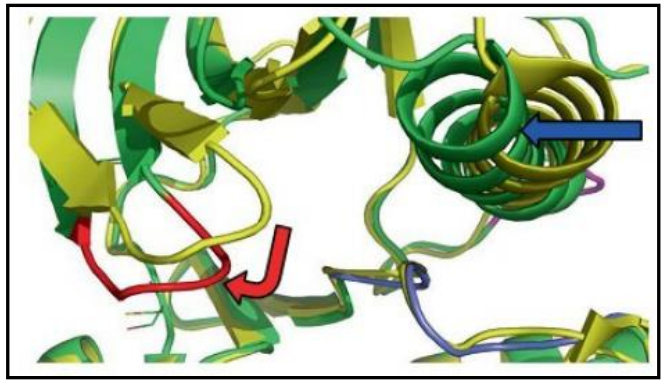




Upon ligand binding, the regulatory C-helix pivots from an outward (inactive) conformation to an inward (active) conformation.

EGFR exon 20 insertions "push" from the C-terminal side to stabilize the active state of EGFR even in the absence of a ligand.

3D modeling of *EGFR* D770insNPG (green) and *EGFR* T790M (yellow)



Shifts of the P-loop (red arrow) and the α-C-helix (blue arrow) into the binding pocket result in steric hindrance, reducing the size of the binding pocket

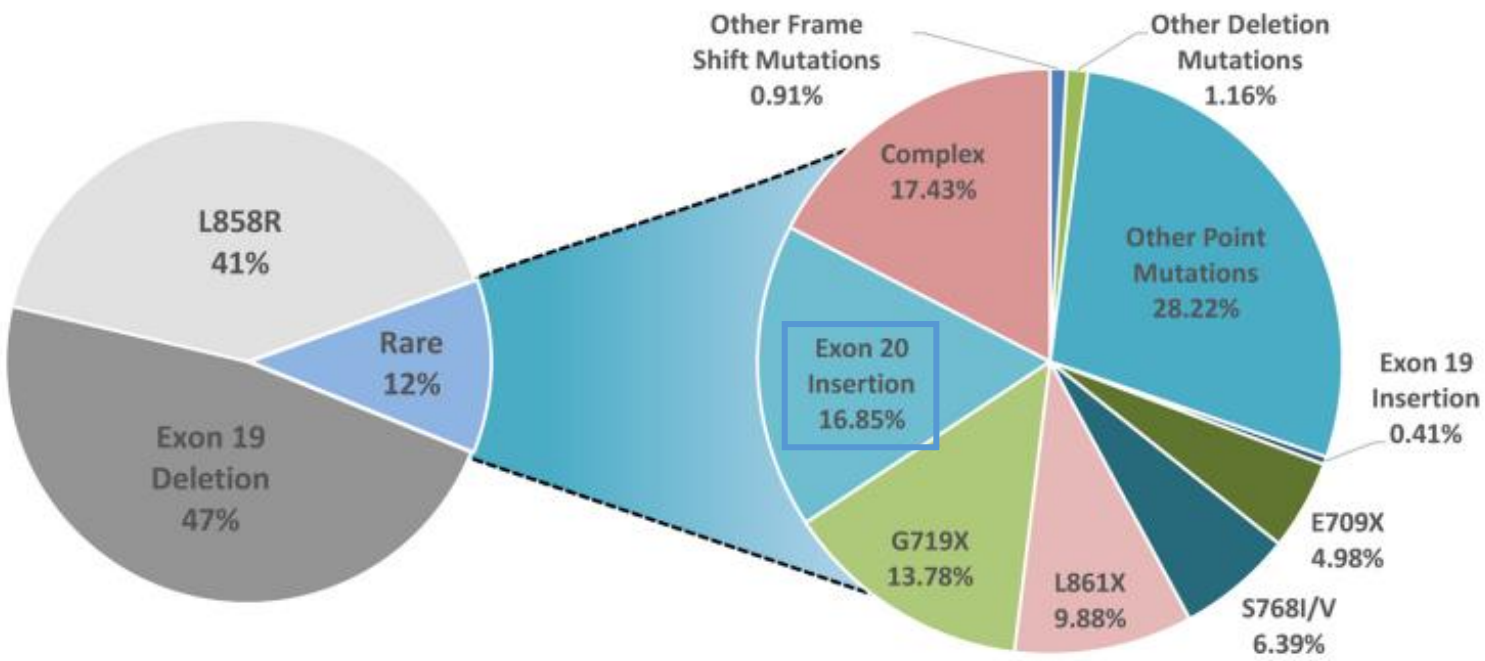
Vyse S, Huang PH. *Signal Transduct Target Ther.* 2019;4:5
Robichaux JP, et al. *Nat Med.* 2018;24:638–46

Target therapies for EGFR exon 20 insertions

- Selective targeting of *EGFR* exon 20 insertions, rather than WT *EGFR*, is a challenge
- The similarity in the structure of *EGFR* exon 20 insertion mutants and WT *EGFR* may lead to normal tissue toxicity

Prevalence of EGFR exon 20 insertion (2-4%)

COSMIC database



≈ 2%

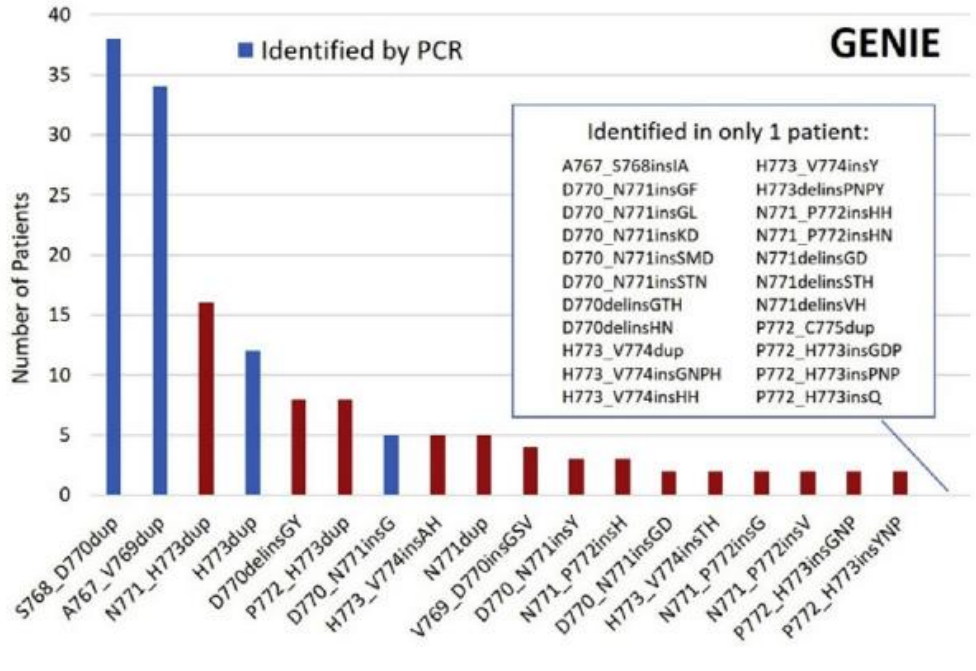
Mol Cancer Ther 2013; 12(2); 220–229, *Cancer Res Treat* 2019;51(2):623-631
Semin Cancer Biol 2020;61:167–179

Detection Methods

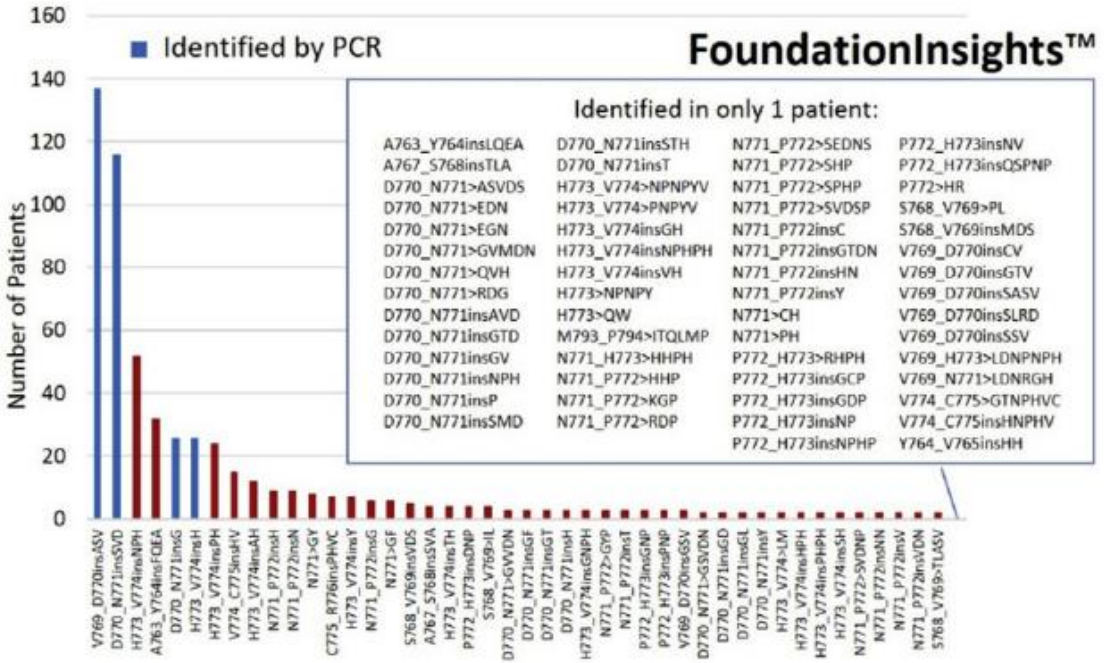
Pusan National University Yangsan Hospital

PCR (therascreen ®/cobas®) *vs* **NGS**

Genomics Evidence Neoplasia Information Exchange (GENIE) database (n= 12,497)



FoundationInsights™ database (n= 627)

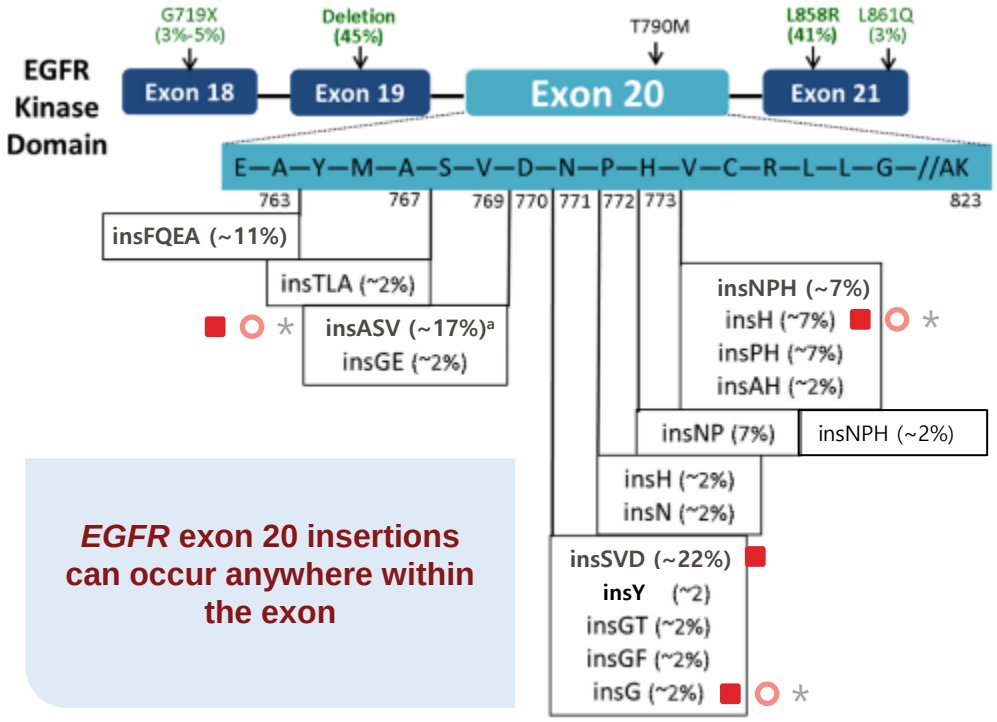


PCR methods are projected to miss 50% or more of Exon20 ins !!

J Thorac Oncol 2021;16(3):S208-209

PCR *vs* NGS

Due to heterogeneity, commonly used PCR testing methods can only detect a subset of EGFR exon 20 insertions, whereas NGS can detect all !!



***EGFR* exon 20 insertions can occur anywhere within the exon**

Exon 20 insertions: PCR testing methods

- **Cobas: detects five different exon 20 insertions** ■
- ***Therascreen*: detects three exon 20 insertions** ○
- **AmoyDx-EGFR29[b]: detects three exon 20 insertions** ⁎

Can detect up to 50% of *EGFR* exon 20 insertions

Exon 20 insertions: NGS testing methods

- **Oncomine Dx**
- **FoundationOne CDx**
- **Guardant360**

Capable of detecting all *EGFR* exon 20 insertions

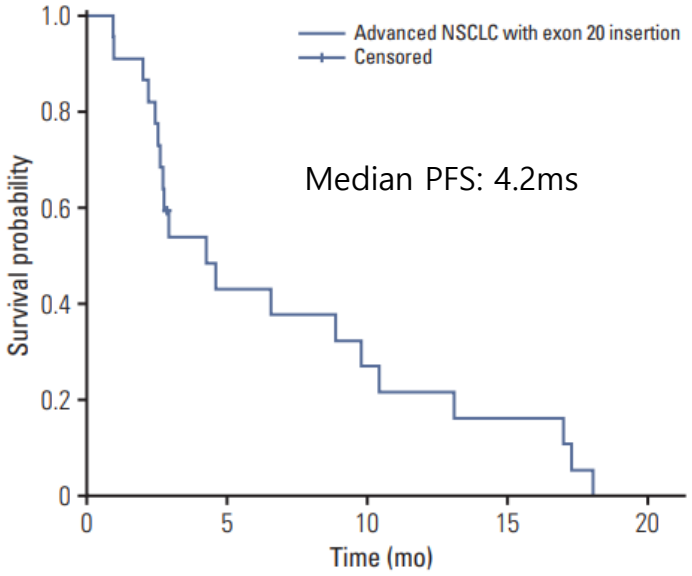
For the detection of *EGFR* exon 20 insertions, NGS testing is more comprehensive than PCR

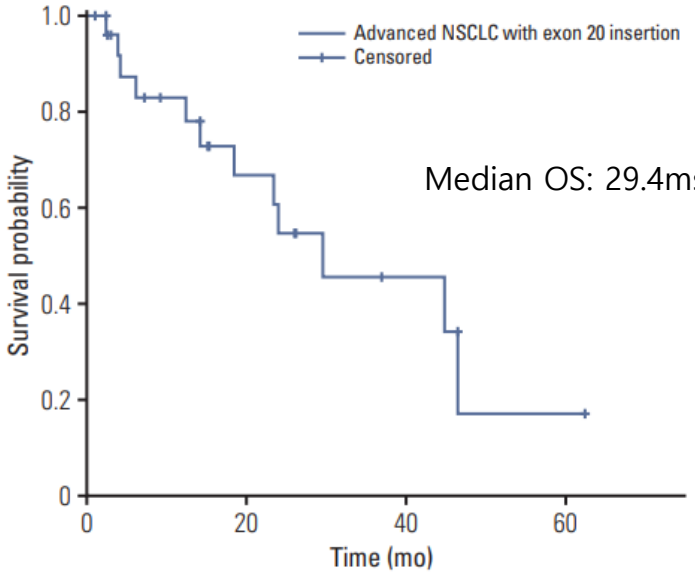
Khoo C, et al. *Transl Lung Cancer Res.* 2015;4:126–41
Planchard D, et al. *Ann Oncol.* 2018;29(Suppl 4):iv192–237

Clinical Response in NSCLC patients with exon 20 insertion

Study	Type of *EGFR* Exon 20 mutation	Patients treated with EGFR TKIs	ORR to TKI (%)	PFS to TKI	OS
Tu et al. [18]	Insertion 20	12	0	3.0 (1.3-4.7)	12.5 (0-25.5)
Lund-Iversen et al. [13]	Insertion 20	3	0	-	-
Arcila et al. [15]	Insertion 20	5	40	2.5	> 48 mo
Naidoo et al. [12]	Insertion 20	11	27	-	-
Yasuda et al. [17]	Insertion 20	19	11	-	-
Kuiper et al. [19]	Insertion 20	16	0	2.9 (2.3-3.6)	9.7
Current study	Insertion 20	4	25	2.6 (0.7-11.4)	29.4 (9.3-49.6)

EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression free survival; OS, overall survival.





Published studies evaluating clinical response to **EGFR-TKIs** in NSCLC patients with exon 20 insertion

ORR to chemotherapy: 50%

Clinical response to **systemic chemotherapy** in NSCLC patients with exon 20 insertion

Cancer Res Treat 2019;51(2):623-631

Real World Evidence of Treatment in exon 20 insertion

A systematic literature review performed in 2019 identified 32 RWE studies in a pooled efficacy analysis

Pooled analysis: RWE outcomes in patients with *EGFR* exon 20 insertion+ NSCLC

Treatments	OS		PFS		ORR	
	Median (95% CI), months	Pooled n	Median (95% CI), months	Pooled n	Median (95% CI), %	Pooled n
All treatments	**16.2 (6.7–25.8)**	666	**4.8 (0–10.4)[a]**	707	**19.8 (9.4–30.2)**	684
EGFR TKI[b]	12.6 (5.5–19.7)	210	4.0 (0–12.4)[a]	317	16.1 (9.8–22.3)	409
Chemotherapy ± TKI[b]	18.6 (8.9–28.4)	330	5.5 (3.5–7.5)	355	27.5 (15.0–40.0)	242
IO	7.5 (NA; 1 study)	29	3.2 (2.7–3.7)	26	10.0 (0–22.4)[a]	30

Outcomes are across all treatment lines

[a]Bounded at 0; [b]EGFR TKI that does not specifically target *EGFR* exon 20 insertions.
+: positive; EGFR: epidermal growth factor receptor; IO: immuno-oncotherapy; NA: not applicable; NSCLC: non-small-cell lung cancer; ORR objective response rate; OS: overall survival; PFS: progression free survival; RWE: real-world experience; TKI: tyrosine kinase inhibitor.
Tomaras D, et al. ESMO 2020. Abstract 1362P.

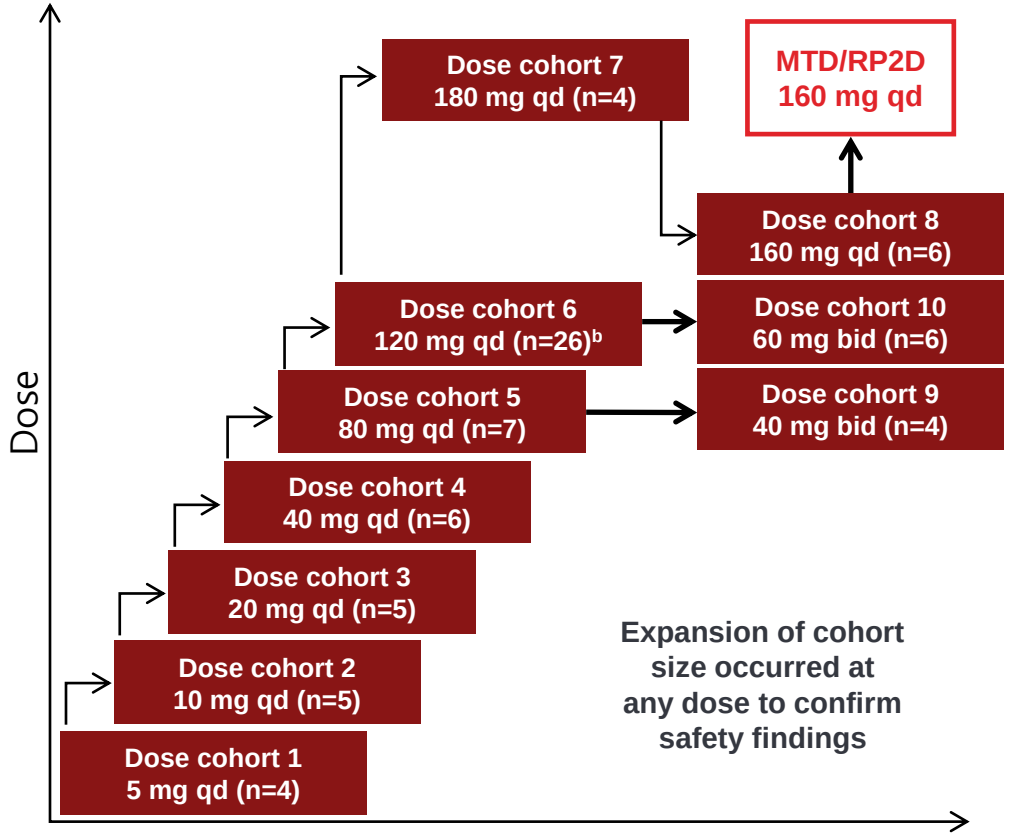
NCT02716116: Mobocertinib Phase 1/2 dose escalation study

Phase 1 dose escalation
3 + 3 design[a]

Eligibility
Patients with Stage IIIB or IV NSCLC (ECOG PS <2)

Primary endpoint
RP2D

Secondary endpoints
MTD
Safety
Tolerability
DLTs
PK



DLTs during dose escalation	Dose; n
Missed >25% of planned dose due to drug-related AEs	180 mg; 1
Grade 3	
Diarrhea	180 mg; 1
Mucositis	160 mg; 1
Pneumonitis	80 mg; 1
Grade 5	
Pneumonitis	120 mg; 1

DLTs occurred in 3 of 40 patients receiving mobocertinib ≤160 mg qd

[a]The dose level for each new cohort was up to 100% higher than the dose level in the previous cohort until a Grade 2 drug-related toxicity of diarrhea or skin rash occurred, based on expected class effects for EGFR TKIs, or until other DLTs were identified; further dose escalation involved increments of no more than 50% of the previous dose, depending on safety findings. [b]Five additional patients were enrolled to further confirm the safety observations.
AE: adverse event; bid: twice a day; DLT: dose-limiting toxicity; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; MTD: maximum tolerated dose; NSCLC: non-small-cell lung cancer; PK: pharmacokinetics; PS: performance status; qd: once a day; RP2D: recommended phase 2 dose; TKI: tyrosine kinase inhibitor.

Riely GJ, et al. *Cancer* Discovery. 2021;11:1688–99.

NCT02716116: Mobocertinib Phase 2 expansion study

Phase 2 expansion
Open label mobocertinib 160 mg qd[1]

Eligibility
Patients with Stage IIIB or IV NSCLC[a] (ECOG PS <2)

Primary endpoint
ORR by RECIST v1.1

Secondary endpoints
Safety
Tolerability
PK
Efficacy

Cohort 1
Patients with refractory *EGFR* exon 20 insertion+ NSCLC[b,d]

Cohort 2
Patients with refractory *HER2* exon 20 insertion+ or point mutation+ NSCLC[b,d]

Cohort 3
Patients with refractory *EGFR* exon 20 insertion+, *HER2* exon 20 insertion+, or point mutation+ NSCLC[c,d]

Cohort 4
Patients with treatment-naïve or refractory NSCLC with other *EGFR* mutations[e]

Cohort 5
Patients with refractory *EGFR* exon 20 insertion+ NSCLC with prior response to EGFR TKIs

Cohort 6
Patients with treatment-naïve *EGFR* exon 20 insertion+ NSCLC

Cohort 7
Patients with refractory *EGFR*/*HER2* mutation+ non-NSCLC

Pivotal Phase 2 "EXCLAIM" extension cohort[h]

Eligibility
Patients with refractory advanced *EGFR* exon 20 insertion+ NSCLC

Current analysis[2,3]
Efficacy[f]
n=28 (patients from dose escalation: n=6; patients from expansion cohort 1: n=22)
Safety
n=70: All patients with ≥1 dose of mobocertinib 5–180 mg qd
n=136: All patients with ≥1 dose of mobocertinib 160 mg qd[g]

[a]Except for cohort 7; [b]Participants with active or measurable CNS metastases, but not both, were eligible to participate; [c]Patients had measurable, active CNS metastases; [d]Active CNS metastases: untreated or treated and progressing; measurable CNS metastases: ≥10 mm in longest diameter by contrast-enhanced MRI; [e]Including EGFR mutations ±T790M and uncommon *EGFR* mutations; [f]Key eligibility criteria for efficacy data: ≥1 prior regimens of systemic therapy (history of prior TKI therapy allowed if there was no response); no patients with active and measurable brain metastases; [g]Patients received mobocertinib 160 mg qd as an initial dose during dose escalation or in expansion cohorts 1–7; [h]Locations for the EXCLAIM extension study included: United States only for phases 1 and 2; United States, European Union, and Asia.
+: positive; CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; HER2: human epidermal growth factor receptor 2; MRI: magnetic resonance imaging; NSCLC: non-small-cell lung cancer; ORR: objective response rate; PK: pharmacokinetics; PS: performance status; qd: once a day; RECIST: Response Evaluation Criteria in Solid Tumors; TKI: tyrosine kinase inhibitor.

Ramalingam SS, et al. *J Clin Oncol.* 2021;39(Suppl 15). Abstract 9014; Janne PA, et al. *J Clin Oncol.* 2019;37(Suppl 15). Abstract 9007; Riely GJ, et al. *Cancer Discovery*. 2021;11:1688–99.

Patients with EGFR exon 20 insertions had a confirmed ORR of 43% following treatment with ≥ 1 dose of 160mg of mobocertinib

Data cutoff: January 27, 2020

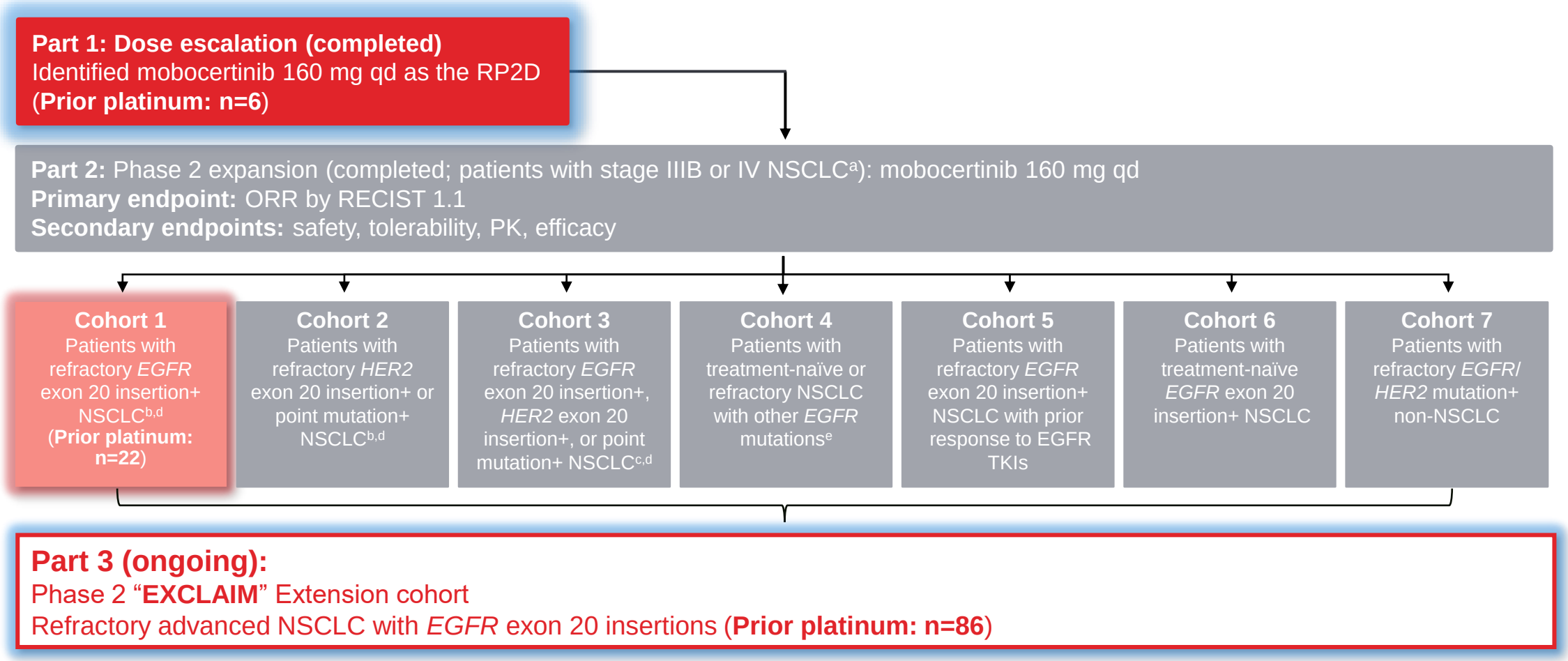
	Mobocertinib 5–40 mg qd (n=12)	Mobocertinib 80 mg t otal daily dose (n=9)	Mobocertinib 120 mg qd (n=21)	Patients with *EGFR* exon 20 insertions treated with mobocertinib 160 mg qd (n=28)[a]
Best response (confirmed), n (%)[b]				
CR	0	1 (11)	1 (5)	0
PR	0	1 (11)	3 (14)	12 (43)
SD[c]	3 (25)	6 (67)	11 (52)	12 (43)
PD	7 (58)	1 (11)	3 (14)	2 (7)
Not evaluated	2 (17)	0	3 (14)	2 (7)
Confirmed objective response, n (%) [95% CI]	0 (NA) [0–26]	2 (22) [3–60]	4 (19) [5–42]	12 (43) [24–63]
Disease control, n (%) [95% CI]	3 (25) [5–57]	8 (89) [52–100]	15 (71) [48–89]	24 (86) [67–96]
Median DOR, months (95% CI)[d]	NR	NR	NR	13.9 (5.0–not reached)

The median PFS in all patients was 7.3 months (95% CI, 4.4–15.6)

[a]Includes patients who received ≥1 dose of mobocertinib; [b]By RECIST v1.1; [c]SD observed ≥6 weeks after first study drug administration; [d]In confirmed responders.
CR: complete response; DOR: duration of response; EGFR: epidermal growth factor receptor; NA: not applicable; NR: not reported; ORR: objective response rate; PD: progressive disease; PFS: progression free survival; PR: partial response; qd: once a day; RECIST: Response Evaluation Criteria in Solid Tumors; SD: stable disease.

Riely GJ, et al. *Cancer Discov*. 2021;11:1688–99.

NCT02716116: The efficacy and safety of mobocertinib in patients with EGFR exon 20 insertion+ NSCLC (**EXCLAIM** and **PPP populations**)



[a]Except for cohort 7; [b]Participants with active or measurable CNS metastases, but not both, were eligible to participate; [c]Patients had measurable, active CNS metastases; [d]Active CNS metastases: untreated or treated and progressing; measurable CNS metastases: ≥10 mm in longest diameter by contrast-enhanced MRI; [e]Including EGFR mutations ±T790M and uncommon *EGFR* mutations.
+: positive; CNS: central nervous system; EGFR: epidermal growth factor receptor; HER2: human epidermal growth factor receptor 2; MRI: magnetic resonance imaging; NSCLC: non-small-cell lung cancer; ORR: objective response rate; PK: pharmacokinetics; PPP: platinum-pretreated patient; qd: once a day; RECIST: Response Evaluation Criteria in Solid Tumors; RP2D: recommended phase 2 dose; TKI: tyrosine kinase inhibitor.

Ramalingam SS, et al. *J Clin Oncol*. 2021;39(Suppl 15). Abstract 9014.

Baseline characteristics: PPP and EXCLAIM populations

Data cutoff: November 1, 2020

Demographic and baseline characteristic	PPP population (n=114)	EXCLAIM population (n=96)
Median age, years (range)	60 (27–84)	59 (27–80)
Female, %	66	65
Ethnicity, % Asian, White, Black, NR	60, 37, 3, 1	69, 29, 2, 0
NSCLC subtype, % Adenocarcinoma, SCC, large-cell	98, 1, 1	99, 1, 0
ECOG PS, % 0, 1	25, 75	29, 71
Smoking history, % Never, current, former	71, 2, 27	73, 2, 25
Brain metastases at baseline, %	35	34
Prior systemic anticancer regimens: 1, 2, ≥3	41, 32, 27	51, 31, 18
Median number of prior regimens, n	2	1
Prior platinum-based chemotherapy, %	100	90
Prior EGFR TKI, %	25	31
Prior IO, %	43	34

ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; IO: immuno-oncotherapy; NR: not reported; NSCLC: non-small-cell lung cancer; PPP: platinum-pretreated patient; PS: performance status; qd: once a day; SCC: squamous cell carcinoma; TKI: tyrosine kinase inhibitor.

Zhou C, et al. *JAMA Oncol*. 2021;7:e214761

Response: PPP and EXCLAIM populations

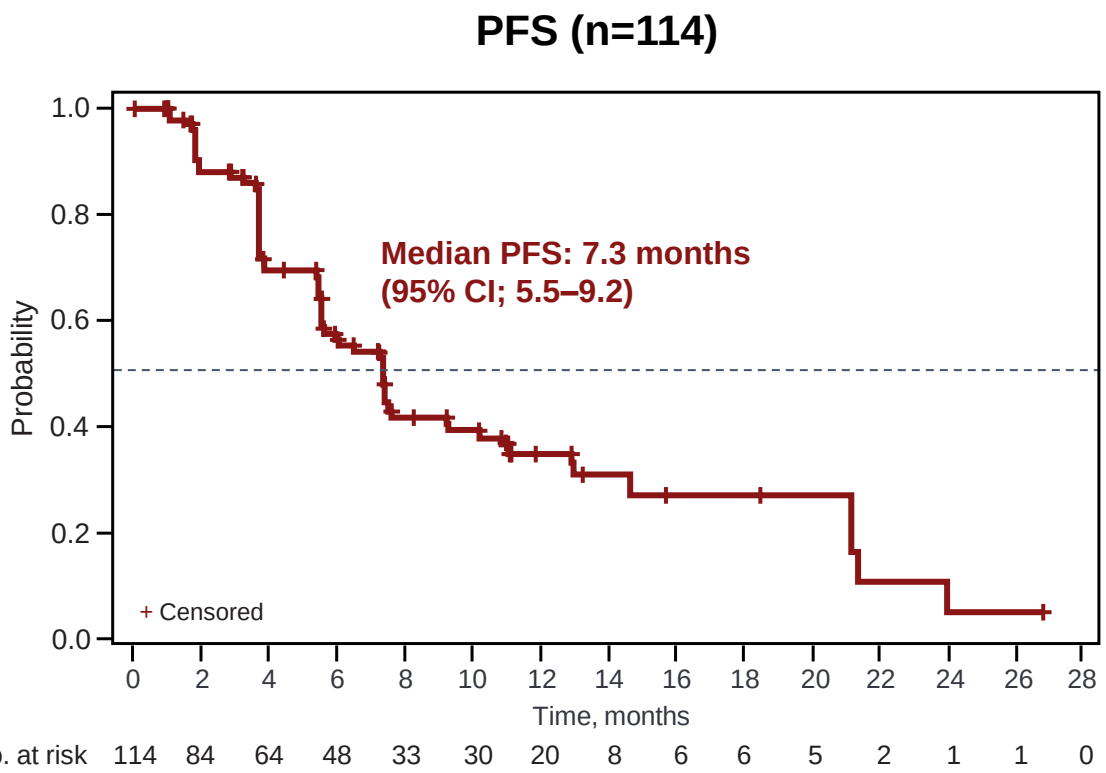
Data cutoff: November 1, 2020

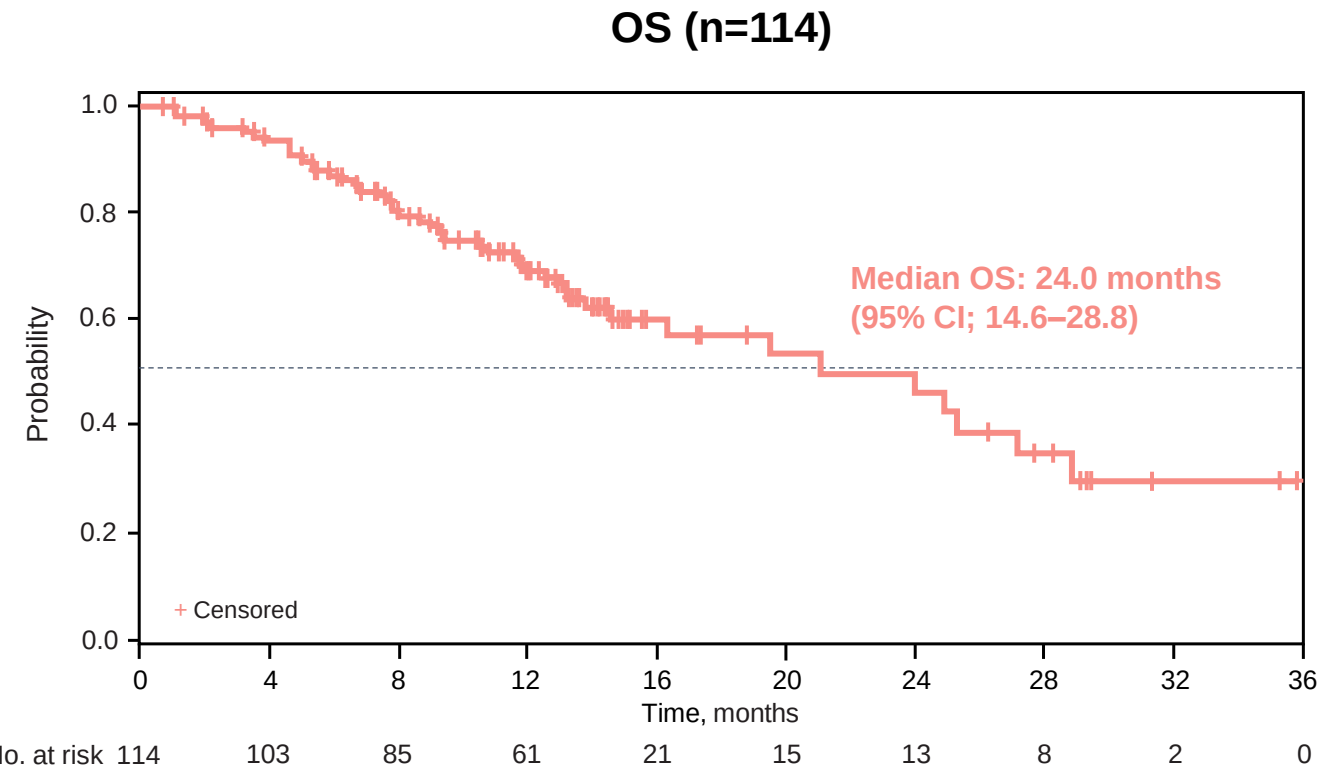
Responses	PPP population (n=114)		EXCLAIM population (n=96)	
	By IRC	By Investigator	By IRC	By Investigator
Median time on treatment, months (range)	7.4 (0.0–34.0)		6.8 (0.0–18.8)	
Median follow-up, months (range)	14.2 (0.7–35.8)		13.0 (0.7–18.8)	
Confirmed ORR, n (%) [95% CI] CR, % PR, %	32 (**28**) [20–37] 0 28	40 (**35**) [26–45] <1 34	24 (**25**) [17–35] 0 25	31 (**32**) [23–43] 1 31
Median DOR[a], months (95% CI)	**17.5** (7.4–20.3)	11.2 (5.6–Not reached)	Not reached (5.6–Not reached)	11.2 (7.0–Not reached)
DCR[b], n (%) [95% CI]	89 (78) [69–85]	89 (78) [69–85]	73 (76) [66–84]	72 (75) [65–83]
Median PFS, months (95% CI)	7.3 (5.5–9.2)	7.3 (5.6–8.8)	7.3 (5.5–9.1)	7.3 (5.6–9.1)

[a]DOR per Kaplan-Meier analysis; [b]Defined as confirmed CR, PR, or best response of SD for ≥6 weeks after initiation of study drug.
CR: complete response; DCR: disease control rate; DOR: duration of response; IRC: independent review committee; ORR: objective response rate; PFS: progression free survival; PPP: platinum-pretreated patient; PR: partial response; qd: once a day; SD: stable disease.

Zhou C, et al. *JAMA Oncol*. 2021;7:e214761

Survival : PPP populations (IRC-assessment)





Data cutoff: November 1, 2020

IRC: independent review committee; OS: overall survival; PFS: progression free survival; PPP: platinum-pretreated patient; qd: once a day

Zhou C, et al. *JAMA Oncol*. 2021;7:e214761
Ramalingam SS, et al. *J Clin Oncol*. 2021;39(Suppl 15). Abstract 9014

Safety profile: PPP population/EXCLAIM

Data cutoff: November 1, 2020

Overall Adverse Events

n (%)	PPP population (n=114)	EXCLAIM population (n=96)
Any TRAE	113 (99)	95 (99)
Grade ≥3 TRAE	54 (47)	40 (42)
Serious AEs	56 (49)	45 (47)
AE leading to dose reduction	29 (25)	21 (22)
AE leading to treatment discontinuation	19 (17)	10 (10)
TRAE leading to death	1 (1)	1 (1)

Grade ≥ 3 TRAEs

TRAEs of any grade reported in ≥10% of patients or Grade ≥3 in ≥3% of patients	All grades, n (%)	Grade ≥3, n (%)
Diarrhea	104 (91)	24 (21)
Rash	51 (45)	0
Paronychia	43 (38)	1 (<1)
Decreased appetite	40 (35)	1 (<1)
Nausea	39 (34)	5 (4)
Dry skin	35 (31)	0
Vomiting	34 (30)	3 (3)
Blood creatinine increased	29 (25)	2 (2)
Stomatitis	27 (24)	5 (4)
Pruritis	24 (21)	1 (<1)
Lipase increased	22 (19)	4 (4)
Amylase increased	21 (18)	3 (3)
Fatigue	16 (14)	3 (3)
Anemia	20 (18)	1 (<1)
Electrocardiogram QT prolonged	12 (11)	3 (3)

AE: adverse event; EGFR: epidermal growth factor receptor; PPP: platinum-pretreated patient; TKI: tyrosine kinase inhibitor; TRAE: treatment-related adverse event.

Ramalingam SS, et al. *J Clin Oncol.* 2021;39(Suppl 15). Abstract 9014
Zhou C, et al. *J Thorac Oncol.* 2021;16(Suppl 3). Abstract 04, *JAMA Oncol*. 2021;7:e214761

NCT04129502: Mobocertinib Phase 3 EXCLAIM-2 study of 1L mobocertinib vs chemotherapy in patients with *EGFR* exon 20 insertion+ advanced NSCLC

EXCLAIM-2: An ongoing, multicenter, randomized, open-label Phase 3 study of mobocertinib as 1L treatment vs chemotherapy for patients with *EGFR* exon 20 insertion+ advanced NSCLC[1a]

N=318[1,2]

Eligibility

Patients with LA, recurrent, or metastatic NSCLC

EGFR exon 20 insertions by local testing and central Confirmation[b]

≥1 measurable lesion

ECOG PS 0/1

No prior systemic treatment

Randomization 1:1

Stratified by:
- Baseline CNS Metastases (yes vs no)
- Race (Asian vs non-Asian)

Arm A
Mobocertinib
160 mg orally qd

Crossover allowed after IRC-assessed PD[c] is documented, and crossover eligibility criteria are met (intolerable toxicity and other discontinuation criteria)

Arm B
Pemetrexed + cisplatin IV or
Pemetrexed + carboplatin IV

Primary endpoint:

IRC-assessed PFS per RECIST v1.1 (up to ≈40 months after the first patient randomization)[1]

Secondary endpoints:
- IRC- and investigator-assessed confirmed ORR
- DOR, time to response
- DCR
- Investigator-assessed PFS
- OS
- HRQOL assessed by EORTC QLQ-C30 and QLQ-LC13[1]

Global study: including North America, Europe, Middle East, and Asia Pacific[2]

[a]Recruiting patients based on ClinicalTrials.gov register as of April 2022 (first patient in was January 2020); [b]*EGFR* exon 20 insertions are assessed by a clinical laboratory improvements amendment-certified (US sites) or an accredited (outside of the US) local laboratory and confirmed by central laboratory; [c]Randomized treatment with mobocertinib or platinum-based chemotherapy may be continued after PD, at the discretion of the investigator and with the sponsor's approval if there is still evidence of clinical benefit.
+: positive; 1L: first-line; CNS: central nervous system; DCR: disease control rate; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; EORTC: European Organisation for Research and Treatment of Cancer; HRQOL: health-related quality of life; IRC: independent review committee; IV: intravenous; LA: locally advanced; NSCLC: non-small-cell lung cancer; ORR: objective response rate; OS: overall survival; PD: progressive disease; PFS: progression free survival; PS: performance status; qd: once a day; QLQ(-LC): quality of life questionnaire(-lung cancer module); RECIST: Response Evaluation Criteria in Solid Tumors.

ClinicalTrials.gov. NCT04129502. Available at: https://clinicaltrials.gov/ct2/show/NCT04129502.
Gonzalvez F, et al. AACR. 2020.

NCT02609776: CHRYSALIS Phase I study (Amivantamab)

CHRYSALIS: A multicenter, open-label, first-in-human study consisting of 2 parts

Eligibility

- Metastatic/unresectable NSCLC
- Ineligible for, or progressed while receiving, platinum-based chemotherapy
- Advanced NSCLC (part 1) or measurable disease (part 2)
- Activating or resistance *EGFR* or *MET* mutations or amplifications (part 2)
- Patients with brain metastases who received previous treatment and were asymptomatic at screening

Dose escalation objective:

- Establish the RP2D

Dose expansion objectives:

- Safety and efficacy at the RP2D

Dose escalation
140–1750 mg
(n=77)

RP2D:
- 1050 mg (<80 kg)
- 1400 mg (≥80 kg)

IV dosing; C1 weekly, C2+ every other week

Dose expansion
Cohort D: *EGFR* exon 20 insertion
(n=142)

Post-platinum exon 20 insertion treated at RP2D
n=114 (safety population)

Post-platinum exon 20 insertion with ≥3 disease assessments at clinical cutoff
n=81 (efficacy population)

+: positive; EGFR: epidermal growth factor receptor; IV: intravenous; MET: MET proto-oncogene; NSCLC: non-small-cell lung cancer; RP2D: recommended phase 2 dose.

Park K, et al. *J Clin Oncol*. 2021;30:3391–402.

Demographic and clinical characteristics

Demographic and clinical characteristics	Efficacy population (n=81)
Median age, years (range)	62 (42–84)
Sex, n (%)	
Male	33 (41)
Female	48 (59)
Ethnicity, n (%)	
Asian	40 (49)
White	30 (37)
Black	2 (2)
NR	9 (11)
ECOG PS, n (%)	
0	26 (32)
1	54 (67)
2	1 (1)
Median time from diagnosis, months (range)	17 (1–130)
NSCLC subtype, n (%)	
Adenocarcinoma	77 (95)
SCC	3 (4)
Others	1 (1)

Demographic and clinical characteristics	Efficacy population (n=81)
Smoking history, n (%)	
Does not smoke	43 (53)
Smokes	38 (47)
Location of metastases[a], n (%)	
Lymph node	45 (53)
Bone	34 (42)
Brain	18 (22)
Liver	7 (9)
Adrenal gland	3 (4)
Others	45 (56)
Prior systemic therapy, n (%)	
Platinum-based chemotherapy	81 (100)
IO	81 (100)
EGFR TKI	37 (46)
First-generation[b]	20 (25)
Second-generation[c]	7 (9)
Third-generation[d]	6 (7)
Exon 20 insertion-targeted[e]	6 (7)
	1 (1)

[a]Patients could be counted in more than one category; [b]Erlotinib or gefitinib; [c]Afatinib; [d]Osimertinib, ASP8273, and nintedanib; [e]Poziotinib or mobocertinib.
ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; IO: immuno-oncotherapy; NR: not reported; NSCLC: non-small-cell lung cancer; PS: performance status; SCC: squamous cell carcinoma; TKI: tyrosine kinase inhibitor.

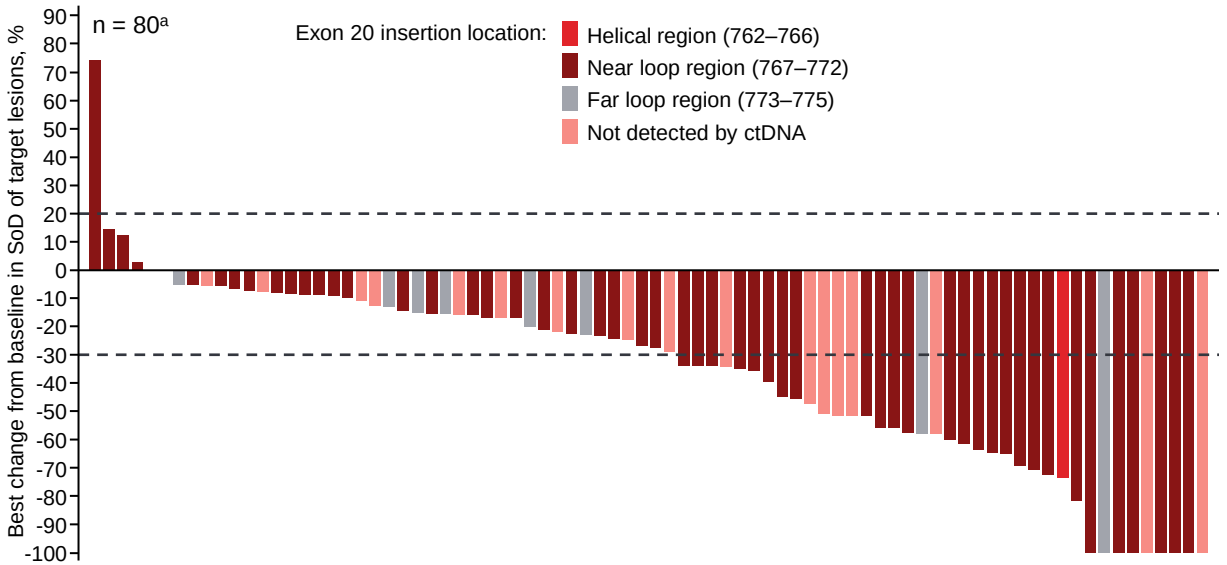
Park K, et al. *J Clin Oncol*. 2021;30:3391–402.

Efficacy: CHRYSALIS Phase I study

Data cutoff: October 8, 2020

At the data cutoff on October 8, 2020, 3 patients experienced CR while 29 patients experienced PR

- ✓ The median follow up was 9.7 months
- ✓ 15 responders remained on treatment at data cutoff



Efficacy	IRC-assessed	Investigator-assessed
ORR, % (95% CI)[b]	40 (29–51)	36 (25–47)
CBR, % (95% CI)[c]	74 (63–83)	73 (62–82)
Best response, n (%)		
CR	3 (4)	0
PR	29 (36)	29 (36)
SD	39 (48)	39 (48)
PD	8 (10)	12 (15)
NE	2 (2)	1 (1)
Median DOR, months (95% CI)	11.1 (6.9–Not reached)	NR
Median PFS, months (95% CI)	8.3 (6.5–10.9)	8.3 (5.5–10.6)
Median OS, months (95% CI)[d]	22.8 (14.6–Not reached)	

[a]One patient discontinued before any disease assessment and is not included in the plot; [b]Proportion of total patients in efficacy population who had PR or CR; [c]Proportion of total patients in efficacy population who had PR or CR or SD for at least 11 weeks; [d]With 23 deaths at data cutoff, OS remains immature.
CBR: clinical benefit rate; CR: complete response; ctDNA: circulating tumor deoxyribonucleic acid; DOR: duration of response; NE: not evaluable; NR: not reported; ORR: objective response rate; OS: overall survival; PFS: progression free survival; PD: progressive disease; PR: partial response; SD: stable disease; SoD: sum of lesion diameter.

Park K, et al. *J Clin Oncol*. 2021;30:3391–402.

Safety profile: CHRYSALIS Phase I

AEs, n (%)	Safety population (n=114)	Patients treated at RP2D (n=258)
Any AE	113 (99)	257 (100)
Grade ≥3 AEs	40 (35)	101 (39)
SAEs	34 (30)	79 (31)
AEs leading to death	8 (7)	13 (5)
AEs leading to discontinuation	11 (10)	17 (7)
AEs leading to dose reduction	15 (13)	26 (10)
AEs leading to dose interruption[a]	40 (35)	88 (34)

Most common AEs (≥20%) of any grade, n (%)	Safety population (n=114)	Patients treated at RP2D (n=258)
Rash[b]	98 (86)	202 (78)
Infusion-related reaction	75 (66)	167 (65)
Paronychia	51 (45)	104 (40)
Hypoalbuminemia	31 (27)	63 (24)
Constipation	27 (24)	58 (23)
Stomatitis	24 (21)	50 (19)
Nausea	22 (19)	55 (21)
Dyspnea	22 (19)	52 (20)

Grade ≥3 AEs occurring in >1% of patients in the safety population were:

- Hypokalemia (5%)
- Rash (4%)
- Diarrhea (4%)
- Infusion-related reaction (3%)
- Hypoalbuminemia (3%)
- Dyspnea (2%)
- Fatigue (2%)

Grade ≥3 TRAEs occurred in 16% (18/114) of patients in the safety population. The most common were:

- Rash (4%)
- Infusion-related reaction (3%)
- Neutropenia (3%)

Treatment-related SAEs occurred in 9% (10/114) of patients and included infusion-related reaction and diarrhea (2%)

Infusion-related reactions were observed, but were low grade and primarily limited to the first infusion

[a]Excludes infusion-related events; [b]Rash is defined by acne, dermatitis, dermatitis acneiform, erythema, erythema multiforme, folliculitis, macule, perineal rash, pustule, rash, rash erythematous, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin lesion, and toxic epidermal necrolysis.
AE: adverse event; EGFR: epidermal growth factor receptor; MET: MET proto-oncogene; RP2D: recommended phase 2 dose; SAE: serious adverse event.

Park K, et al. *J Clin Oncol*. 2021;30:3391–402.

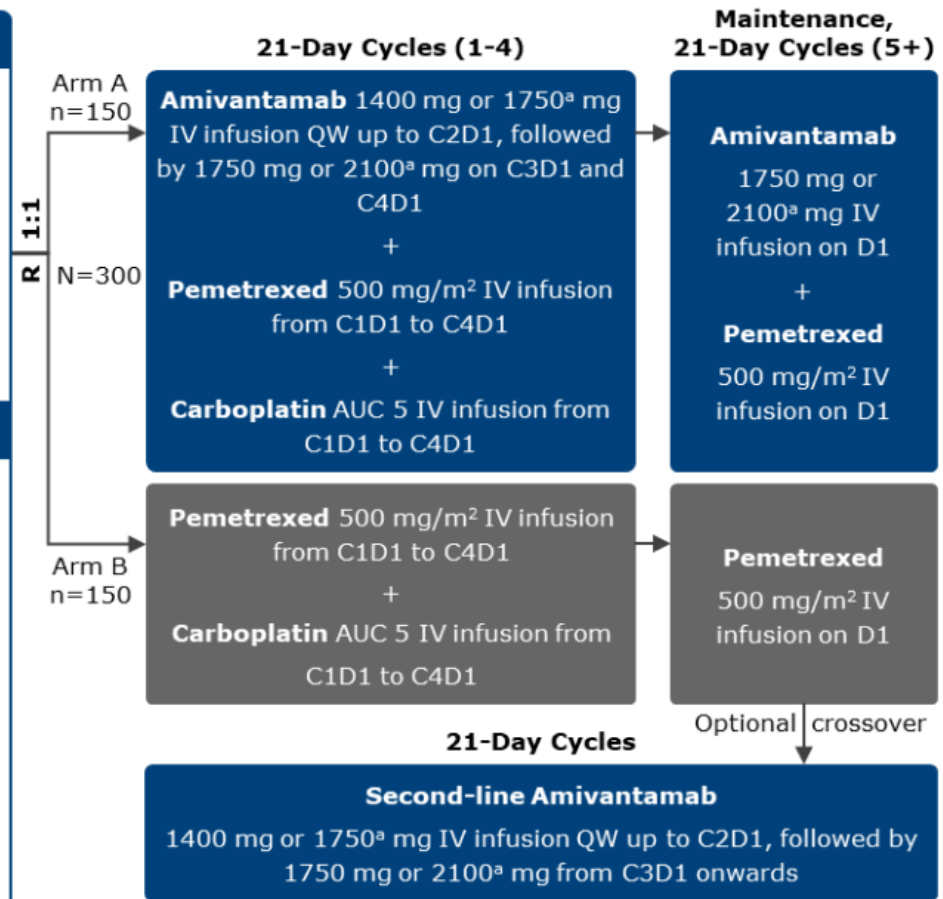
PAPILLON Study

Key Inclusion Criteria

- Age ≥18 years
- Locally advanced or metastatic NSCLC with a documented EGFR Exon20ins activating mutation
- Measurable disease[b]
- ECOG PS ≤1
- Adequate organ and bone marrow function

Key Exclusion Criteria

- Prior systemic treatment for locally advanced or metastatic disease (with exceptions)[c]
- Synchronous NSCLC with an EGFR mutation other than Exon20ins
- Untreated brain metastases
- History of leptomeningeal disease, medical history of ILD (including drug-induced ILD), or radiation pneumonitis
- Active malignancy (with exceptions)[c]
- History of clinically significant cardiovascular disease



Primary Endpoint

- PFS by BICR[b]

Secondary Endpoints

- ORR
- DOR
- OS
- Incidence and severity of AEs[d]
- Patient-reported outcomes
- Serum amivantamab concentrations and anti-amivantamab antibodies

Stratification

- Brain metastases (yes vs no)
- ECOG PS (0 vs 1)
- Prior EGFR TKI use (yes vs no)

Agrawal T, et al. PAPILLON: a randomized phase 3 study of amivantamab plus chemotherapy vs chemotherapy alone in EGFR exon 20ins NSCLC. Poster presented at WCLC 2020

Comparative effectiveness of mobocertinib vs amivantamab (Matching-adjusted indirect comparison)

Step 3: Comparing outcomes

After matching, the treatment outcomes for the mobocertinib trial were recalculated and compared against those for the amivantamab trial

Outcome	Unweighted mobocertinib (n=144)	Weighted mobocertinib (ESS=61)	Amivantamab (N=81)	Unweighted analysis	Weighted analysis
Median OS, months (95% CI)	24.0 (14.6–28.8)	24.8 (14.6–NE)	22.8 (14.6–NE)	HR 1.12 (0.71–1.77)	HR 0.95 (0.55–1.67)
Median PFS by IRC, months (95% CI)	7.3 (5.5–9.2)	7.4 (5.5–14.6)	8.3 (6.5–10.9)	HR 1.00 (0.69–1.44)	HR 0.82 (0.52–1.32)
Median DOR by investigator, months (95% CI)	11.2 (5.6–NE)	14.2 (7.0–NE)	11.1 (6.5–13.1)*	HR 0.71 (0.38–1.30)	HR 0.44 (0.19–1.00)
Median DOR by IRC, months (95% CI)	17.5 (7.4–20.3)	17.5 (8.3–20.3)	11.1 (6.9–NE)	HR 0.66 (0.33–1.32)	HR 0.56 (0.25–1.23)
cORR by investigator, % (95% CI)	35 (27–45)	36 (24–49)	36 (25–47)	OR 0.97 (0.53–1.77)	OR 0.99 (0.48–2.02)
cORR by IRC, % (95% CI)	28 (20–37)	30 (19–43)	40 (29–51)	OR 0.60 (0.32–1.10)	OR 0.64 (0.31–1.33)

HR <1 favors mobocertinib
OR <1 favors amivantamab

From evaluation via MAIC, mobocertinib and amivantamab appear to have similar efficacy overall

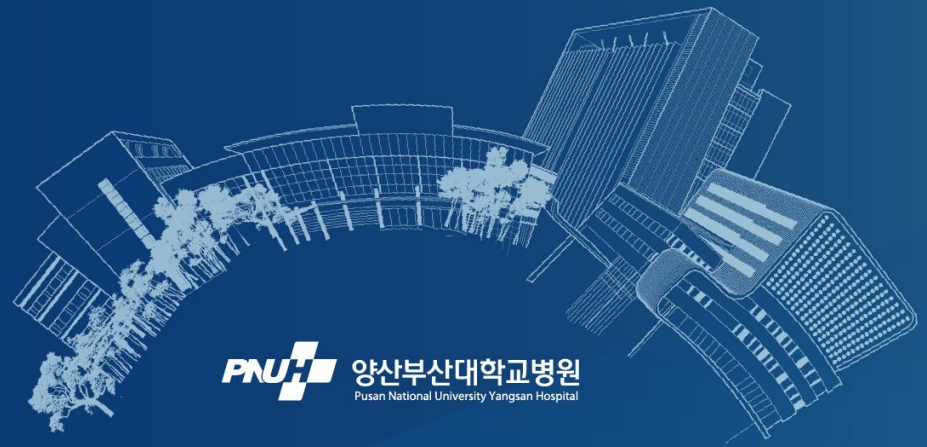
*Estimated using reconstructed patient-level data from swimmer and survival plots for amivantamab

CI, confidence interval; cORR, confirmed overall response rate; HR, hazard ratio; NE, not estimable; OR, odds ratio; OS, overall survival; PFS, progression-free survival

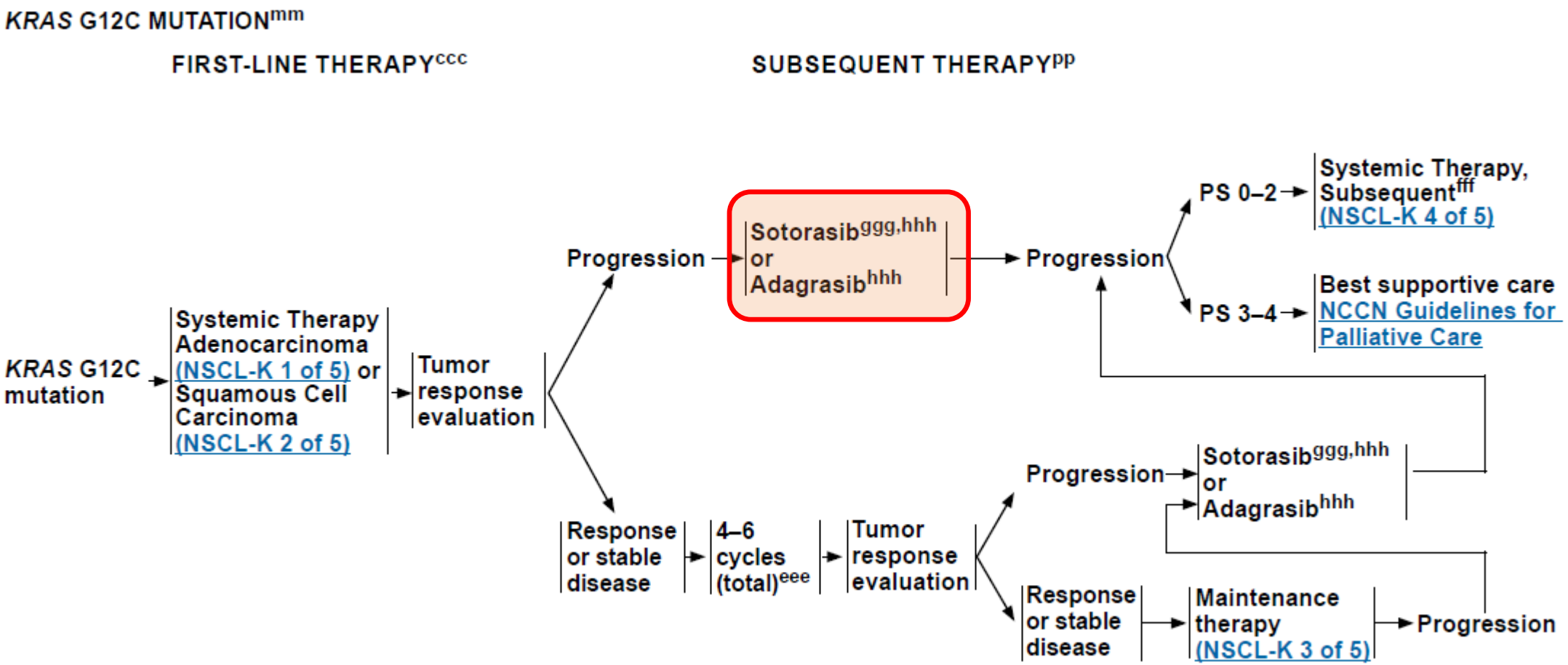
Ou S-H, et al. ASCO 2022. Abstract 9115

KRAS G12C mutation

Pusan National University
Yangsan Hospital



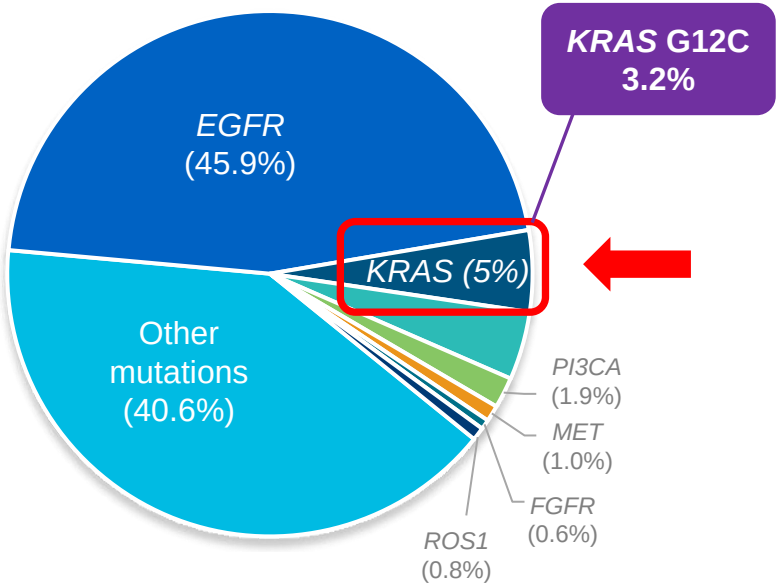
NCCN Guidelines: Ver2. 2023



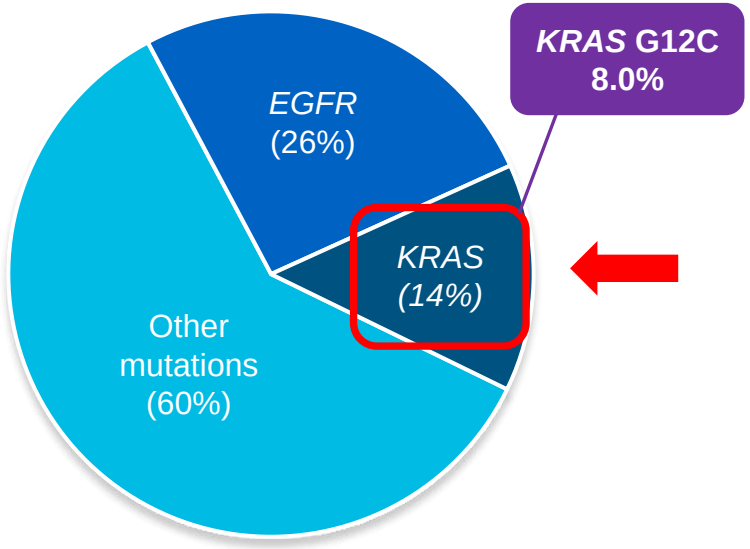
Version 2 2023, National Comprehensive Cancer Network

Prevalence of *KRAS* mutations

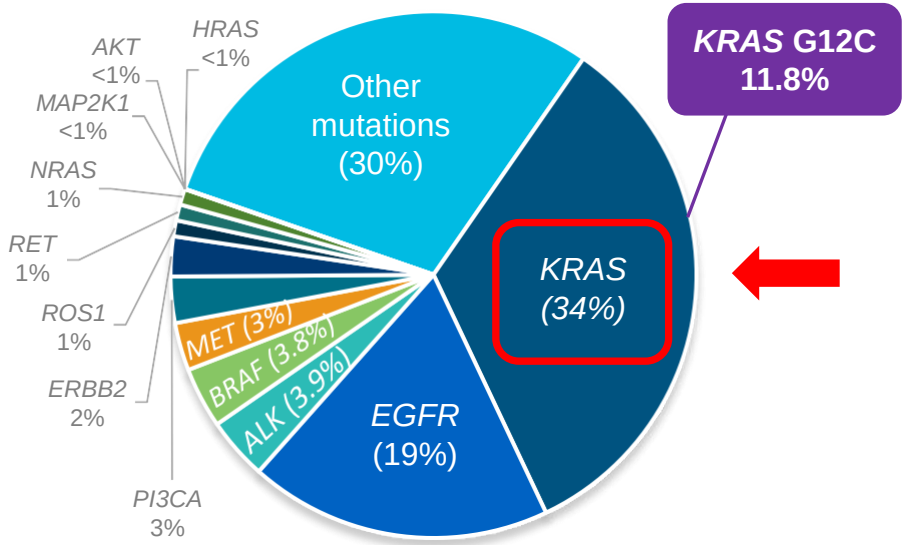
Asian patients
(N=968)[3]



Latin American patients*
(N=5,738)[2]



US and European patients
(N=933)[1]

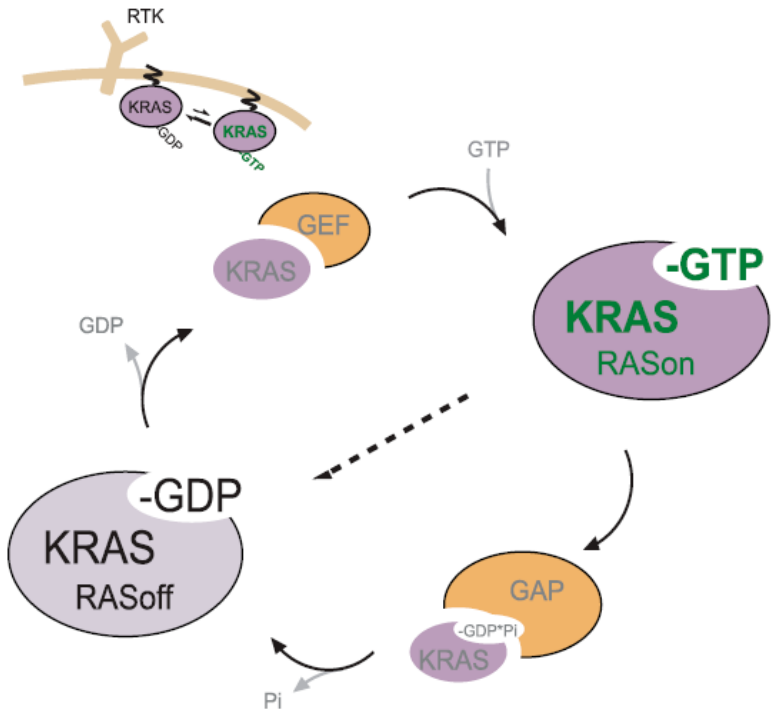


* Patients were assessed in the following countries: Argentina, Mexico, Colombia, Peru, Panama, and Costa Rica

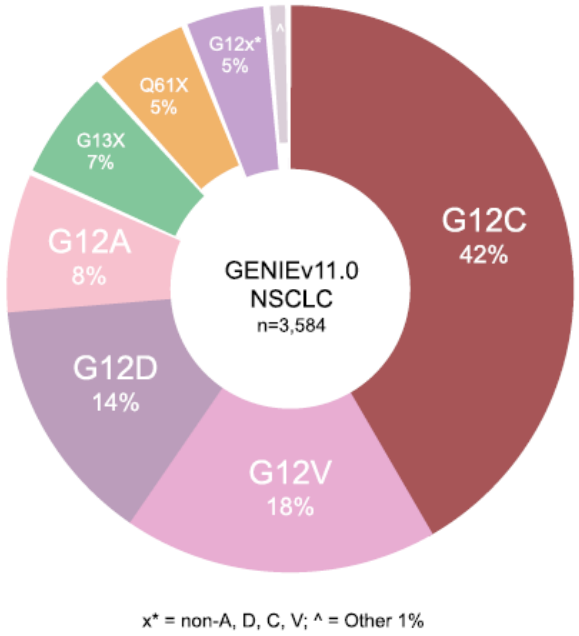
1. Awad MM, *et al. J Clin Oncol* 2016;34:721–730; 2. Arrieta O, *et al. J Thorac Oncol* 2015;10:838–843
3. Liu S, *et al. J Thorac Oncol* 2016;11:1503–1510

KRAS as a Target

KRAS is an enzyme that cycles between the GTP (on) state and GDP (off) state

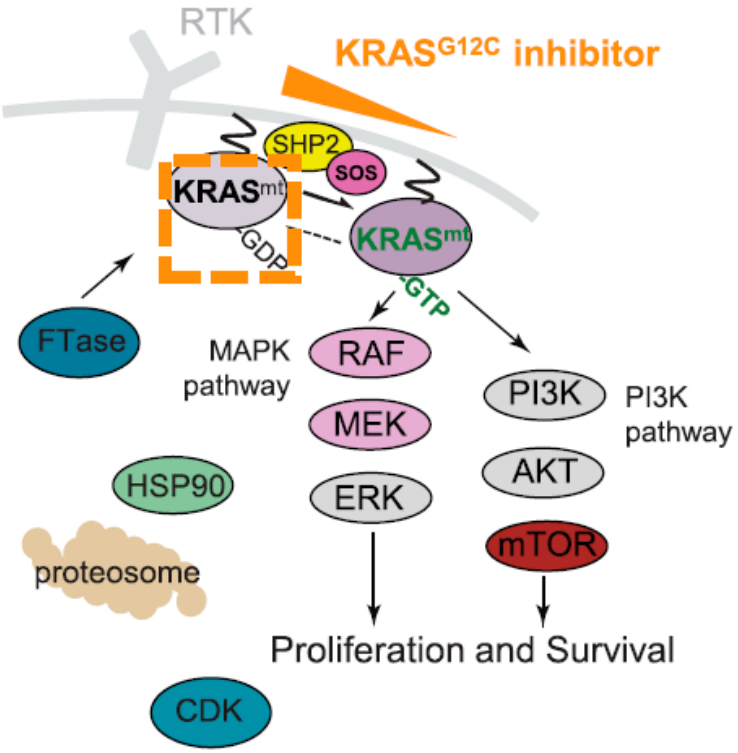


Distribution of KRAS-driven NSCLCs



x* = non-A, D, C, V; ^ = Other 1%

Proteins previously targeted in KRAS-driven lung cancers



Luo J, et al. 2022 ASCO EDUCATIONAL BOOK volume 42

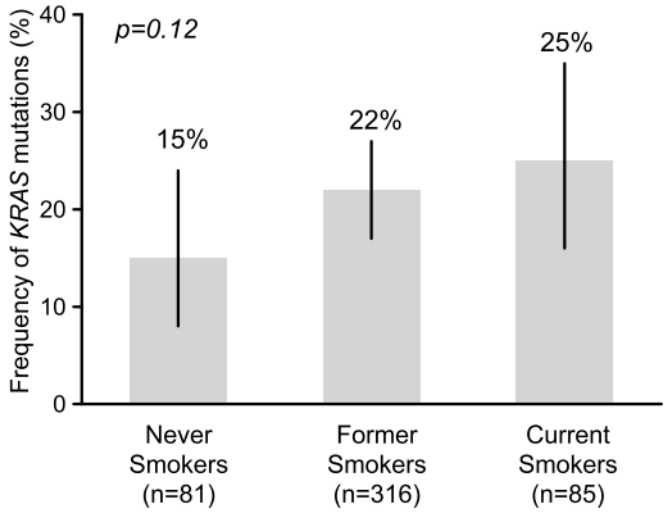
Clinical Characteristics

KRAS codon 12 and 13 mutations and clinical characteristics

	All	Mutant *KRAS*	Wild-type *KRAS*	*P*
Total	482	102 (21%)	380 (79%)	
Men	197 (41%)	40 (39%)	157 (41%)	0.73*
Women	285 (59%)	62 (61%)	223 (59%)	
Never smokers	81 (17%)	12 (12%)	69 (18%)	0.14*
Former/current smokers	401 (83%)	90 (88%)	311 (82%)	
Age, median (range)	68 (30-89)	68 (33-85)	67 (30-89)	0.98 †

*Fisher's exact test.
† Wilcoxon rank sum test.

Frequency of *KRAS* mutation by smoking history

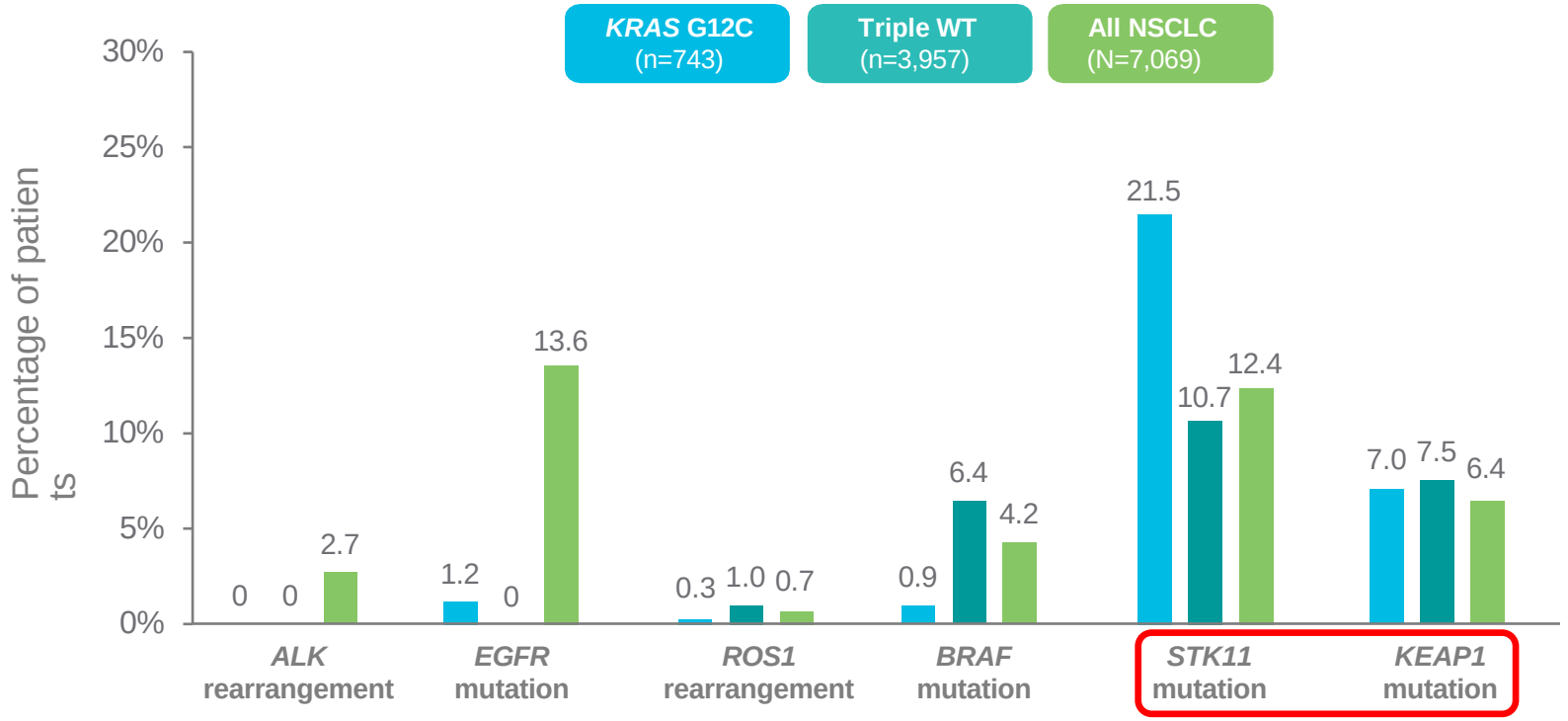


KRAS mutation type as a function of smoking history

KRAS		Former/current	Never	Total
Mutation	**Nucleotide**			
G12A	G**G**T→G**C**T	13	0	13
G12C	**G**GT→**T**GT	38	0	38
G12V	G**G**T→G**T**T	20	1	21
G13C	**G**GC→**T**GC	2	0	2
G13D	G**G**C→G**A**C	1	0	1
G12D	G**G**T→G**A**T	15	10	25
G12S	**G**GT→**A**GT	1	1	2
Total		90	12	

Gregory JR, et al. Clin Cancer Res 2008;14(18):5731-5734

KRAS G12C mutations are generally mutually exclusive of other actionable mutations in NSCLC



NSCLC, non-small cell lung cancer; WT, wild-type.

*Spira. ASCO 2022. Abstr 9002; Jänne PA, et al. *N Engl J Med* 2022;387:120-131
Aggarwal S, *et al. Ann Oncol* 2020;31 (Suppl 4):abstract 1339P.

CodeBreak 100: Sotorasib in Pretreated Advanced *KRAS* G12C Mutation-Positive NSCLC

Screening/ enrollment → **Pooled Phase 1/2: Advanced NSCLC, sotorasib 960 mg orally once daily (N = 174)**
Radiographic scan every 6 weeks up to week 48; once every 12 weeks thereafter → **Safety and long-term follow-up**

Key eligibility criteria

- Locally advanced or metastatic *KRAS* p.G12C-mutated solid tumors
- 1+ prior systemic therapy or ineligible/ intolerant
- Stable brain mets allowed

PHASE 1 (n = 48)

Primary endpoint
- Safety and tolerability

Key secondary endpoints
- PK, ORR, DoR, PFS, duration of stable disease

PHASE 2 (n = 126)

Primary endpoint
- ORR by RECIST 1.1 by BICR

Key secondary endpoints
- DoR, DCR, PFS, OS, time to response, safety

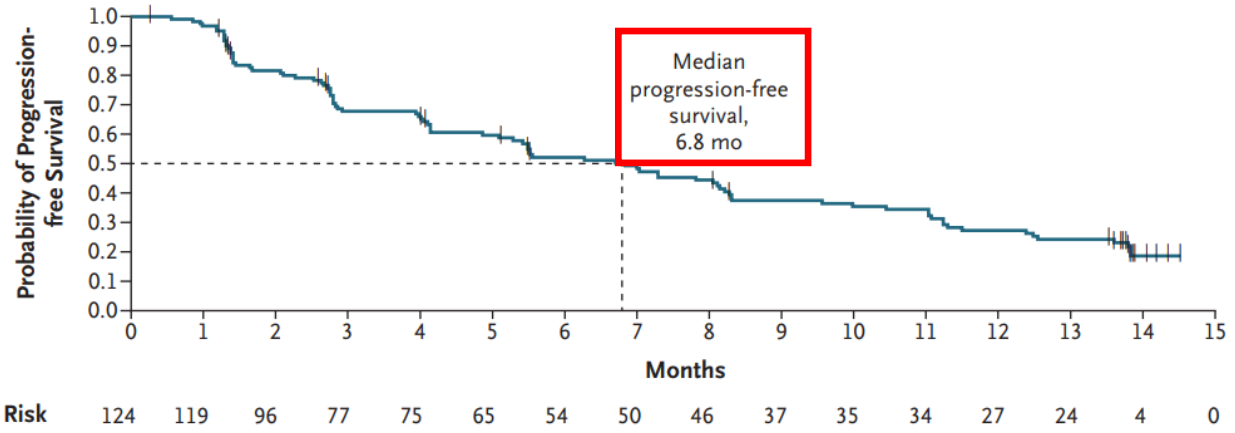
Data cutoff: March 15, 2021

BICR, blinded independent central review; DCR, duration of complete response; DoR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; RECIST, Response Evaluation Criteria In Solid Tumors.

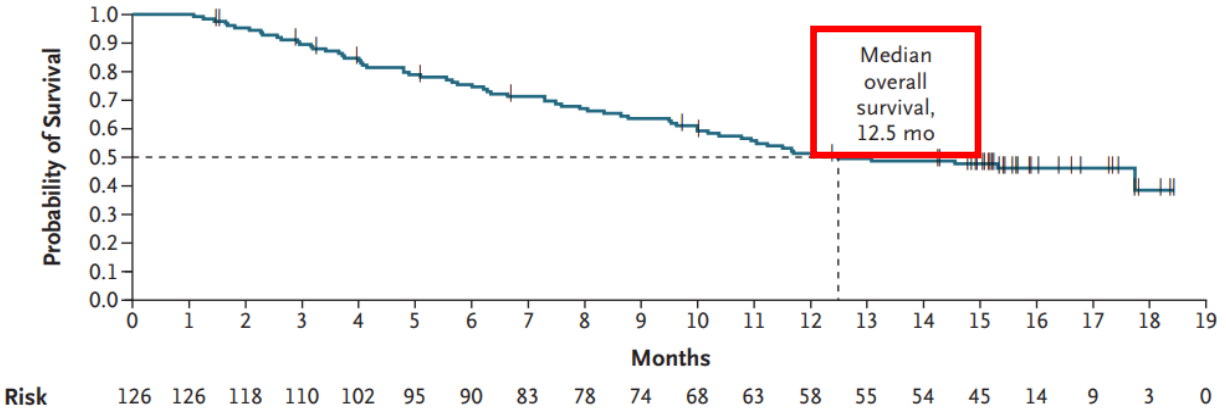
Grace K. Dy, et al. Presented at AACR Annual Meeting, April 8-13, 2022

Phase II CodeBreak 100: Efficacy (n=124)

Progression-free Survival



Overall Survival



Outcome	Evaluated Patients (n = 124)
Confirmed ORR, % (95% CI)*	37.1 (28.6-46.2)
DCR, % (95% CI)	80.6 (72.6-87.2)
Median DoR, mo (95% CI)	11.1 (6.9-NE)

N Engl J Med 2021;384:2371-81

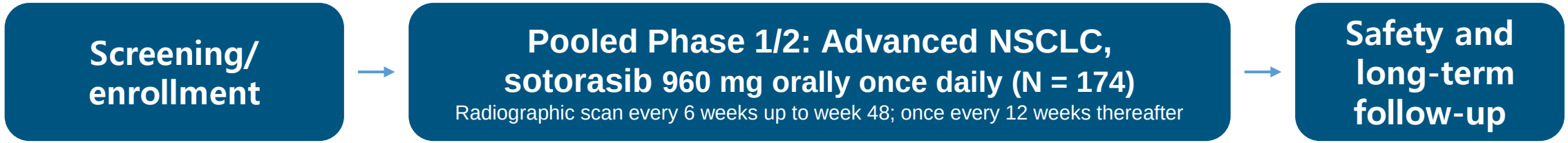
Phase II CodeBreak 100: Safety (n=126)

	Any Grade	Grade 3	Grade 4
Adverse event	125 (99.2)	53 (42.1)	4 (3.2)
Treatment –related adverse event	88 (69.8)	25 (19.8)	1 (0.8)
Treatment-related adverse event leading to dose modification	28 (22.2)	20 (15.9)	0
Treatment-related adverse event leading to discontinuation of therapy	9 (7.1)	4 (3.2)	1 (0.8)

Event	All Patients (N=126)				
	Any Grade	Grade 1 or 2	Grade 3	Grade 4	Fatal
	number of patients (percent)				
Diarrhea	40 (31.7)	35 (27.8)	5 (4.0)	0	0
Nausea	24 (19.0)	24 (19.0)	0	0	0
Alanine aminotransferase increase	19 (15.1)	11 (8.7)	8 (6.3)	0	0
Aspartate aminotransferase increase	19 (15.1)	12 (9.5)	7 (5.6)	0	0
Fatigue	14 (11.1)	14 (11.1)	0	0	0
Vomiting	10 (7.9)	10 (7.9)	0	0	0
Blood alkaline phosphatase increase	9 (7.1)	8 (6.3)	1 (0.8)	0	0
Maculopapular rash	7 (5.6)	7 (5.6)	0	0	0
Hypokalemia	5 (4.0)	4 (3.2)	1 (0.8)	0	0
Drug-induced liver injury	3 (2.4)	1 (0.8)	2 (1.6)	0	0
γ-Glutamyltransferase increase	3 (2.4)	0	3 (2.4)	0	0
Lymphocyte count decrease	3 (2.4)	2 (1.6)	1 (0.8)	0	0
Dyspnea	2 (1.6)	1 (0.8)	0	1 (0.8)	0
Pneumonitis	2 (1.6)	0	1 (0.8)	1 (0.8)	0
Abnormal hepatic function	2 (1.6)	1 (0.8)	1 (0.8)	0	0
Lymphopenia	1 (0.8)	0	1 (0.8)	0	0
Neutropenia	1 (0.8)	0	1 (0.8)	0	0
Hepatotoxic event	1 (0.8)	0	1 (0.8)	0	0
Drug hypersensitivity	1 (0.8)	0	1 (0.8)	0	0

N Engl J Med 2021;384:2371-81

Long-term Outcomes With Sotorasib in Pre-treated *KRAS* p.G12C Mutated NSCLC: 2-year Analysis of CodeBreak 100



Key eligibility criteria

- Locally advanced or metastatic *KRAS* p.G12C-mutated solid tumors
- 1+ prior systemic therapy or ineligible/ intolerant
- Stable brain mets allowed

PHASE 1 (n = 48)

Primary endpoint
- Safety and tolerability

Key secondary endpoints
- PK, ORR, DoR, PFS, duration of stable disease

PHASE 2 (n = 126)

Primary endpoint
- ORR by RECIST 1.1 by BICR

Key secondary endpoints
- DoR, DCR, PFS, OS, time to response, safety

N =176

Data cutoff: February 22, 2022

Median Follow-up for Overall Survival: 24.9 months

BICR, blinded independent central review; DCR, duration of complete response; DoR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; RECIST, Response Evaluation Criteria In Solid Tumors.

Grace K. Dy, et al. Presented at AACR Annual Meeting, April 8-13, 2022

Efficacy Analysis

Response by Central Review	Phase 1/2 NSCLC N = 172*
Objective response rate, % (95% CI)	**40.7 (33.3, 48.4)**
Best overall response, n (%)	
Complete response	5 (2.9)
Partial response	65 (37.8)
Stable disease	74 (43.0)
Progressive disease	23 (13.4)
Not evaluable or missing scan	5 (2.9)
Disease control rate, % (95% CI)	**83.7 (77.3, 88.9)**
Median progression-free survival, months (95% CI)	**6.3 (5.3, 8.2)**
Median overall survival, months (95% CI)	**12.5 (10.0-17.8)**

CI = Confidence Interval.
95% CIs are based on estimated variance for log-log transformation of the Kaplan-Meier survival Estimate Follow-up time is summarized by reversing the status indicator for censored and ev ents. Time to response and duration of response are calculated among confirmed responders.
*2 patients are not included in the efficacy set as they did not have measurable lesions at baseline and were ineligible for response assessment

CodeBreak 200 Phase III Trial: Sotorasib vs Docetaxel for Patients With Previously Treated Advanced NSCLC With *KRAS* G12C mutation

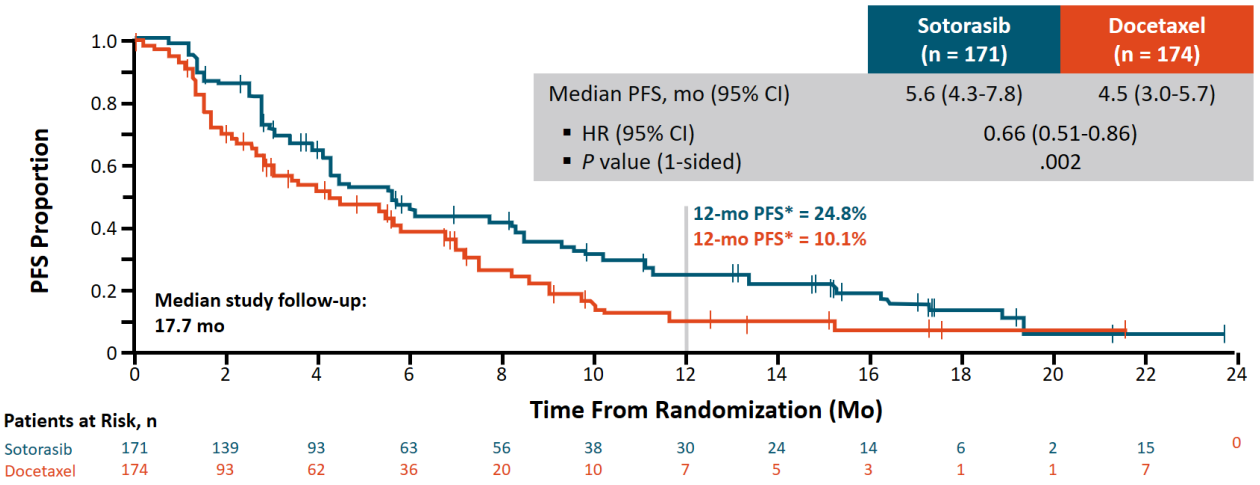
Randomized, double-blind phase III study*

Patients with locally advanced/unresectable or metastatic *KRAS* G12C-mutated NSCLC;
≥1 prior treatment including platinum-based chemotherapy and checkpoint inhibitor*;
no active brain metastases; ECOG PS 0/1
(N = 345)

- **Sotorasib 960 mg oral QD** (n = 171)
- **Docetaxel 75 mg/m² IV Q3W** (n = 174)

- Primary endpoint: PFS by BICR
- Secondary endpoints: Efficacy (OS,† ORR, DoR, TTR, DCR), safety/tolerability, PRO

*Protocol amended to reduce planned enrollment to 330 patients and allow crossover from docetaxel to sotorasib
†Treatment with chemotherapy and checkpoint inhibitor could be concurrent or sequential; patients with contradictions to these therapies could be enrolled with approval



PFS by BICR (Primary Endpoint)

Johnson. ESMO 2022. Abstr LBA10.

KRYSTAL-1 Trial of **Adagrasib** in Patients With Previously Treated Advanced *KRAS* G12C-Mutated NSCLC: Analysis of Registrational Phase II Cohort

Registrational phase II cohort in ongoing multicenter, open-label, nonrandomized phase I/II trial

Adults with unresectable/metastatic NSCLC harboring *KRAS*^{G12C} mutation; previously treated with PD-1/PD-L1 inhibitor in combination or sequence with platinum-based CT; treated, stable CNS mets permitted; ECOG PS 0/1 (N = 116)

→ **Adagrasib** 600-mg capsules BID in fasted state →

Until PD, unacceptable toxicity, consent withdrawal, or death; therapy could continue beyond PD if deriving clinical benefit per investigator

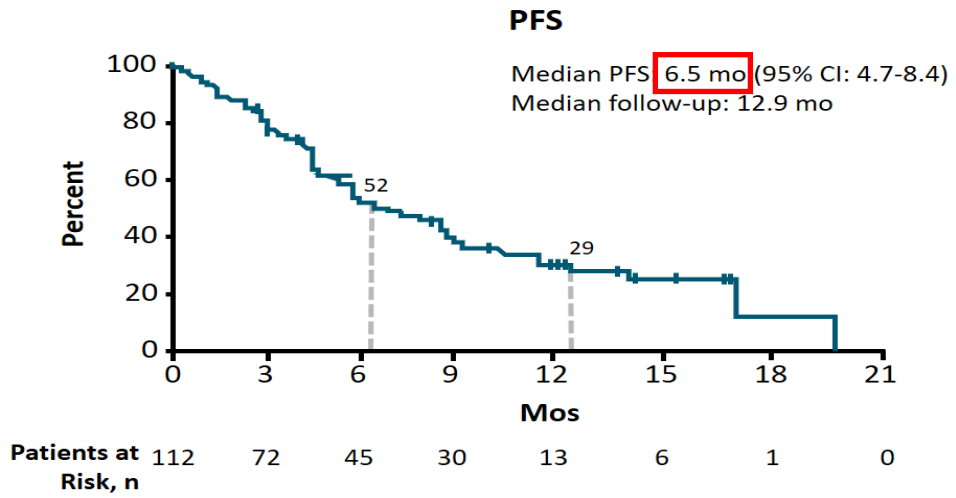
- ✓ Primary endpoint: ORR by BICR
- ✓ Secondary endpoint: DCR, DoR, PFS, OS, 1-yr survival rate

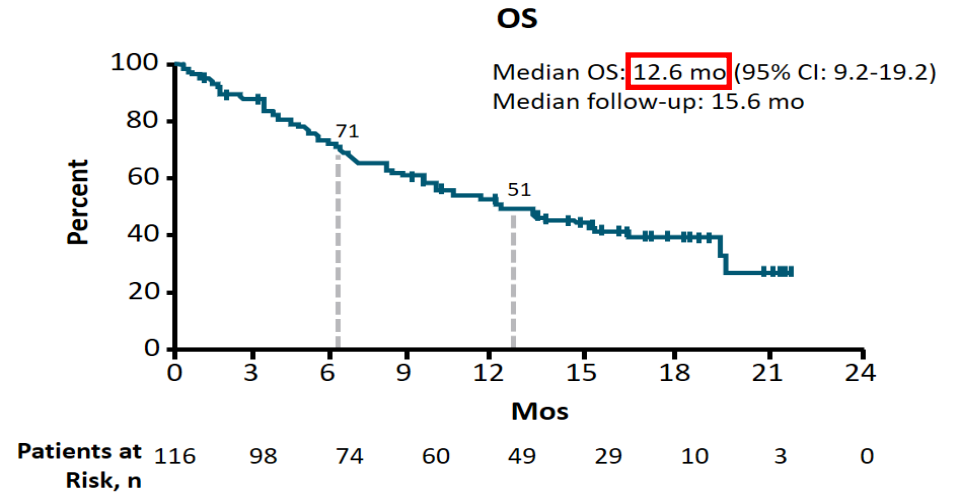
Spira. ASCO 2022. Abstr 9002; Jänne PA, et al. *N Engl J Med* 2022;387:120-131

KRYSTAL-1: Efficacy of Adagrasib

Objective Response per BICR

Outcome, n (%)	Patients (n = 112)
Objective response rate	48 (42.9)
Best overall response	
▪ CR	1 (0.9)
▪ PR	47 (42.0)
▪ SD ≥6 wk	41 (36.6)
▪ PD	6 (5.4)
▪ Not evaluable	17 (5.2)
DCR	89 (79.5)





Spira. ASCO 2022. Abstr 9002; Jänne PA, et al. *N Engl J Med* 2022;387:120-131

KRYSTAL-1: Safety of Adagrasib

TRAEs, n (%)	Patients (N = 116)		
	Any Gr	Gr 3	Gr 4
Any	113 (97.4)	47 (40.5)	3 (2.6)
Most common TRAEs (≥20%)			
Diarrhea	73 (62.9)	1 (0.9)	0
Nausea	72 (62.1)	5 (4.3)	0
Vomiting	55 (47.4)	1 (0.9)	0
Fatigue	47 (40.5)	5 (4.3)	0
ALT increase	32 (27.6)	4 (3.4)	1 (0.9)
Blood creatinine increase	30 (25.9)	1 (0.9)	0
AST increase	29 (25.0)	4 (3.4)	0
Decreased appetite	28 (24.1)	4 (3.4)	0

Spira. ASCO 2022. Abstr 9002; Jänne PA, et al. *N Engl J Med* 2022;387:120-131

Emerging Treatment Options in KRAS-Mutant NSCLC

Sotorasib in Combination with RMC-4630, a SHP2 Inhibitor, in *KRAS* p.G12C-Mutated NSCLC and Other Solid Tumors

Gerald S. Falchook,[1] Bob T. Li,[2] Kristen A. Marrone,[3] Christine M. Bestvina,[4] Corey J. Langer,[5] John C. Krauss,[6] John H. Strickler,[7] Alison R. Meloni,[8] Tian Dai,[8] Tracy L. Varrieur,[8] David S. Hong[9]

[1]Sarah Cannon Research Institute at HealthONE, Denver, CO, USA; [2]Memorial Sloan Kettering Cancer Center, Weill Cornell Medicine, New York, NY, USA; [3]Johns Hopkins School of Medicine, Baltimore, MD, USA; [4]University of Chicago Medicine, Chicago, IL, USA; [5]Perelman Center for Advanced Medicine, Philadelphia, PA, USA; [6]University of Michigan Medical School, Ann Arbor, MI, USA; [7]Duke University Medical Center, Durham, NC, USA; [8]Amgen Inc., Thousand Oaks, CA, USA; [9]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Presented at World Conference on Lung Cancer (WCLC) 2022 Annual Meeting, August 6-9, 2022; Vienna, Austria.

PD1/PDL1 inhibitor

Pan-EGFR TKI

SHP2 inhibitor

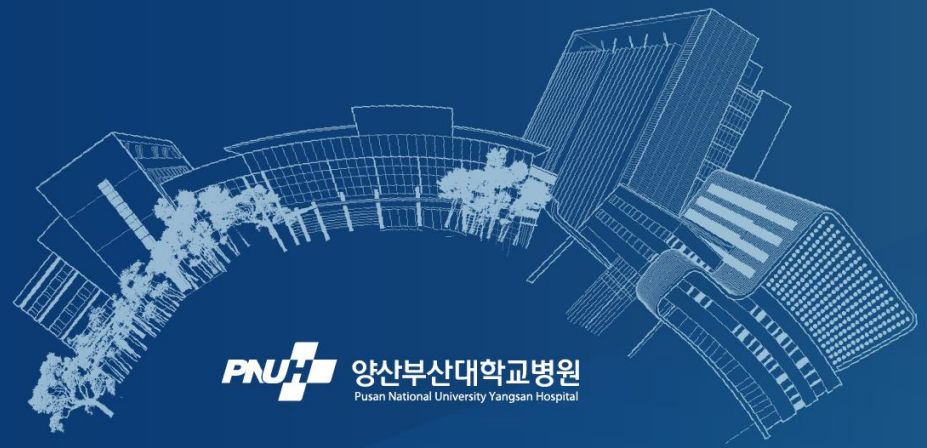
CodeBreaK 100/101: First report of safety and efficacy of sotorasib in combination with pembrolizumab or atezolizumab in advanced *KRAS* p.G12C NSCLC

Bob T. Li,[1] Gerald S. Falchook,[2] Gregory A. Durm,[3] Timothy F. Burns,[4] Ferdinandos Skoulidis,[5] Suresh S. Ramalingam,[6] Alexander Spira,[7] Christine M. Bestvina,[8] Sarah B. Goldberg,[9] Rajwanth Veluswamy,[10] Wade T. Iams,[11] Alberto A. Chiappori,[12] Charlotte R. Lemech,[13] Alison R. Meloni,[14] Victoria A. Ebiana,[14] Tian Dai,[14] Diana M. Gauto,[14] Tracy L. Varrieur,[14] Wendy J. Snyder,[14] Ramaswamy Govindan[15]

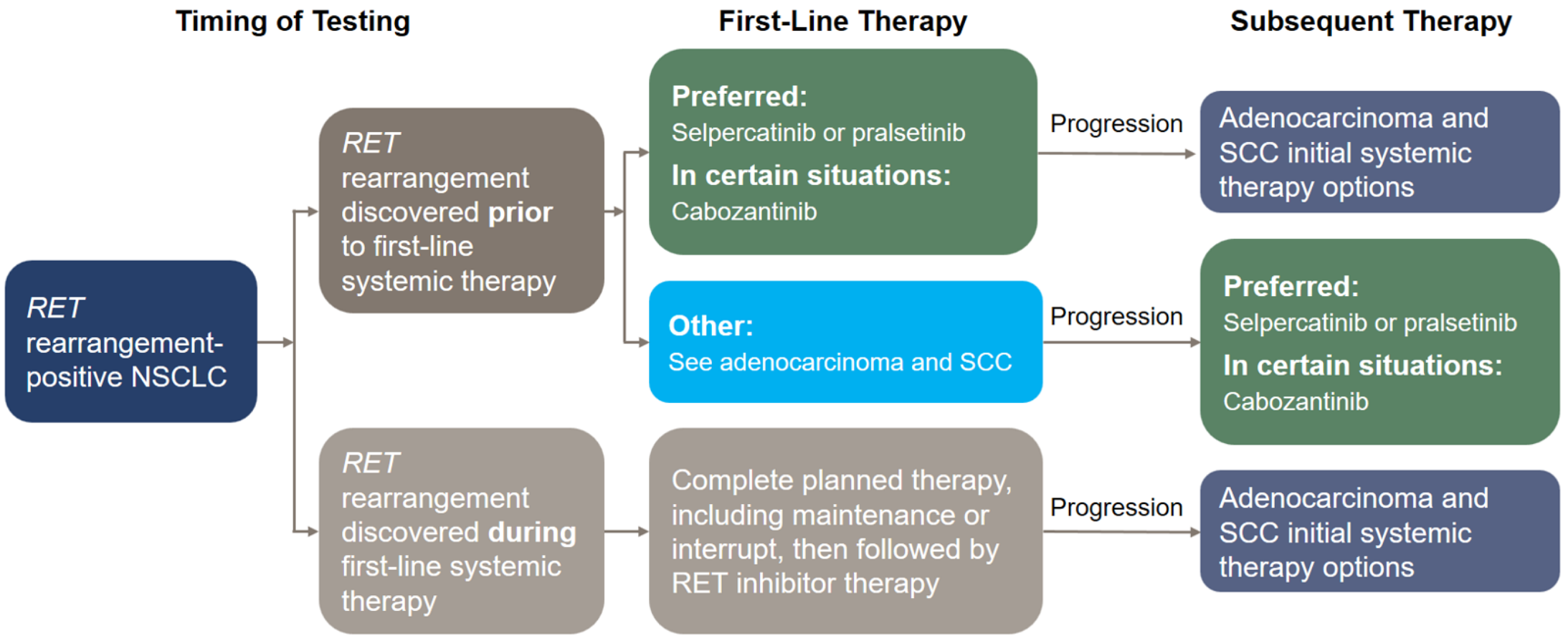
[1]Memorial Sloan Kettering Cancer Center, Weill Cornell Medicine, New York, NY, USA; [2]Sarah Cannon Research Institute at HealthONE, Denver, CO, USA [3]Indiana University School of Medicine, Indianapolis, IN, USA; [4]University of Pittsburgh Medical Center (UPMC) Hillman Cancer Center, Pittsburgh, PA, USA; [5]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [6]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [7]US Oncology Research, The Woodlands, TX, USA; [8]The University of Chicago Medicine, Chicago, IL, USA; [9]Yale School of Medicine, New Haven, CT, USA; [10]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [11]Vanderbilt University Medical Center, Nashville, TN, USA; [12]Moffitt Cancer Center, Tampa, FL, USA; [13]Scientia Clinical Research, Randwick, Australia; [14]Amgen Inc., Thousand Oaks, CA, USA; [15]Washington University School of Medicine, St Louis, MO, USA

Presented at World Conference on Lung Cancer (WCLC) 2022 Annual Meeting, August 6-9, 2022; Vienna, Austria.

RET fusion



NCCN Guidelines: Ver2. 2023

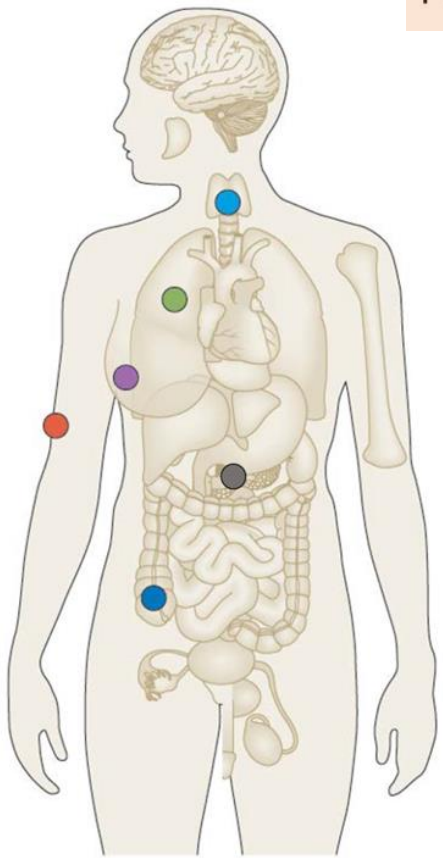


SCC=Squamous Cell Carcinoma.

Ettinger DS, et al. NCCN Guidelines Version 2.2023 Non-Small Cell Lung Cancer

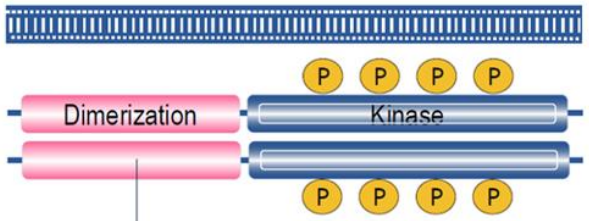
Distribution of *RET* Fusions in Solid Tumors

RET fusions



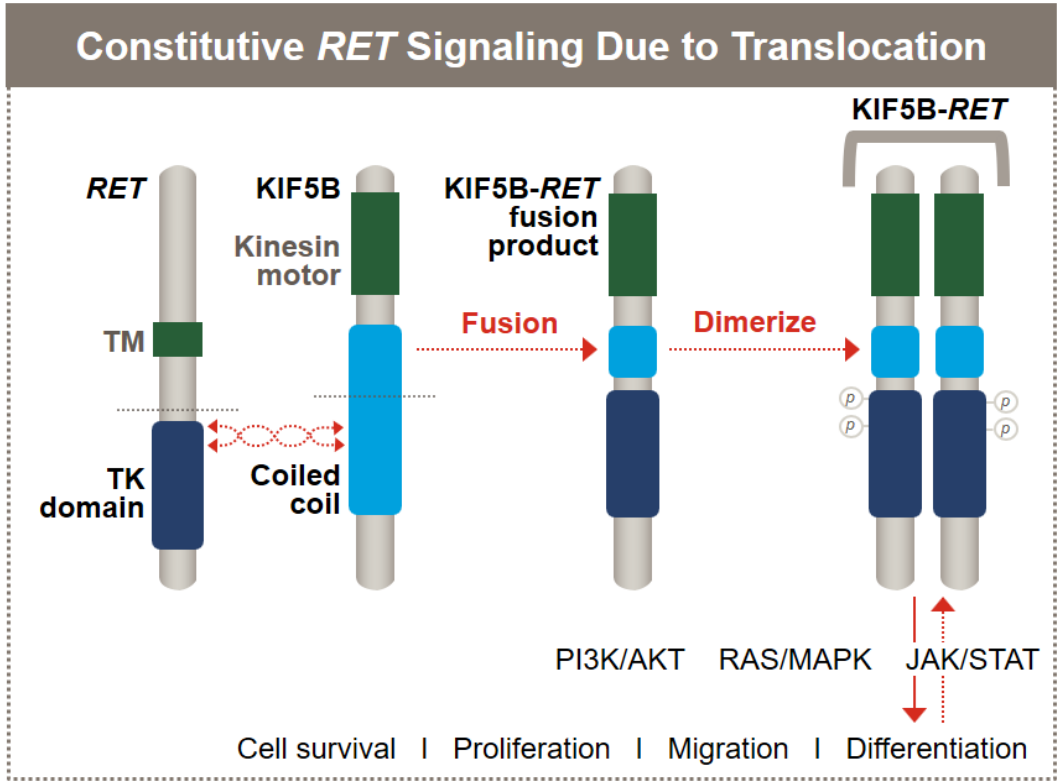
Non-small cell lung cancer (2%)
Papillary and other thyroid cancers (10-20%)

Pancreatic cancer (<1%)
Salivary gland cancer (<1%)
Spitz tumors (<1%)
Colorectal cancer (<1%)
Ovarian cancer (<1%)
Myeloproliferative disorders (<1%)
Many others (<1%)



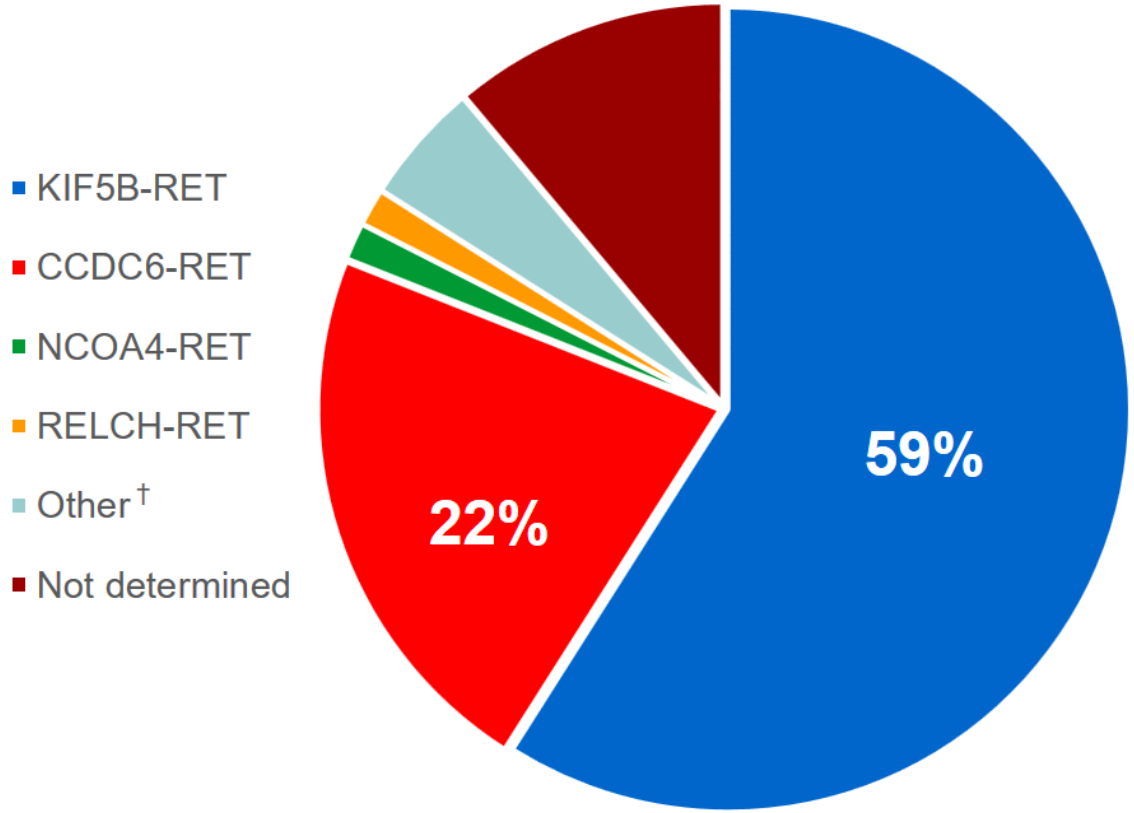
KIF5B (most common in lung cancer)
CCDC6* or *NCOA4 (most common in thyroid cancer)

✓ In **2012**, the first RET fusion in lung cancer, KIF5B-RET, was reported independently by 4 groups



Mulligan L, et al. *Nat Rev Cancer* 2014;14:173-186; *Genome Res* 2012;22(3):436-445
Drilon, et al. *Nat Rev Clin Oncol* 2018;15:151-167

RET Fusion Partner



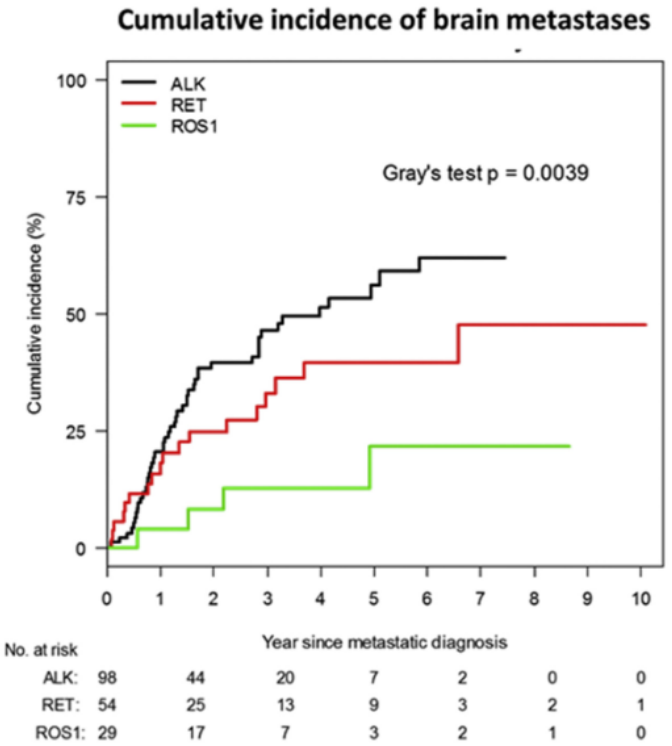
† Other fusions identified in single tumors included *CLIP1-RET*, *RBPMS-RET*, *DOCK1-RET*, *ARHGAP12-RET*, *CCDC88C-RET*, *TRIM24-RET*, *PRKAR1A-RET*, and *ERC1-RET*

J Thorac Oncol 2017;13:27-45; *N Engl J Med* 2020;383:813-24

Clinical Characteristics in *RET* fusion NSCLC

Demographic characteristics of study cohorts at the start of first-line therapy

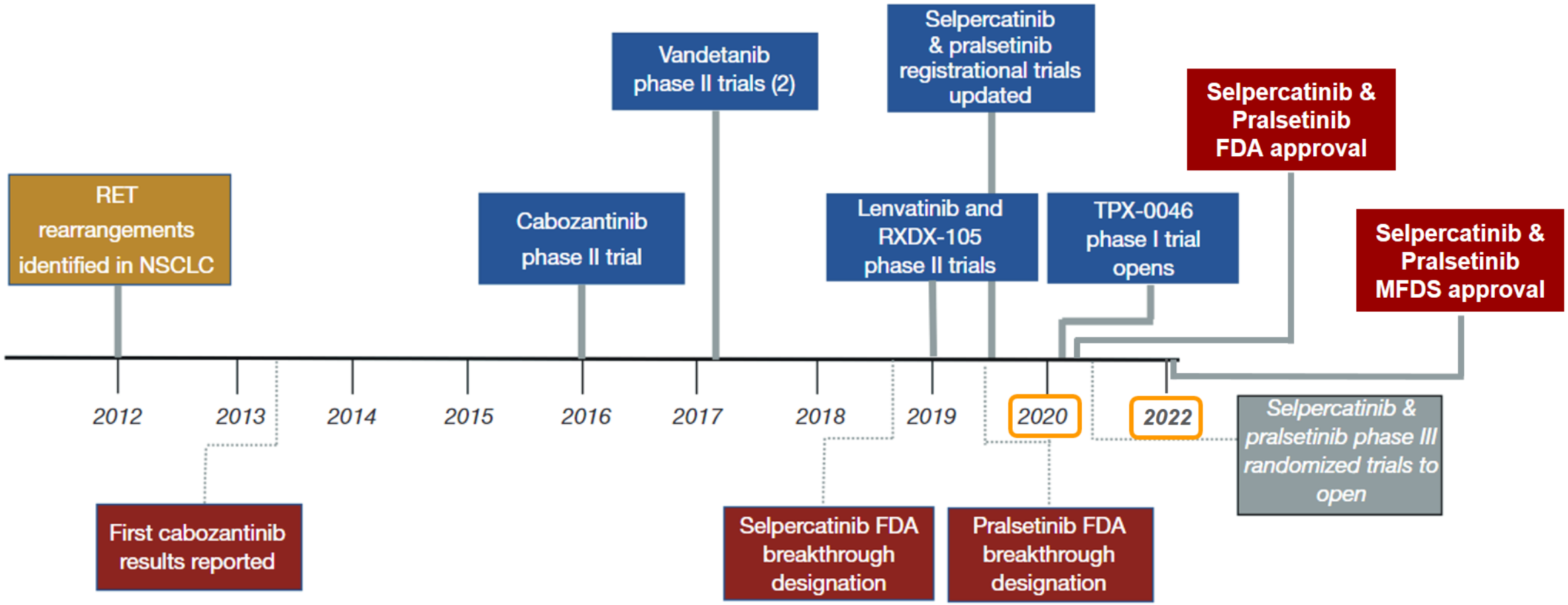
Characteristics	Overall N = 5807	RET+ N = 46	RET- N = 5761	RET+ vs RET- P value*
Age, years				
Mean (Sd)	67.2 (10.2)	62.9 (11.0)	67.2 (10.2)	0.004
Median (IQR)	68.1 (60.2, 74.8)	65 (54.8, 70.1)	68.1 (60.3,74.9)	
Sex, n (%)				
Female	2880 (49.6)	23 (50.0)	2857 (49.6)	1.0
Male	2927 (50.4)	23 (50.0)	2904 (50.4)	
Race, n (%)				
White	4078 (76.5)	31 (72.1)	4047 (76.5)	0.76
Asian	187 (3.5)	2 (4.7)	185 (3.5)	
Black	343 (6.4)	3 (7.0)	340 (6.4)	
Other	723 (13.6)	7 (16.3)	716 (13.5)	
Missing/Unknown	476	3	533	
Practice type, n (%)				



Young female who have never smoked !!
Poor-differentiated ??

J Clin Oncol 2012;30:4352-4359; *BMC Cancer* 2021;21:28
J Thorac Oncol 2018;13(10):1595-1601

Timeline of advances in RET-rearranged NSCLC



Transl Lung Cancer Res 2020;9(6):2571-258

Phase 1/2 Study of LOXO-292 in Patients With Advanced Solid Tumors, RET Fusion-Positive Solid Tumors, and Medullary Thyroid Cancer : LIBRETTO-001

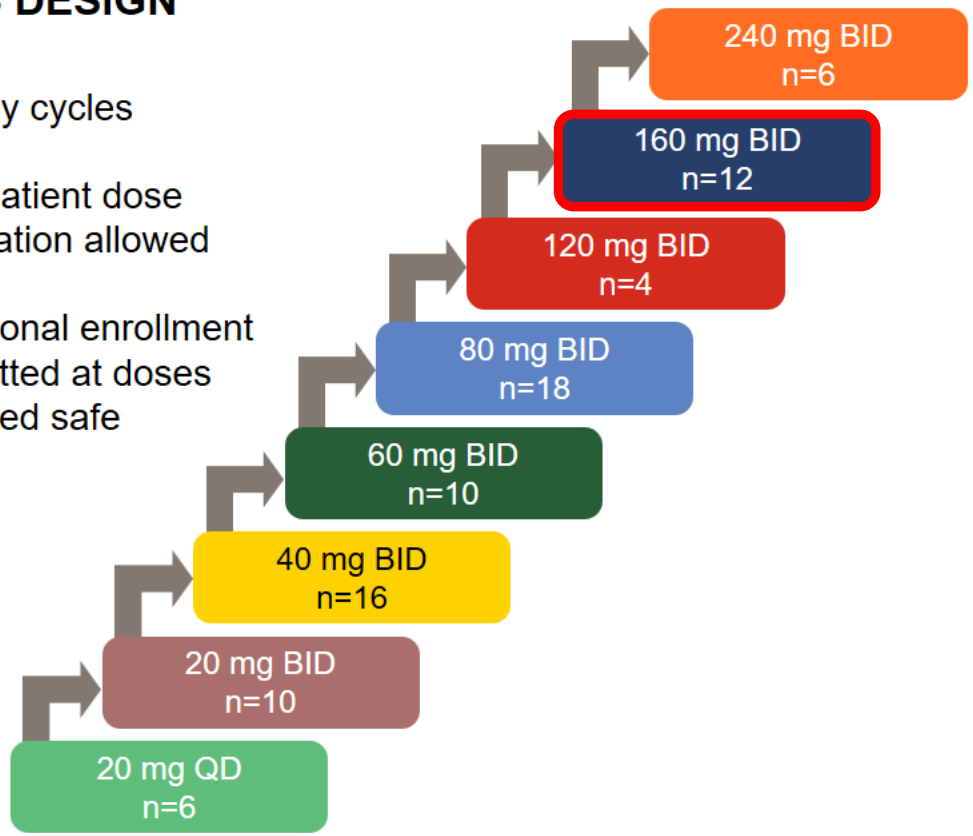
82 patients enrolled across 8 dose levels[1]

3 + 3 DESIGN

28-day cycles

Intrapatient dose escalation allowed

Additional enrollment permitted at doses deemed safe



Data: April 2, 2018.
cfDNA=Circulating Cell-Free DNA; PK=Pharmacokinetics.

Cohorts[2]

Cohort 1: Advanced *RET* fusion-positive solid tumor progressed on/intolerant to standard first-line therapy

Cohort 2: Advanced *RET* fusion-positive solid tumor without standard first-line therapy

Cohort 3: Advanced *RET*-mutant MTC progressed on/intolerant to standard first-line therapy

Cohort 4: Advanced *RET*-mutant MTC without standard first-line therapy or other anti-*RET* kinase inhibitors

Cohort 5: Advanced *RET*-altered solid tumor
- Cohorts 1 and 2, disease not measurable
- MTC not eligible for cohort 3 or 4
- MTC syndrome spectrum cancers or poorly differentiated thyroid cancers with other *RET* alteration/activation may be allowed with prior sponsor approval
- cfDNA-positive for *RET* alteration not known to be present in tumor

Cohort 6: Participants otherwise eligible for cohorts 1-5 who discontinued another RET inhibitor due to intolerance may be eligible with prior sponsor approval

Cohort 7: RET fusion-positive early-stage NSCLC participants who are candidates for definitive surgery
- Participants will receive selpercatinib in a neoadjuvant and adjuvant setting
- Participants will be followed for disease recurrence for up to 5 years from the date of surgery

1. Oxnard G, et al. Presented at WCLC, September 23-26, 2018
2. ClinicalTrials.gov. Accessed July 28, 2021. http://clinicaltrials.gov /ct2/show/NCT03157128

LIBRETTO-001: Selpercatinib in *RET*-altered cancers

Phase 1 dose escalation
Selpercatinib dosed at 20 mg QD–240 mg BID

Phase 2 dose expansion
Selpercatinib dosed at 160 mg BID

Total Enrolled n=531

- ***RET* fusion-positive NSCLC n=253**
- *RET*-mutant medullary thyroid cancer n=226
- *RET* fusion-positive thyroid cancer n=27
- Other n=25

Prior platinum chemotherapy n=184

- Prior non-platinum chemotherapy n=16
- Treatment-naïve n=39
- Non-measurable disease n=14

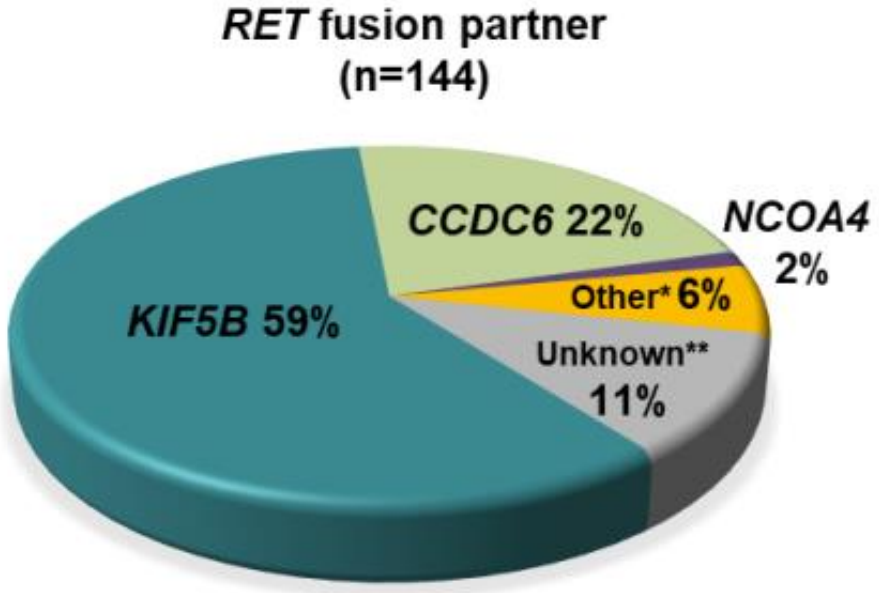
Primary Analysis Set n=105

First 105 patients with *RET* fusion-positive NSCLC who received prior platinum chemotherapy*

- ***RET*-alteration**
  - Determined by local CLIA (or similarly accredited) laboratories
- **Primary endpoint**
  - Objective response rate (RECIST 1.1)
- **Secondary endpoints**
  - Duration of response
  - Progression-free survival
  - Safety
- Treatment beyond progression permitted with continued benefit

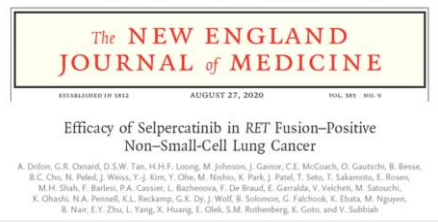
NCT03157128; Data cutoff: June 17th, 2019. *Per agreement with FDA, patients with non-measurable disease enrolled during phase 1 dose escalation were eligible for the primary analysis set.

Patient Characteristics	PAS (n=105)	Treatment-naïve (n=39)
Female / Male, n (%)	62 (59) / 43 (41)	22 (56) / 17 (44)
Median age (range), years	61 (23–81)	61 (23–86)
ECOG performance status, n (%)		
0	31 (30)	19 (49)
1	72 (69)	20 (51)
2	2 (2)	0
Median prior systemic regimens (range)	3 (1–15)	0
Prior platinum-based chemotherapy, n (%)	105 (100)	-
Prior PD-1/PD-L1 inhibitor, n (%)	58 (55)	-
Concurrent with platinum-based chemotherapy	9 (9)	-
Sequential to platinum-based chemotherapy	49 (47)	-
Prior multikinase inhibitor (MKI), n (%)	50 (48)	-
1	37 (35)	-
≥2	13 (12)	-
Brain metastases, n (%)‡	37 (35)	7 (18)
Measurable disease	104 (99)	39 (100)



Data cut-off: June 17th, 2019. Total % may be different than the sum of the individual components due to rounding. *Includes *KIAA1468* (2), *ARHGAP12*, *CCDC88C*, *CLIP1*, *DOCK1* + *RBPMS*, *ERC1*, *PRKAR1A* and *TRIM24* (all 1 each).
**FISH-positive or PCR-positive; ‡Includes patients with non-target CNS metastases.

LIBRETTO-001 (data cut off: Dec 16th, 2019)


The NEW ENGLAND JOURNAL of MEDICINE

AUGUST 27, 2020

Efficacy of Selpercatinib in *RET* Fusion–Positive Non–Small-Cell Lung Cancer

Efficacy

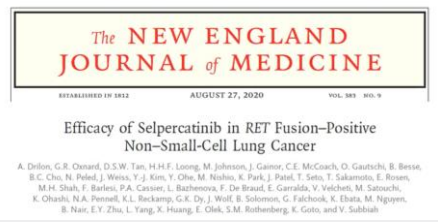
Response	Previous Platinum Chemotherapy		Previously Untreated	
	Independent Review (N=105)	Investigator Assessment (N=105)	Independent Review (N=39)	Investigator Assessment (N=39)
Objective response — % (95% CI)	64 (54–73)	70 (60–78)	85 (70–94)	90 (76–97)
Best response — no. (%)				
Complete response	2 (2)	2 (2)	0	1 (3)
Partial response	65 (62)	71 (68)	33 (85)	34 (87)†
Stable disease	30 (29)	25 (24)	4 (10)	2 (5)
Progressive disease	4 (4)	2 (2)	1 (3)	1 (3)
Could not be evaluated	4 (4)	5 (5)	1 (3)	1 (3)
Duration of response				
Patients with a response — no.	67	73	33	33‡
Patients with censored data — no./total no. (%)	44/67 (66)	45/73 (62)	26/33 (79)	26/33 (79)
Median duration of response — mo (95% CI)	17.5 (12.0–NE)	20.3 (15.6–24.0)	NE (12.0–NE)	NE (12.0–NE)
Median follow-up — mo	12.1	14.8	7.4	7.4
Progression-free survival				
Patients with censored data — no. (%)	61 (58)	58 (55)	30 (77)	30 (77)
Median progression-free survival — mo (95% CI)	16.5 (13.7–NE)	18.4 (16.4–24.8)	NE (13.8–NE)	NE (13.8–NE)
Median follow-up — mo	13.9	16.4	9.2	9.2
1-yr progression-free survival — % (95% CI)	66 (55–74)	68 (58–76)	75 (56–87)	75 (55–87)

<Previous platinum Chemotherapy>

Intracranial response rate	**91%**	[95% CI, 59 to 100]
Median DOR	**17.5 months**	[95% CI, 12.0 to NE]
Median PFS	**16.5 months**	[95% CI, 13.7 to NE]

N Engl J Med 2020;383:813-824

LIBRETTO-001 (data cut off: Dec 16th, 2019)


The NEW ENGLAND JOURNAL of MEDICINE

AUGUST 27, 2020

Efficacy of Selpercatinib in *RET* Fusion–Positive Non–Small-Cell Lung Cancer

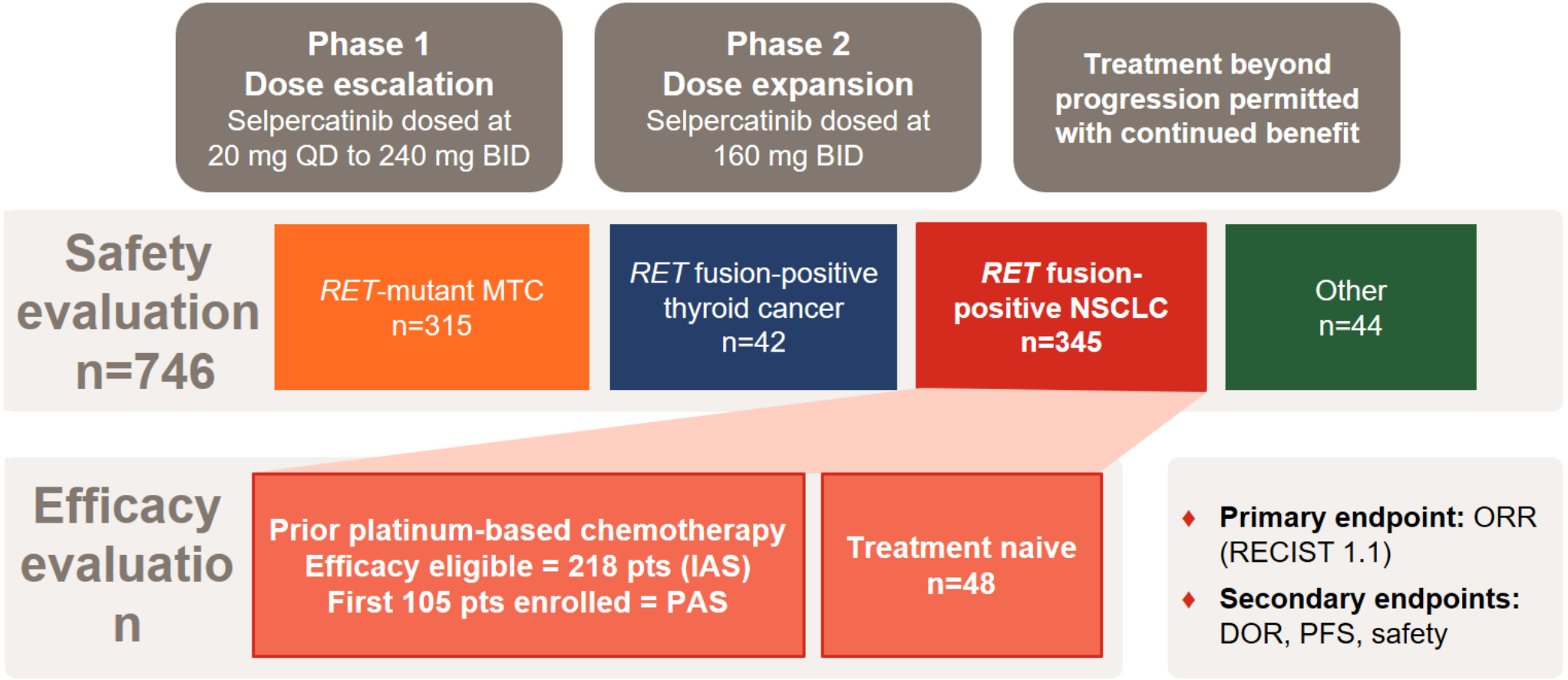
Adverse Events in 144 Patients with *RET* Fusion-Positive NSCLC

Adverse Event	Adverse Events, Regardless of Attribution (N=144)					Treatment-Related Adverse Events (N=144)		
	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade
	number of patients (percent)							
Any adverse event	8 (6)	47 (33)	69 (48)	14 (10)	144 (100)	39 (27)	2 (1)	131 (91)
Diarrhea	46 (32)	18 (12)	5 (3)	0	69 (48)	2 (1)	0	36 (25)
Dry mouth	48 (33)	11 (8)	0	0	59 (41)	0	0	52 (36)
Hypertension	3 (2)	22 (15)	20 (14)	0	45 (31)	13 (9)	0	25 (17)
Increased aspartate aminotransferase level	18 (12)	11 (8)	12 (8)	2 (1)	43 (30)	7 (5)	1 (1)	32 (22)
Fatigue	26 (18)	16 (11)	0	0	42 (29)	0	0	19 (13)
Increased alanine aminotransferase level	14 (10)	6 (4)	15 (10)	3 (2)	38 (26)	11 (8)	2 (1)	29 (20)
Constipation	33 (23)	3 (2)	2 (1)	0	38 (26)	1 (1)	0	16 (11)
Nausea	32 (22)	5 (3)	1 (1)	0	38 (26)	0	0	14 (10)
Peripheral edema	29 (20)	6 (4)	0	0	35 (24)	0	0	19 (13)
Urinary tract infection	4 (3)	21 (15)	7 (5)	0	32 (22)	0	0	0
Headache	21 (15)	7 (5)	2 (1)	0	30 (21)	0	0	6 (4)
Rash	20 (14)	6 (4)	2 (1)	0	28 (19)	2 (1)	0	17 (12)
Abdominal pain	18 (12)	8 (6)	1 (1)	0	27 (19)	0	0	5 (3)
Cough	24 (17)	3 (2)	0	0	27 (19)	0	0	3 (2)
Increased blood creatinine level	21 (15)	3 (2)	0	0	24 (17)	0	0	13 (9)
Dyspnea	15 (10)	6 (4)	3 (2)	0	24 (17)	0	0	4 (3)
Vomiting	17 (12)	6 (4)	1 (1)	0	24 (17)	1 (1)	0	5 (3)
Prolonged QT on electrocardiography	9 (6)	7 (5)	7 (5)	0	23 (16)	3 (2)	0	14 (10)
Pyrexia	14 (10)	8 (6)	1 (1)	0	23 (16)	1 (1)	0	8 (6)
Dry skin	19 (13)	3 (2)	0	0	22 (15)	0	0	13 (9)
Thrombocytopenia	13 (9)	6 (4)	3 (2)	0	22 (15)	2 (1)	0	15 (10)

- ✓ Dose reduction rate: 30%
- ✓ Discontinuation rate : **2%**

N Engl J Med 2020;383:813-824

LIBRETTO-001: Selpercatinib in RET Fusion-Positive NSCLC



Data: March 30, 2020.

BID=Twice Daily; DOR=Duration of Response: IAS=Integrated Analysis Set; MTC=Medullary Thyroid Cancer/Carcinoma; ORR=Objective Response Rate; PAS=Primary Analysis Set; PFS=Progression-Free Survival; QD=Once Daily.

Besse B, et al. Poster presented at: American Society of Clinical Oncology 2021; June4-8, 2021

LIBRETTO-001: Efficacy (Independent Review)

	Prior platinum PAS (n=105)	Prior platinum IAS (n=218)	Treatment naive (n=48)
ORR, % (95% CI)	64 (54, 73)	57 (50, 64)	85 (72, 94)
CR, %	3	4	2
PR, %	61	53	83
SD, %	29	37	8
Median DOR, mo (95% CI)	17.5 (12.1, NE)	17.5 (12.1, NE)	NE (12.0, NE)
Median PFS, mo (95% CI)	19.3 (13.9, NE)	19.3 (16.5, NE)	NE (13.8, NE)
2-year overall survival, mo (95% CI)	68 (55.3, 77.8)	67 (55.4, 76.7)	88 (68.6, 95.8)

Data: March 30, 2020.
Percentages may not total 100 because of rounding.
CR=Complete Response; IAS=Integrated Analysis Set; NE=Not Estimable/Evaluated; PR=Partial Response; SD=Stable Disease.

Besse B, et al. Poster presented at: American Society of Clinical Oncology 2021; June4-8, 2021

ARROW: Pralsetinib Phase 1/2 study

Phase 2 study design

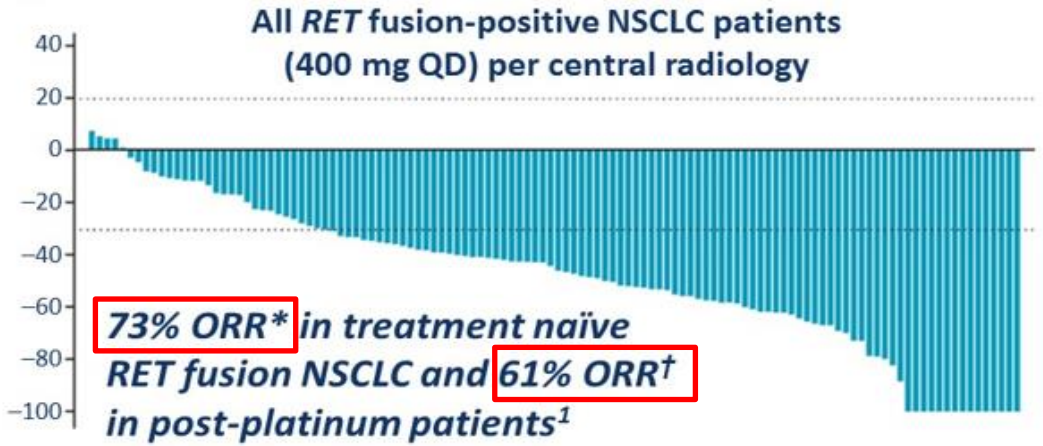
- Advanced solid tumors
- RET-altered (local testing)
- No other driver mutations
- ECOG PS 0-1

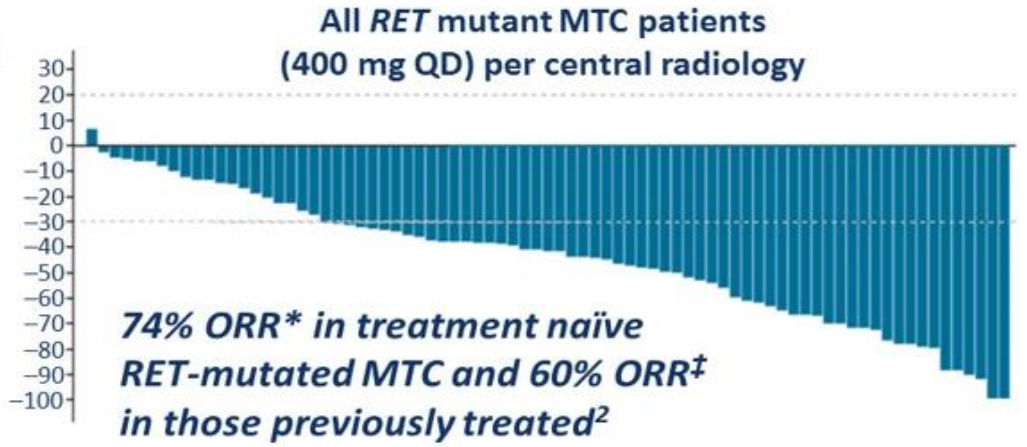
Pralsetinib dosing: 400 mg PO QD

- *RET* fusion-positive NSCLC
- *RET* mutation-positive MTC
- *RET* fusion-positive other tumors

Primary endpoints

- **Centrally reviewed ORR per RECIST v1.1**
- **Safety**





ARROW is registered with clinicaltrials.gov (NCT03037385). Data cutoff, November 18, 2019. AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance score; MTC, medullary thyroid cancer; NCI, National Cancer Institute; NSCLC, non-small cell lung cancer; ORR, overall response rate; PO, orally; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RET, rearranged during transfection. Data shown for response evaluable population. *All responses confirmed. †Two responses pending confirmation. ‡One response pending confirmation.

1. Phase 1/2 ARROW trial data in patients with RET fusion-positive NSCLC reported on January 8, 2020. Data cutoff: November 18, 2019. 2. Phase 1/2 ARROW trial data in patients with RET-mutated MTC reported on April 1, 2020. Data cutoff: February 13, 2020.

ARROW (data cut off: May 22th, 2020)

Pralsetinib for *RET* fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study

Methods ARROW is a multi-cohort, open-label, phase 1/2 study done at 71 sites (community and academic cancer centres) in 13 countries (Belgium, China, France, Germany, Hong Kong, Italy, Netherlands, Singapore, South Korea, Spain, Taiwan, the UK, and the USA). Patients aged 18 years or older with locally advanced or metastatic solid tumours, including *RET* fusion-positive NSCLC, and an Eastern Cooperative Oncology Group performance status of 0–2 (later limited to 0–1 in a protocol amendment) were enrolled. In phase 2, patients received 400 mg once-daily oral pralsetinib, and could continue treatment until disease progression, intolerance, withdrawal of consent, or investigator decision. Phase 2 primary endpoints were overall response rate (according to Response Evaluation Criteria in Solid Tumours version 1.1 and assessed by blinded independent central review) and safety. Tumour response was assessed in patients with *RET* fusion-positive NSCLC and centrally adjudicated baseline measurable disease who had received platinum-based chemotherapy or were treatment-naive because they were ineligible for standard therapy. This ongoing study is registered with ClinicalTrials.gov, NCT03037385, and enrolment of patients with treatment-naive *RET* fusion-positive NSCLC was ongoing at the time of this interim analysis.

Findings Of 233 patients with *RET* fusion-positive NSCLC enrolled between March 17, 2017, and May 22, 2020 (data cutoff), 92 with previous platinum-based chemotherapy and 29 who were treatment-naive received pralsetinib before July 11, 2019 (efficacy enrolment cutoff); 87 previously treated patients and 27 treatment-naive patients had centrally adjudicated baseline measurable disease. Overall responses were recorded in 53 (61%; 95% CI 50–71) of 87 patients with previous platinum-based chemotherapy, including five (6%) patients with a complete response; and 19 (70%; 50–86) of 27 treatment-naive patients, including three (11%) with a complete response. In 233 patients with *RET* fusion-positive NSCLC, common grade 3 or worse treatment-related adverse events were neutropenia (43 patients [18%]), hypertension (26 [11%]), and anaemia (24 [10%]); there were no treatment-related deaths in this population.

	Previous platinum-based chemotherapy group (n=92)	No previous systemic treatment group (n=29)
Age, years	60 (53–68)	65 (54–69)
≥65 years	33 (36%)	15 (52%)
Sex		
Female	46 (50%)	15 (52%)
Male	46 (50%)	14 (48%)
Region		
USA	30 (33%)	7 (24%)
Europe	32 (35%)	14 (48%)
Asia	30 (33%)	8 (28%)
Race		
White	49 (53%)	17 (59%)
Asian	32 (35%)	10 (34%)
Other or unknown	11 (12%)	2 (7%)
Smoking history		
Current or former	32 (35%)	13 (45%)
Never or unknown	60 (65%)	16 (55%)
Histology		
Adenocarcinoma	88 (96%)	29 (100%)
Other*	4 (4%)	0
Eastern Cooperative Oncology Group performance status		
0	34 (37%)	11 (38%)
1	53 (58%)	17 (59%)
2†	5 (5%)	1 (3%)
Brain metastases‡	38 (41%)	12 (41%)
RET fusion partner		
KIF5B	69 (75%)	20 (69%)
CCDC6	16 (17%)	3 (10%)
Other	2 (2%)§	0
Unknown	5 (5%)¶	6 (21%)‖

(Table 1 continues in next column)

	Previous platinum-based chemotherapy group (n=92)	No previous systemic treatment group (n=29)
(Continued from previous column)		
RET assay**		
Next-generation sequencing -based	41 (45%)	8 (28%)
ctDNA	61 (66%)	16 (55%)
FISH	18 (20%)	9 (31%)
Other	7 (8%)	6 (21%)
Lines of previous therapy	2 (1–3)	0
Previous therapy type		
Chemotherapy	92 (100%)	0
PD-(L)1 inhibitor	41 (45%)	0
Multikinase inhibitor	24 (26%)	0

Data are median (IQR) or n (%). The efficacy population includes all patients with *RET* fusion–positive non-small-cell lung cancer who initiated 400 mg once daily pralsetinib by Jul 11, 2019. ctDNA=circulating tumour DNA. FISH=fluorescence in situ hybridisation. NGS=next-generation sequencing. PD-(L)1=programmed cell death-1 or programmed cell death-ligand 1. *RET*=rearranged during transfection. *Includes squamous, undifferentiated, and other not specified. †ECOG performance status of 2 was permitted before a protocol amendment (July 25, 2018). ‡History of or current. §*EML4*, n=1; *DOCK1*, n=1. ¶Fusion present but specific partner unknown; subgroup consisted of five patients with unknown *RET* fusion partner (five assessed by FISH) where central analysis of ctDNA or tissue was not done or did not detect a specific *RET* fusion. ‖Fusion present but specific partner unknown; subgroup consisted of six patients with unknown *RET* fusion partner (three assessed by FISH, three by other methods) where central analysis of ctDNA or tissue was not done or did not detect a specific *RET* fusion. **Fusion status was assayed by multiple techniques in some patients. Other assay types included nanoString nCounter (nanoString, Seattle, WA, USA) and unknown.

Table 1: **Baseline characteristics**

Lancet Oncol 2021; 22: 959–69

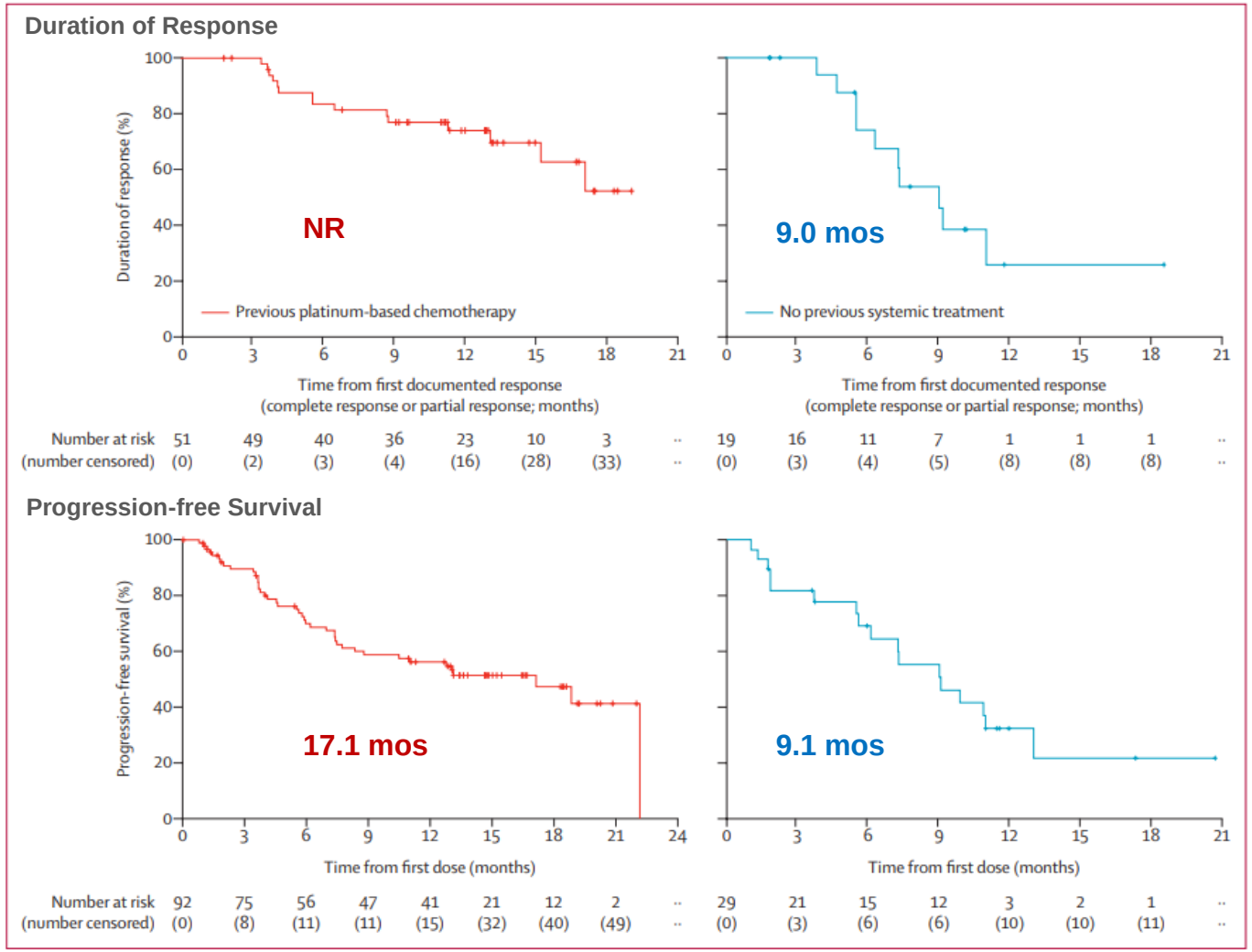
ARROW (data cut off: May 22th, 2020)

Response in patients with measurable disease

	Previous platinum group (n=87)	No previous systemic treatment group (n=27)†
Overall response rate	53 (61%; 50–71)‡	19 (70%; 50–86)
Disease control rate	79 (91%; 83–96)	23 (85%; 66–96)
Best overall response		
Complete response	5 (6%)	3 (11%)
Partial response	48 (55%)‡	16 (59%)
Stable disease	26 (30%)	4 (15%)
Progressive disease	4 (5%)	3 (11%)
Not evaluable	4 (5%)	1 (4%)
Median duration of response, months	NR (15·2–NE)	9·0 (6·3–NE)
Rate at 6 months	83%; 73–94	74%; 52–96
Rate at 12 months	74%; 61–87	26%; 0–52
Clinical benefit rate§	69% (58–79)	70% (50–86)

Data are n (%; 95% CI), n (%), or median (95% CI). NE=not estimable. NR=not reached. *Includes patients with non-small-cell lung cancer who initiated 400 mg pralsetinib once daily by July 11, 2019, and had measurable disease per Response Evaluation Criteria in Solid Tumours version 1.1 at baseline by blinded independent central review. †Group consisted of patients who were not candidates for platinum-based chemotherapy. ‡Includes two patients who continued treatment with partial responses pending confirmation. §Confirmed complete response, partial response, or stable disease with duration ≥16 weeks.

Analyses of DOR and PFS



Lancet Oncol 2021; 22: 959–69

ARROW (data cut off: May 22th, 2020)

	Grade 1–2	Grade 3	Grade 4
Neutropenia*	48 (21%)	34 (15%)	9 (4%)
Elevated aspartate aminotransferase	82 (35%)	4 (2%)	2 (1%)
Anaemia*	50 (21%)	24 (10%)	0
Decreased white blood cell count*	50 (21%)	14 (6%)	0
Elevated alanine aminotransferase	56 (24%)	4 (2%)	1 (<1%)
Asthenia*	49 (21%)	4 (2%)	0
Constipation	51 (22%)	2 (1%)	0
Hypertension*	24 (10%)	26 (11%)	0
Dysgeusia	31 (13%)	0	0
Elevated blood creatinine	30 (13%)	0	0
Thrombocytopenia*	23 (10%)	5 (2%)	2 (1%)
Diarrhoea	28 (12%)	1 (<1%)	0
Dry mouth	29 (12%)	0	0
Elevated blood creatine phosphokinase	19 (8%)	8 (3%)	0
Pneumonitis*	22 (9%)	3 (1%)	1 (<1%)
Hyperphosphataemia	25 (11%)	0	0
Lymphopenia*	14 (6%)	9 (4%)	2 (1%)
Oedema*	24 (10%)	0	0
Pneumonia*	5 (2%)	7 (3%)	1 (<1%)
Hypophosphataemia	6 (3%)	5 (2%)	1 (<1%)
Hyponatraemia*	6 (3%)	4 (2%)	1 (<1%)
Stomatitis	6 (3%)	4 (2%)	0

Data are n (%). Listed are adverse events of any grade reported in at least 10%, and of grade 3–4 reported in at least 2% of the 233 patients with *RET* fusion-positive non-small-cell lung cancer who initiated 400 mg pralsetinib and were deemed treatment-related by the investigators. No grade 5 treatment-related adverse events were reported in this population. *Grouped terms; adverse events that were similar were pooled together (eg, neutrophil count decreased and neutropenia).

Treatment-related adverse events

- ✓ Grade 3 and higher TRAEs : 48%
- ✓ Dose reduction rate: 38%
- ✓ Discontinuation rate : **6%** (d/t TRAEs)

Lancet Oncol 2021; 22: 959–69

Selpercatinib *vs* Pralsetinib

Baseline Characteristics

	Pralsetinib (ARROW) data cut off: 2020.5.22		**Selpercatinib (LIBRETTO-001)** data cut off: 2019.12.16	
	Previous Platinum chemotherapy (n=92)	Treatment naïve (n=29)	Previous Platinum chemotherapy (n=105)	Treatment naïve (n=39)
Median age (yr)	60 (28-85)	65 (30-87)	61 (23-81)	61 (23-86)
Male	50%	48%	41%	44%
Race	53% White/35% Asian	59% White/34% Asian	52% White/38% Asian	72% White/18% Asian
Smoking	65% Non-smoker	55% Non-smoker	71% Non-smoker	74% Non-smoker
Brain mets at baseline	41%	31%	36%	18%
RET fusion partner	75% *KIF5B*/17% *CCDC6*	69% *KIF5B*/10% *CCDC6*	56% *KIF5B*/23% *CCDC6*	67% *KIF5B*/21% *CCDC6*
Prior therapy	100% chemotherapy 45% PD-(L)1 inhibitor 26% Multikinase inhibitor	-	100% chemotherapy 55% PD-(L)1 inhibitor 48% Multikinase inhibitor	-

N Engl J Med 2020;383:813-824
Lancet Oncol 2021; 22: 959–69

Selpercatinib *vs* Pralsetinib

Efficacy and Toxicities

	Pralsetinib (ARROW) data cut off: 2020.5.22		**Selpercatinib (LIBRETTO-001)** data cut off: 2019.12.16	
	Previous Platinum chemotherapy (n=92)	Treatment naïve (n=29)	Previous Platinum chemotherapy (n=105)	Treatment naïve (n=39)
ORR*	61%	70%	64% [IAS, n=218; 57%]	85%
CR rate	6%	11%	2%	-
Median DoR*, month	NR	9.0	17.5	NR
Median PFS*, month	17.1	9.1	16.5	NR
Intracranial response* (n)	70% (10)		85% (26)	
Any TRAE (grade 3 ↑)	48%		27%	
Common Aes (grade 3 ↑)	9% HTN/8% elevated AST level/5% elevated ALT level		15% neutropenia/11% HTN/10% anemia	
Specific AE	Pneumonia (4%, grade 3 ↑)		QT prolongation (2%, grade 3 ↑)	
Discontinuation rate	6%		2%	

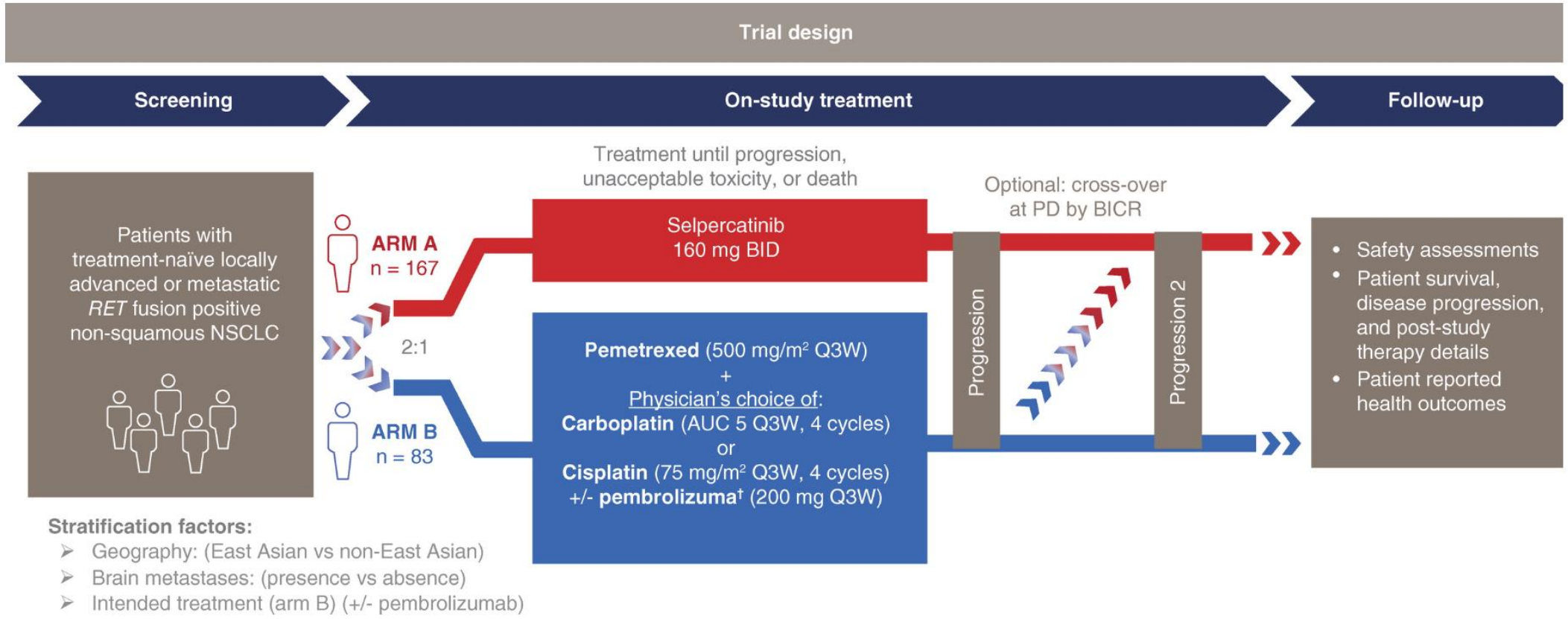
* Central review; NR, not reached

Pralsetinib SmPC 2021, Drilon A, et al. Ann Onol 2022;33(suppl):Abstral 27P
N Engl J Med 2020;383:813-824; *Lancet Oncol* 2021; 22: 959–69

Frontline RET inhibitors

LIBRETTO-431

Phase III study of selpercatinib versus chemotherapy ± pembrolizumab in untreated *RET* positive non-small-cell lung cancer



Future Oncol 2021;17(7):763-773

Frontline RET inhibitors

AcceleRET Lung

Phase 3 Study of First-Line Pralsetinib in Patients with RET Fusion + Advanced/Metastatic Non-Small-Cell Lung Cancer

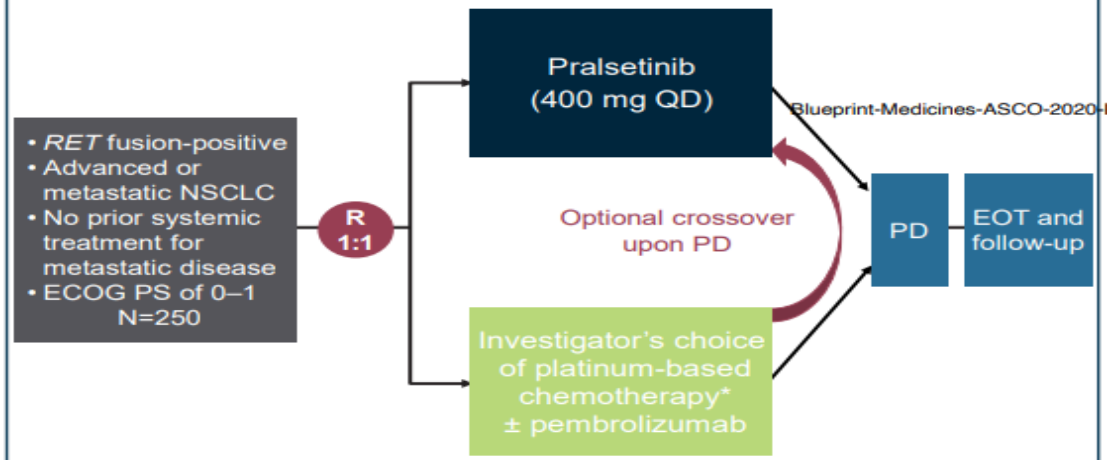
Inclusion criteria	Exclusion criteria
• Adult patients aged ≥18 years • Pathologically confirmed advanced or metastatic NSCLC • Measurable disease (RECIST 1.1) determined by local site investigator or central radiographic imaging review assessment • *RET* fusions assessed by next generation in situ hybridization and circulating tumor DNA methods • ECOG performance status of 0–1 • Prior therapy in the neo/adjuvant setting is allowed if recurrence occured after ≥6 months from completion of treatment	• Prior systemic treatment for metastatic disease • Tumor has an additional primary targetable driver mutation • Prior treatment with a selective RET inhibitor • CNS metastases or primary CNS tumor associated with progressive neurological symptoms

CNS, central nervous system; ECOG, Eastern Cooperative Group; NSCLC, non-small-cell lung cancer; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RT, radiation therapy.

tinib-AcceleRET-NSCLC-Poster

Study design

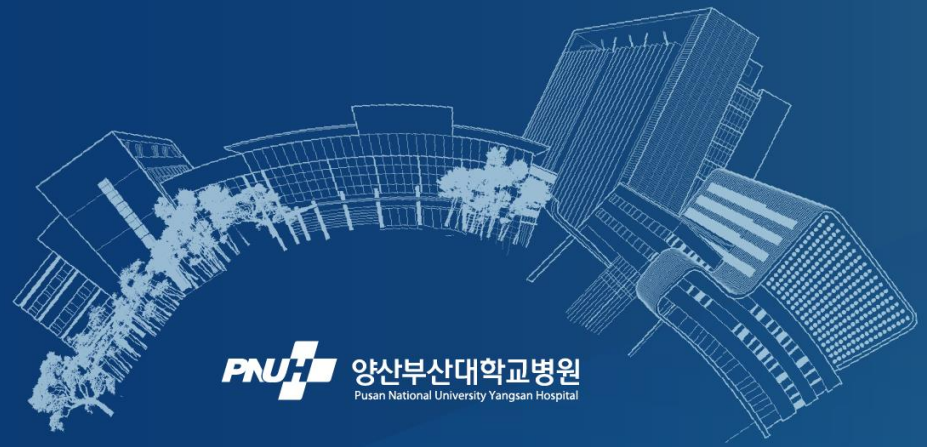
Figure 2: AcceleRET Lung study design



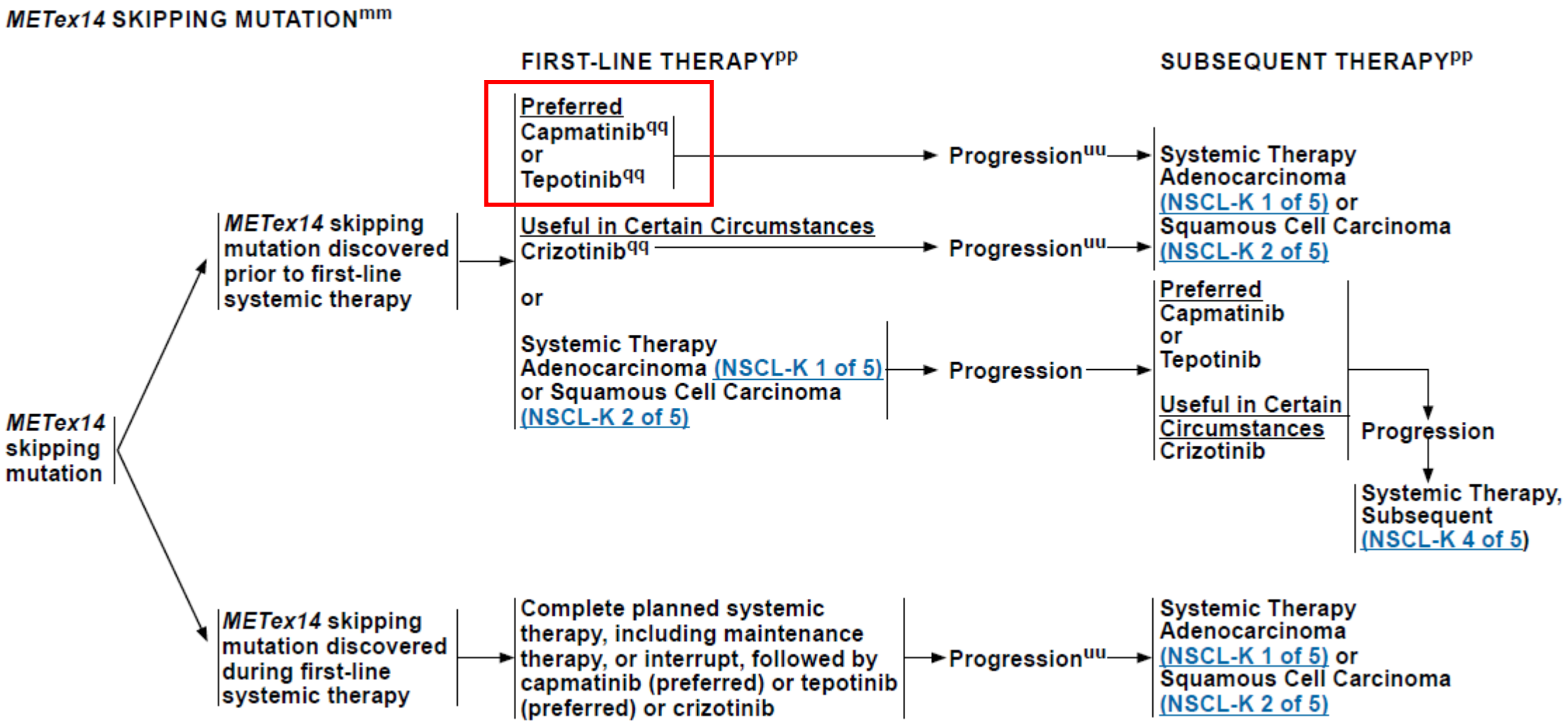
*Patients with non-squamous histology will receive platinum/pemetrexed with or without pembrolizumab; patients with squamous histology will receive platinum/gemcitabine
ECOG PS, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS); EOT, end of treatment; NSCLC, non-small-cell lung cancer; PD, progressive disease; QD, once daily; R, randomized; RET, rearranged during transfection.

Presented by Benjamin Besse at ASCO 2020

MET skipping mutation



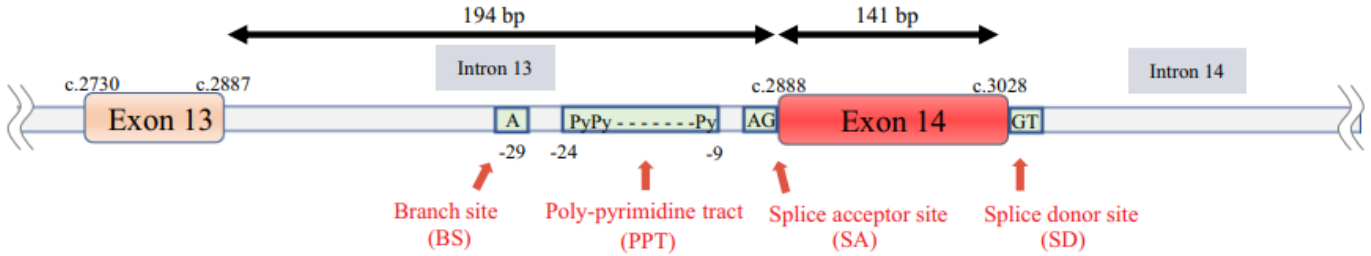
NCCN Guidelines: Ver2. 2023



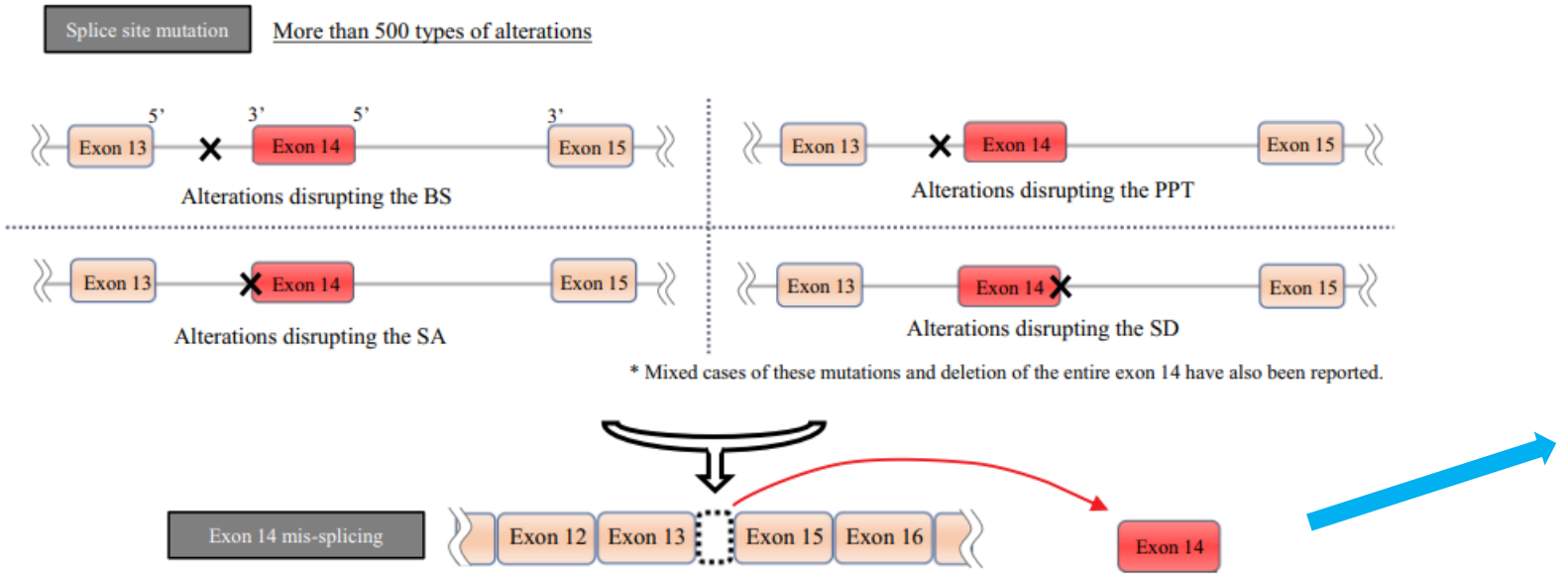
Ettinger DS, et al. NCCN Guidelines Version 2.2023 Non-Small Cell Lung Cancer

MET exon 14 skipping mutation ??

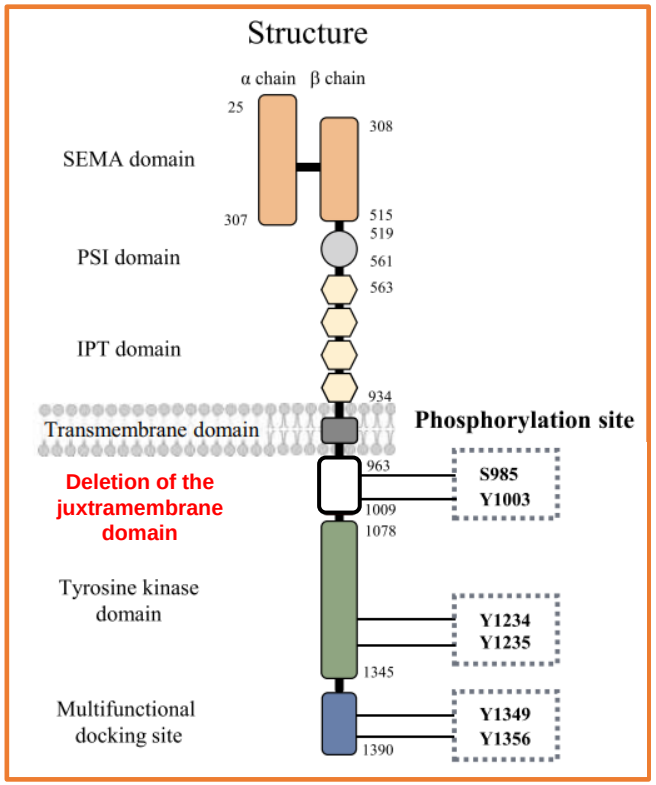
Splicing consensus sequence



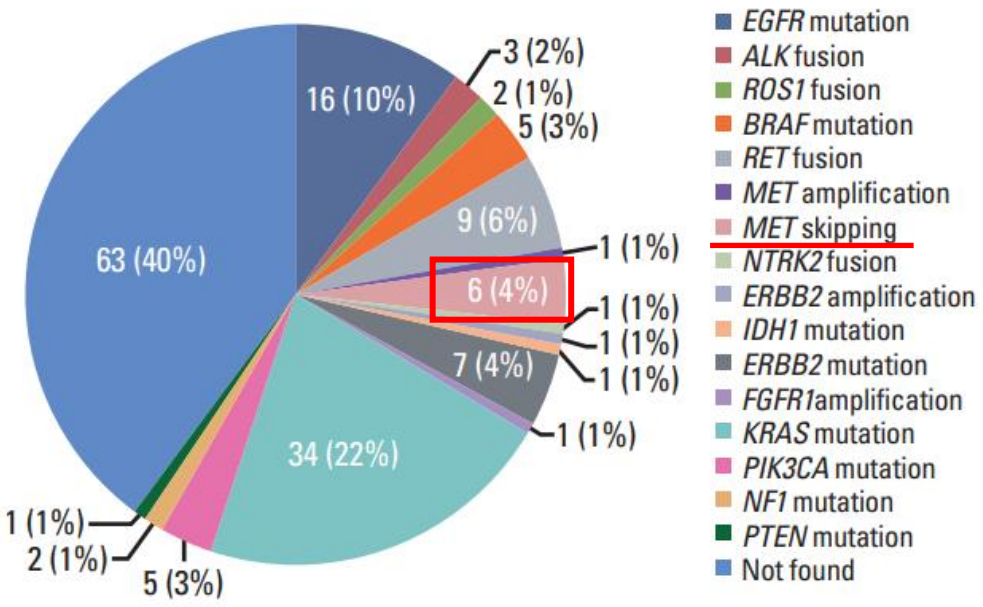
Molecular aberrations that cause MET exon 14 skipping



Structure of normal MET



Prevalence of *MET* exon 14 skipping (2-4%)

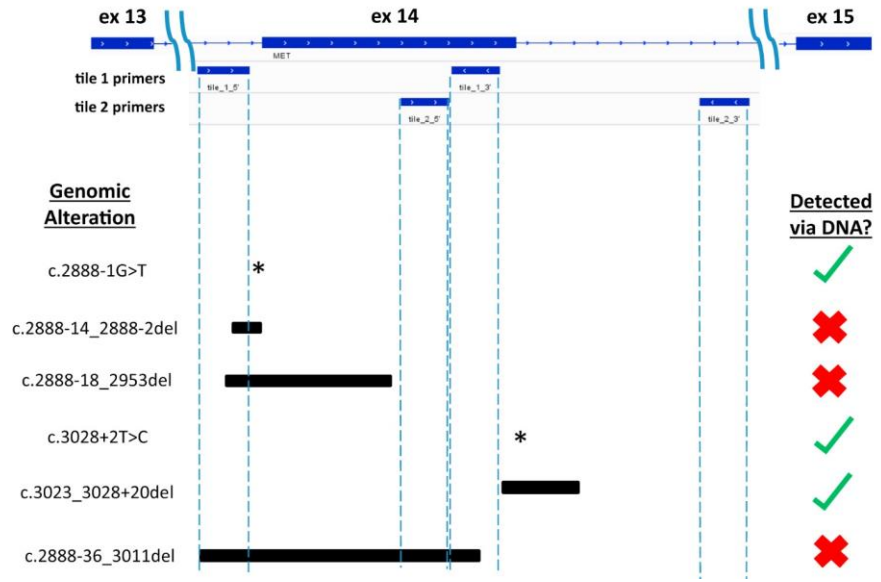


NGS : TruSight Tumor 170 (Illumina, San Diego, CA) or a customized cancer panel (NgeneBio, Seoul, Korea).

DNA-Based vs RNA-Based Methods

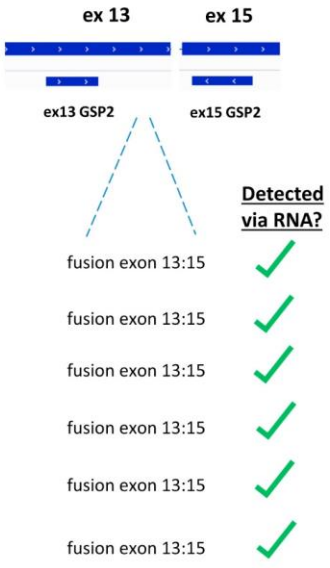
TruSight Tumor 26 assay (Illumina)

DNA-Based Analysis



FusionPlex Solid Tumor assay (ArcherDx)

RNA-Based Analysis

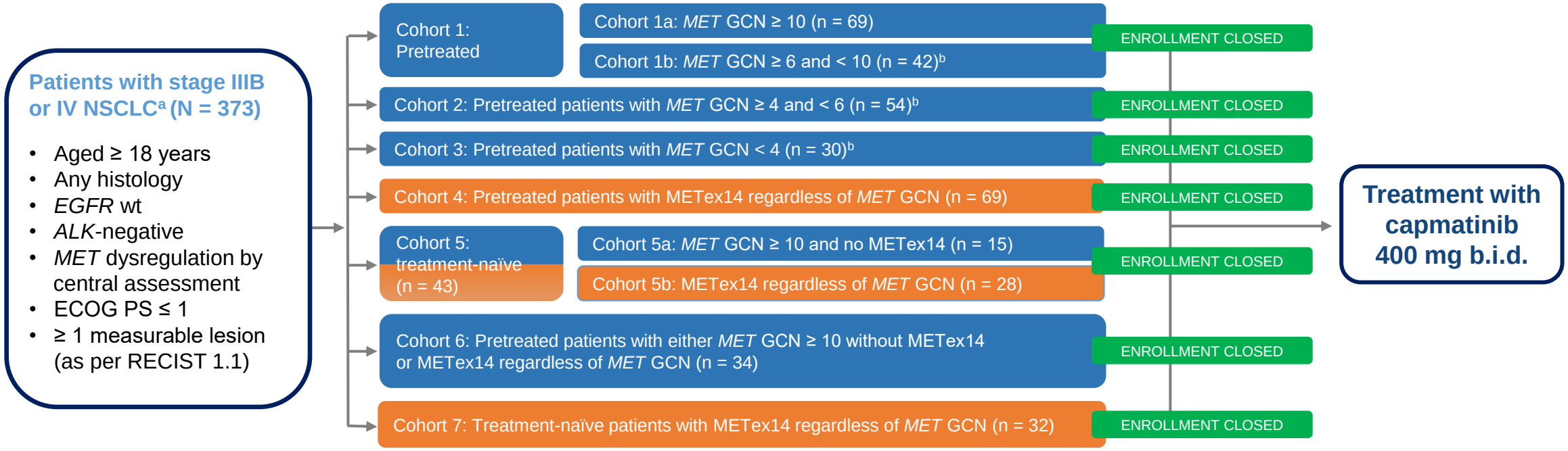


Detected Prevalence of *MET* Exon 14 Skipping, n/N (%)	**11/856 (1.3)***	**17/404 (4.2)***

Davies KD, et al. *J Thorac Oncol* 2019;14:737-741
Park EH, et al. *Cancer Res Treat* 2020;52(2):543-551

GEOMETRY mono-l: study design

Global, prospective, multicenter, open-label, phase 2 trial evaluating the efficacy and safety of single-agent **capmatinib** in adults with METex14 or *MET* amplification



* Primary endpoint : ORR assessed by BIRC

[a] Patients were allocated based on *MET* central molecular prescreening.
[b] Cohorts 1b, 2, and 3 included patients with lower amplifications; these cohorts were closed for futility but continue to be evaluated for safety within the full data set.

Wolf J, et al. N Engl J Med. 2020;383:944-57. Wolf J, et al. Presented at ASCO 2021; abstract 9020.

GEOMETRY mono-1: Efficacy of Capmatinib

Clinically meaningful responses were observed in **treatment-naïve patients** (n = 60) with METex14 advanced NSCLC[1,2]

		Cohort 5b[a] (n = 28) Fasting restrictions		Cohort 7[b] (n = 32) No fasting restrictions	
		BIRC assessed[2]	Investigator assessed[1]	BIRC assessed[2]	Investigator assessed[1]
Best OR, n (%)	CR	1 (3.6)	0	0	NR
	PR	18 (64.3)	17 (60.7)	21 (65.6)	NR
	SD	7 (25.0)	10 (35.7)	11 (34.4)	NR
	Non-CR/non-PR	1 (3.6)	0	0	NR
	PD	1 (3.6)	1 (3.6)	0	NR
	Not evaluable[c]	0	0	0	NR
Primary endpoint ORR (95% CI),[d] %		67.9 (47.6–84.1)[a]	60.7 (40.6–78.5)	65.6 (46.8–81.4)	NR
DCR (95% CI), %		96.4 (81.7–99.9)	96.4 (81.7–99.9)	100.0 (89.1–100.0)	NR
Median PFS (95% CI), months		12.4 (8.2–23.4)	12.0[d] (5.5–16.9)	10.8[e] (6.9–NE)	NR
Median OS (95% CI), months		20.8[e] (12.4–NE)	NA	NE[e] (10.6–NE)	NA
Key secondary endpoint Median DoR (95% CI),[b] months		12.6[e] (5.6–NE)	13.8 (4.3–25.3)	NE[e] (5.5–NE)	NR

[a] Data mature as of January 6, 2020. [b] Data cutoff September 18, 2020. [c] Not qualifying for confirmed CR or PR and without SD after > 6 weeks or progression within the first 12 weeks. [d] Primary endpoint. [e] Data not yet mature.

1. Wolf J, et al. N Engl J Med. 2020;383:944-57
2. Wolf J, et al. Presented at ASCO 2021; abstract 9020

GEOMETRY mono-1: Efficacy of Capmatinib

Clinically meaningful responses were observed in **pretreated patients** (n = 100) with METex14 advanced NSCLC[1,2]

		Cohort 4[a] (n = 69) Fasting restrictions		Cohort 6[b] (n = 31) No fasting restrictions	
		BIRC assessed[2]	Investigator assessed[1]	BIRC assessed[2]	Investigator assessed[1]
Best OR, n (%)	CR	0	1 (1.4)	0	NR
	PR	28 (40.6)	29 (42.0)	16 (51.6)	NR
	SD	25 (36.2)	21 (30.4)	11 (35.5)	NR
	Non-CR/non-PR	1 (1.4)	2 (2.9)	1 (3.2)	NR
	PD	6 (8.7)	7 (10.1)	0	NR
	Not evaluable[c]	9 (13.0)	9 (13.0)	3 (9.7)	NR
Primary endpoint ORR (95% CI),[d] %		40.6 (28.9–53.1)	43.5 (31.6–56.0)	51.6 (33.1–69.8)	NR
DCR, (95% CI), %		78.3 (66.7–87.3)	76.8 (65.1–86.1)	90.3 (74.2–98.0)	NR
Median PFS (95% CI),[b] months		5.4 (4.2–7.0)	4.8[d] (4.1–7.7)	6.9 (4.2–13.3)	NR
Median OS (95% CI), months		13.6 (8.6–22.2)	NA	NE (13.5–NE)[e]	NA
Key secondary endpoint Median DoR (95% CI),[b] months		9.7 (5.6–13.0)	8.3[d] (5.4–12.1)	8.4 (4.2–NE)[e]	NR

[a] Data mature as of January 6, 2020. [b] Data cutoff September 18, 2020. [c] Not qualifying for confirmed CR or PR and without SD after > 6 weeks or progression within the first 12 weeks. [d] Primary endpoint. [e] Data not yet mature.

1. Wolf J, et al. N Engl J Med. 2020;383:944-57
2. Wolf J, et al. Presented at ASCO 2021; abstract 9020

GEOMETRY mono-1: Safety of Capmatinib

Most common TRAEs (≥ 10% in safety population)

	All patients N = 373		Patients with METex4 and brain metastasis n = 29	
	All grades n (%)	Grade 3–4 n (%)	All grades n (%)	Grade 3–4 n (%)
Number of patients with at least 1 TRAE	324 (86.9)	147 (39.4)	26 (89.7)	14 (48.3)
Peripheral edema[a]	178 (47.7)	34 (9.1)	14 (48.3)	4 (13.8)
Nausea	128 (34.3)	6 (1.6)	15 (51.7)	1 (3.4)
Increased blood creatinine	74 (19.8)	0	2 (6.9)	0
Vomiting	71 (19.0)	7 (1.9)	8 (27.6)	0
Fatigue	51 (13.7)	10 (2.7)	4 (13.8)	2 (6.9)
Decreased appetite	47 (12.6)	3 (0.8)	4 (13.8)	0
Diarrhea	40 (10.7)	1 (0.3)	0	0

There were 4 (1.1%) treatment-related fatal SAEs: cardiac arrest, hepatitis, organizing pneumonia, and pneumonitis in 1 (0.3%) patient each

Heist RS, et al. Poster presented at ESMO 2021; abstract 1256P

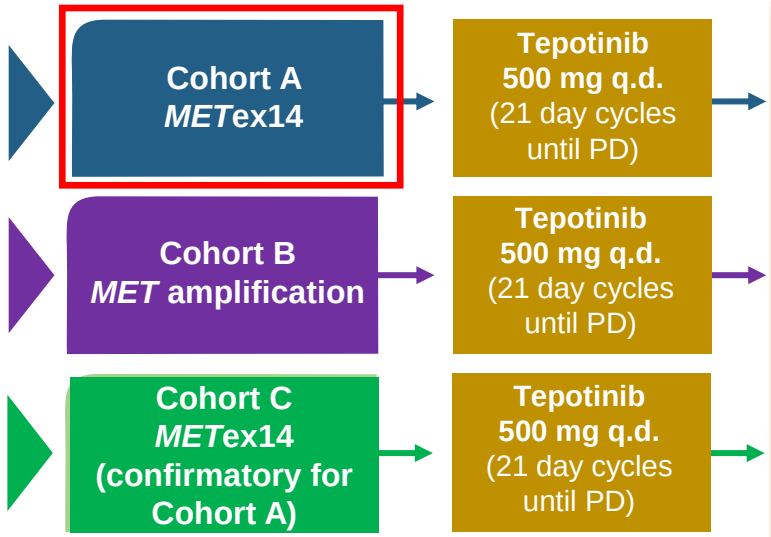
VISION Phase 2 trial (Tepotinib): study design

Study design

- **Stage IIIB/IV NSCLC**
  - **All histologies** (including squamous and sarcomatoid)
  - Exclusion of active brain metastases or brain as only measurable lesion
- **Tissue- or blood-based *MET* alterations** (central lab testing)
  - *A. MET*ex14 detected:
    - **Plasma,** liquid biopsy (DNA based)

    OR
    - **Tissue,** tissue biopsy (RNA based)
  - *B. MET* amplification only
- **1st, 2nd, 3rd line of therapy**
  - Prior anti-MET therapy was not allowed
  - Prior immunotherapy was allowed

N = up to 120



Selected endpoints

Primary endpoint
- ORR by independent review

Secondary endpoint
- ORR by investigator assessment
- DOR
- Objective disease control
- PFS
- OS
- Safety
- Health-related QoL

Paik PK, et al. Presentation at ASCO 2019. J Clin Oncol. 2019;37(15_suppl):9005.
Paik PK, et al. N Engl J Med. 2020; doi:10.1056/NEJMoa2004407.

VISION Phase 2 trial: Efficacy and Safety

Tepotinib showed clinical activity regardless of previous treatment

Efficacy according to IRC	Treatment-naive (n = 69)	Previously treated (n = 83)	Overall (N = 152)
ORR (95% CI), %	44.9 (32.9–57.4)	44.6 (33.7–55.9)	44.7 (36.7–53.0)
Best overall response, n (%)			
CR	0	0	0
PR	31 (44.9)	37 (44.6)	68 (44.7)
SD	16 (23.2)	23 (27.7)	39 (25.7)
PD	13 (18.8)	13 (15.7)	26 (17.1)
NE	9 (13.0)	10 (12.0)	19 (12.5)
Median DOR (95% CI), months	10.8 (6.9–NE)	11.1 (9.5–18.5)	11.1 (8.4–18.5)
Median PFS (95% CI), months	8.5 (6.8–11.3)	10.9 (8.2–12.7)	8.9 (8.2–11.2)

Data cutoff July 1, 2020.

Most common TRAEs (≥10% in the safety population)

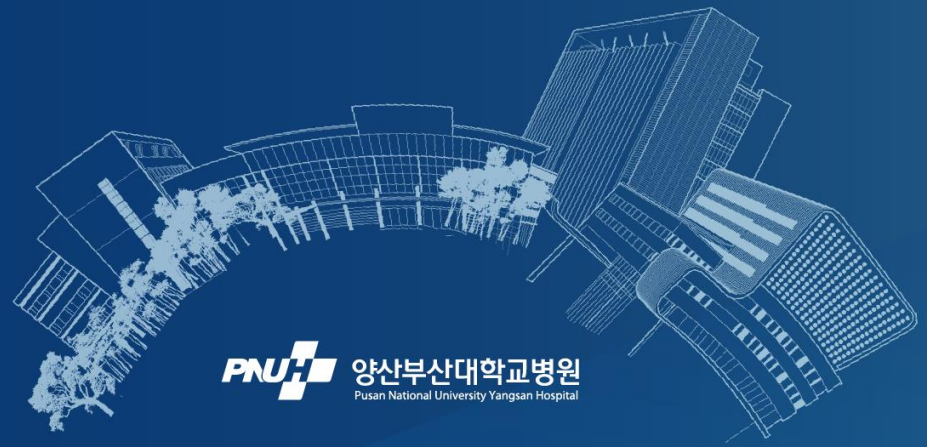
Characteristic	VISION Cohort A+C (N=255)		GEOMETRY Mono-1 All patients (N=373)
	All grades, n (%)	Grade 3/4, n (%)	Grade 3/4, n (%)
Number of patients with at least 1 TRAE	220 (86.3)	62 (24.3)	151 (40.5)
Peripheral edema[a]	138 (54.1)	19 (7.5)	34 (9.1)
Nausea	51 (20.0)	1 (0.4)	6 (1.6)
Increased blood creatinine	45 (17.6)	1 (0.4)	1 (0.3)
Vomiting	14 (5.5)	1 (0.4)	7 (1.9)
Fatigue	18 (7.1)	1 (0.4)	10 (2.7)
Decreased appetite	21 (8.2)	1 (0.4)	3 (0.8)
Diarrhea	50 (19.6)	1 (0.4)	1 (0.3)
Hypoalbuminemia	37 (14.5)	6 (2.4)	
Amylase increased	19 (7.5)	5 (2.0)	

[a]Peripheral edema includes peripheral swelling, peripheral edema and fluid overload.
BM, brain metastasis; *MET*ex14, *MET* exon 14 skipping mutation; TRAE, treatment-related adverse event

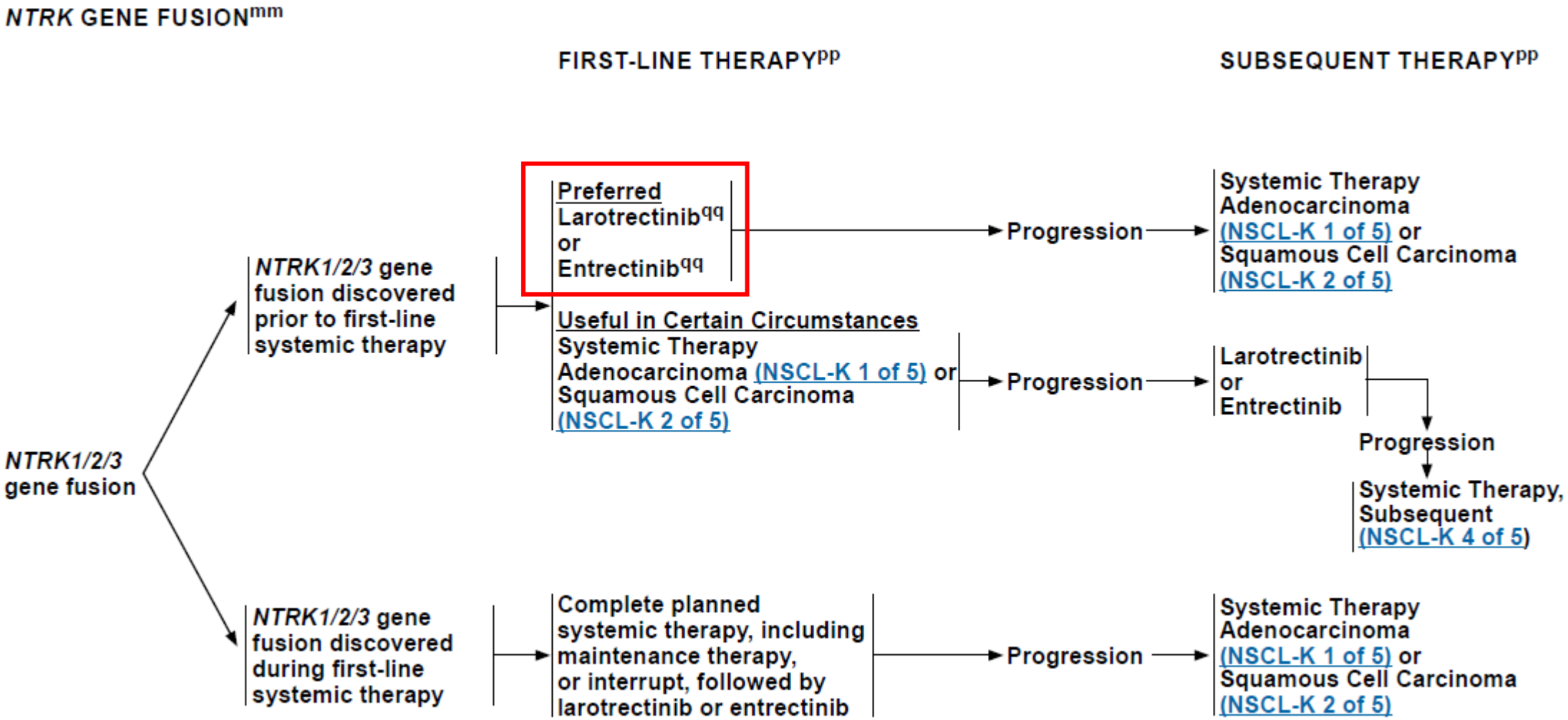
Paik PK, et al. J Thorac Oncol. 2021;16(3 Suppl):S174[MA11.05]
Wolf J, et al. ELCC 2022. poster presentation 26P; Le S, et al. *Clin Cancer Res* (2022) 28 (6): 1117–1126

NTRK Fusion

Pusan National University
Yangsan Hospital



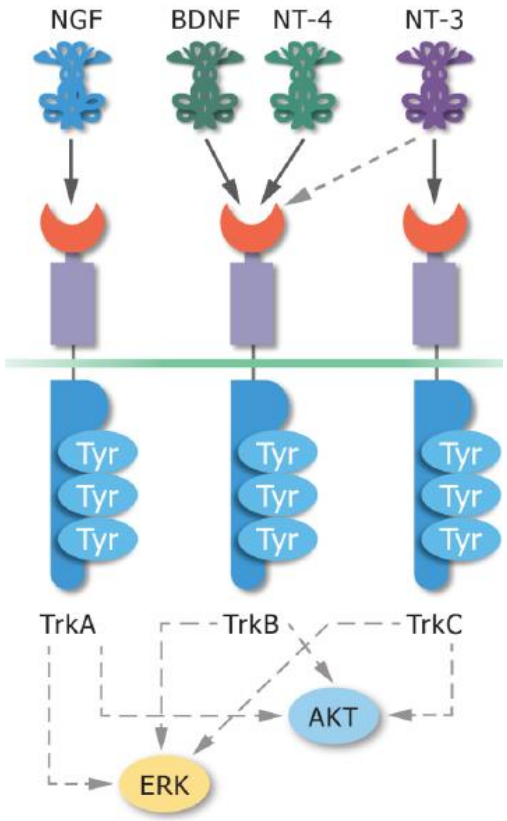
NCCN Guidelines: Ver2. 2023



Ettinger DS, et al. NCCN Guidelines Version 2.2023 Non-Small Cell Lung Cancer

TRK Receptor mediate neurotrophin signaling

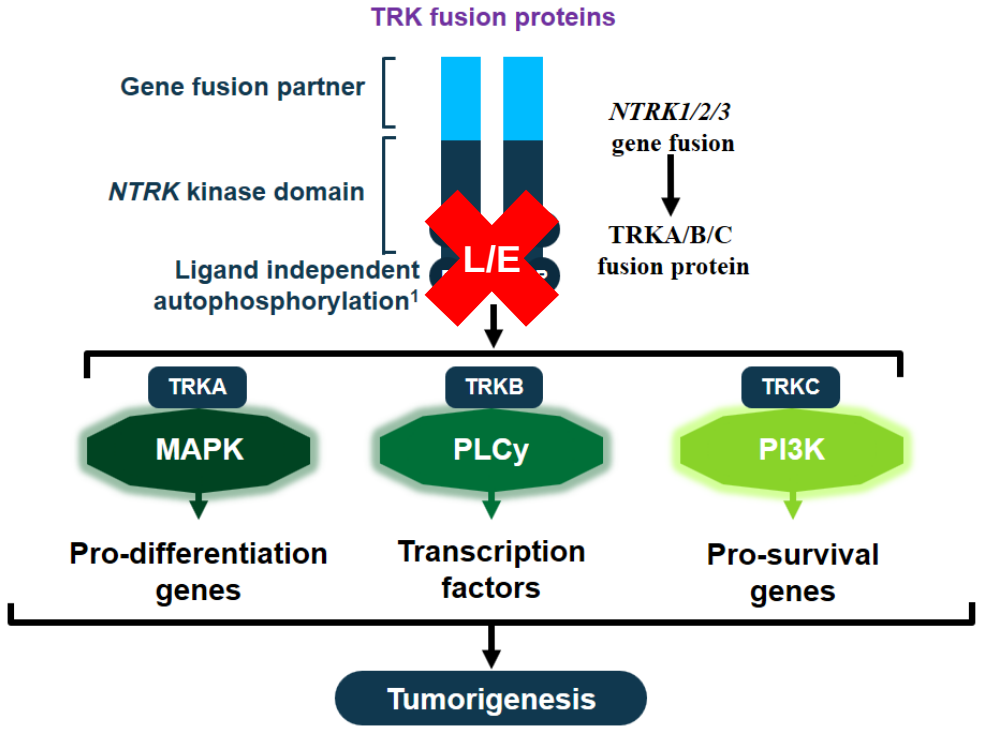
Neurotrophin signaling



Neurotrophin family of receptors

TRK receptor	Gene (chromosomal location)	Functions	Natural ligands
TRKA	*NTRK1* (1q23.1)	Pain signaling, thermo-Regulation	Nerve growth factor (NGF), neurotrophin-3 (NT-3)
TRKB	*NTRK2* (9q21.33)	Regulation of movement, memory, mood, appetite, body weight	Brain-derived neurotrophic factor (BDNF), neurotrophin-4 (NT-4), NT-3
TRKC	*NTRK3* (15q25.3)	Proprio-ception	NT-3

TRK fusion proteins result in ligand-independent, constitutive activation of TRK receptor signaling

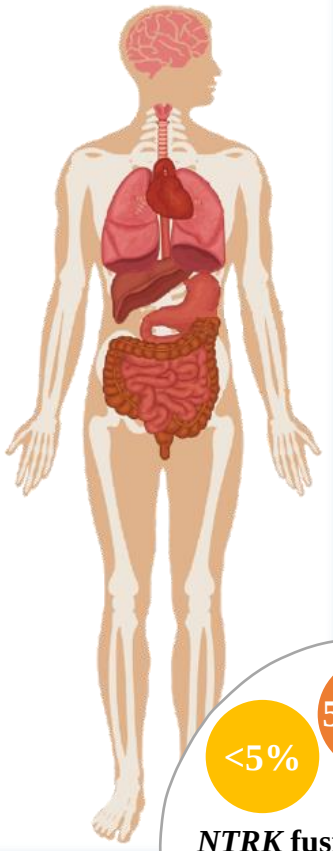


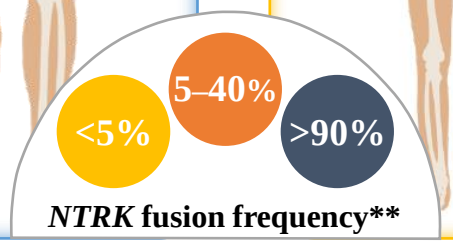
Drilon A, et al. *N Engl J Med* 2018;378:731–739
Vaishnavi A, et al. *Cancer Discov* 2015;5:25–34

NTRK gene fusions occur in a range of adult and pediatric tumor types

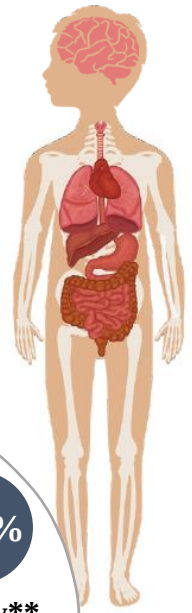
Adult

- Glioma (0.2–3.1%)
- Secretory carcinoma of the salivary gland*† (42.9–100%)
- Secretory breast cancer‡ (66.7–100%)
- Pancreatic adenocarcinoma (0.1–0.6%)
- Cholangiocarcinoma (0–3.6%)
- Papillary thyroid cancer (0–35.7%)
- NSCLC§ (0–2.6%)
- GIST (0.5–3.2%)
- CRC¶ (0.1–2.0%)
- Cutaneous melanoma (0.2–1.3%)
- Soft-tissue sarcoma‡ (0–2.9%)





Pediatric



- Glioma (0–6.3%)
- Spitzoid neoplasm (1.9–33.3%)
- Papillary thyroid cancer (8.6–25.9%)
- Infantile fibrosarcoma† (90.9–100%)
- Congenital nephroma†† (41.5–92.9%)
- Secretory breast cancer‡ (66.7–100%)
- Mesenchymal tumor‡‡ (0.4–8.4%)
- Langerhans cell histiocytosis (1.1%)

*Previously termed MASC; †*NTRK* gene fusions are considered pathognomonic for this tumor type[89]; ‡Frequency in adult versus pediatric patients not specified; §Only studies with N≥200 included; ¶Only studies with N≥100 included; **Where frequency spans legend ranges, the upper limit is used; ††Cellular and/or mixed histologic subtypes; ‡‡See notes for included tumor types.

Vokuhl C, et al. *Pediatr Blood Cancer*. 2018;65:e26925
Cocco E, et al. *Nat Rev Clin Oncol*. 2018;15:731–747

Efficacy of **Larotrectinib** in Lung Cancer

Pusan National University Yangsan Hospital

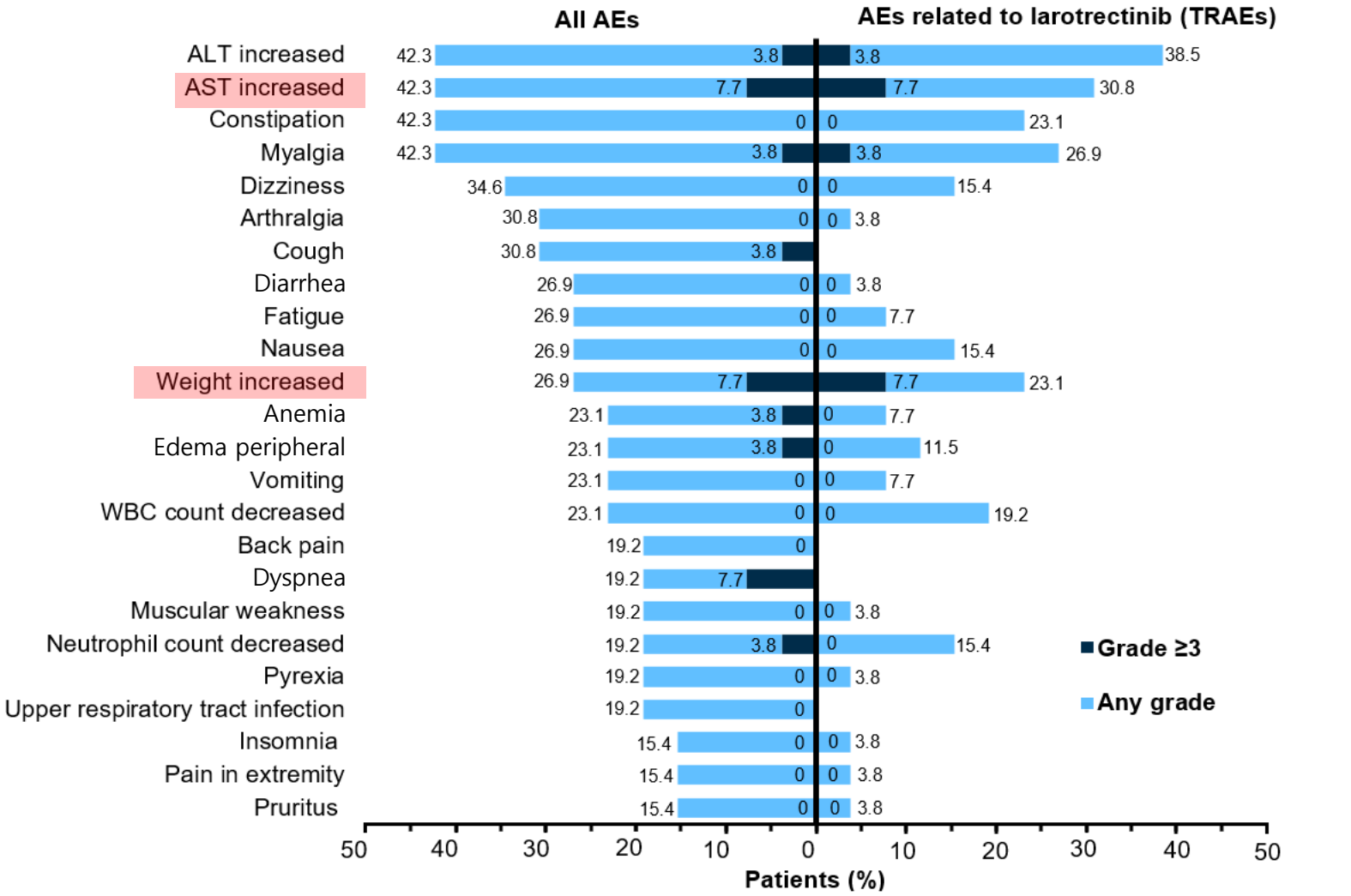
	WCLC 2021[1]	ELCC 2022[2]	ASCO 2022[3]
Study 1 phase 1	**N=20** n=1 n=0 n=19	**N=20** n=1 n=0 n=19	**N=26** n=1 n=0 n=25
Study 2 SCOUT	**ORR**: **87%**/73%* • **CR,** n=2 (13%)/n=1 (7%) • **PR,** n=11 (73%)/n=10 (67%)	**ORR**: **87%*** • **CR,** n=2 (13%) • **PR,** n=11 (73%)	**ORR**: **83%**‡ • **CR,** n=2 (9%) • **PR,** n=17 (74%)
Study 3 NAVIGATE	**IRC/INV assessment**	**IRC assessment**	**IRC assessment**
	mDoR: Not reached (95% CI 5.5, NE)† **mPFS: 33.0 mo** (95% CI 7.6, NE) **mOS: 40.7 mo** (95% CI 17.2, NE)	**mDoR:** Not reached (95% CI 5.5, NE)† **mPFS: 33.0 mo** (95% CI 7.6, NE) **mOS: 40.7 mo** (95% CI 17.2, NE)	**mDoR:** Not reached (95% CI 9.5, NE)§ **mPFS:** Not reached (95% CI 9.9, NE) **mOS: 40.7 mo** (95% CI 19.4, NE)
	Data cut-off: July 20, 2020	**Data cut-off: July 20, 2020**	**Data cut-off: July 20, 2021**

*In 15 evaluable patients; †At a median follow up of 15.6 months; ‡In 23 evaluable patients; §At a median follow up of 12.9 months.
ASCO, American Society of Clinical Oncology; CI, confidence interval; CR, complete response; ELCC, European Lung Cancer Congress; INV, investigator; IRC, independent review committee; mDoR, median duration of response; mo, months; mOS, median overall survival; mPFS, median progression-free survival; NE, not estimable; ORR, objective response rate; PR, partial response ; WCLC, World Conference on Lung Cancer.

1. Drilon A, et al. Presented at WCLC 2021; Abstract P53.02; 2. Moreno V, et al. Presented at ELCC 2022; Abstract 61P; 3. Drilon A, et al. Presented at ASCO 2022; Abstract 9024

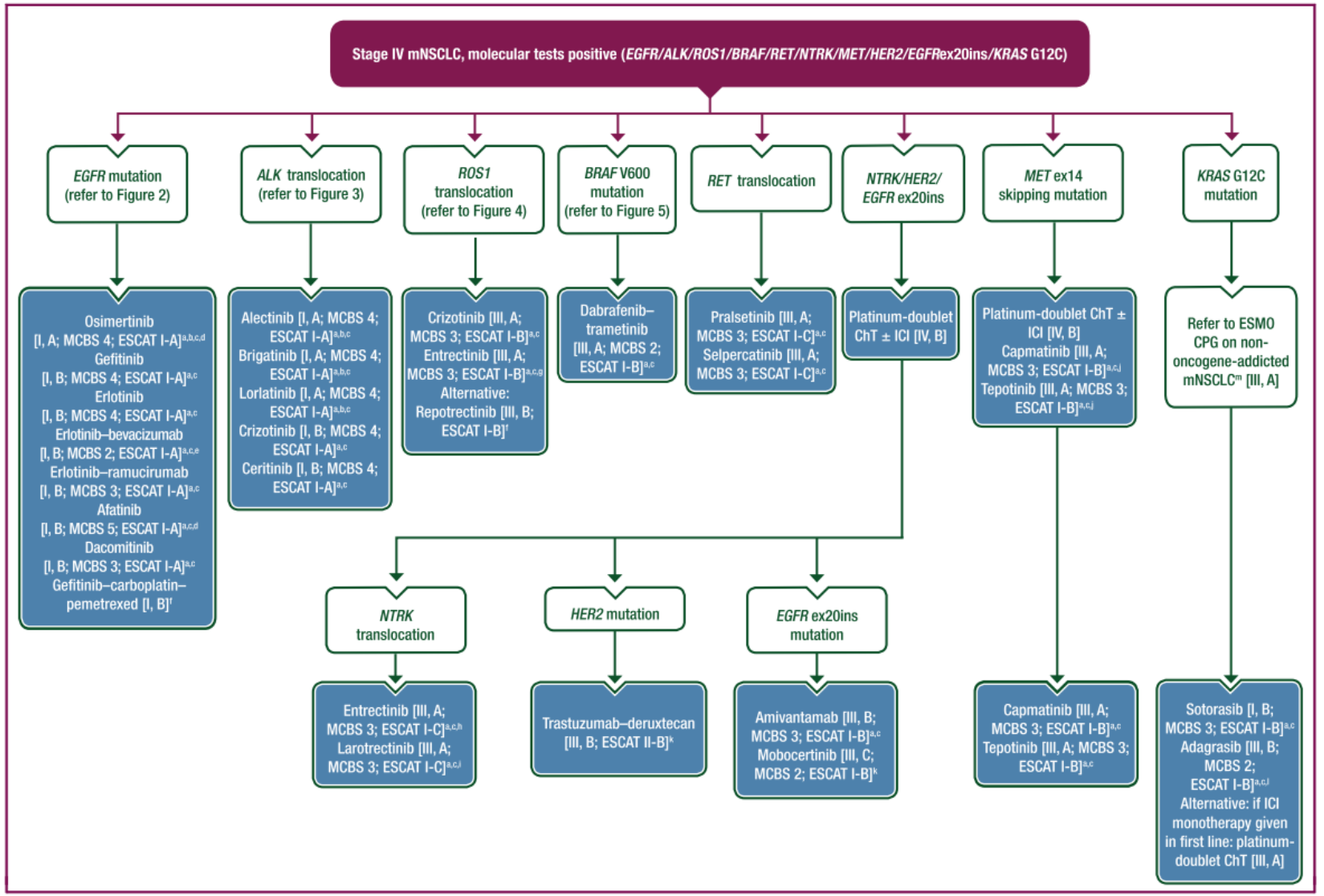
Safety of **Larotrectinib** in Lung Cancer

AEs occurring in ≥15% of patients from Group 2 (n=26)



Moreno V, et al. Poster presentation at WCLC 2022: Abstract 980.

Targeted Therapy Algorithm in advanced NSCLC



Hendriks LE, et al. Ann Oncol 2023; doi: https://doi.org/10.1016/j.annonc.2022.12.009.

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Thank You for Your Attention

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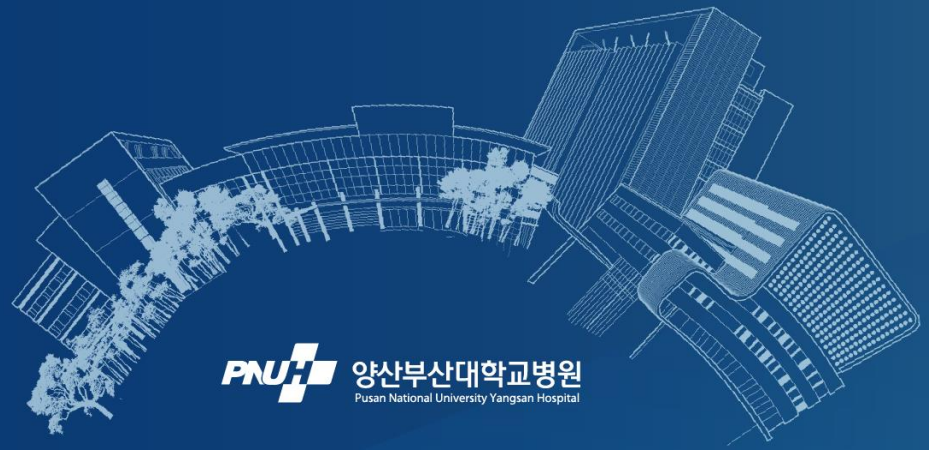

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