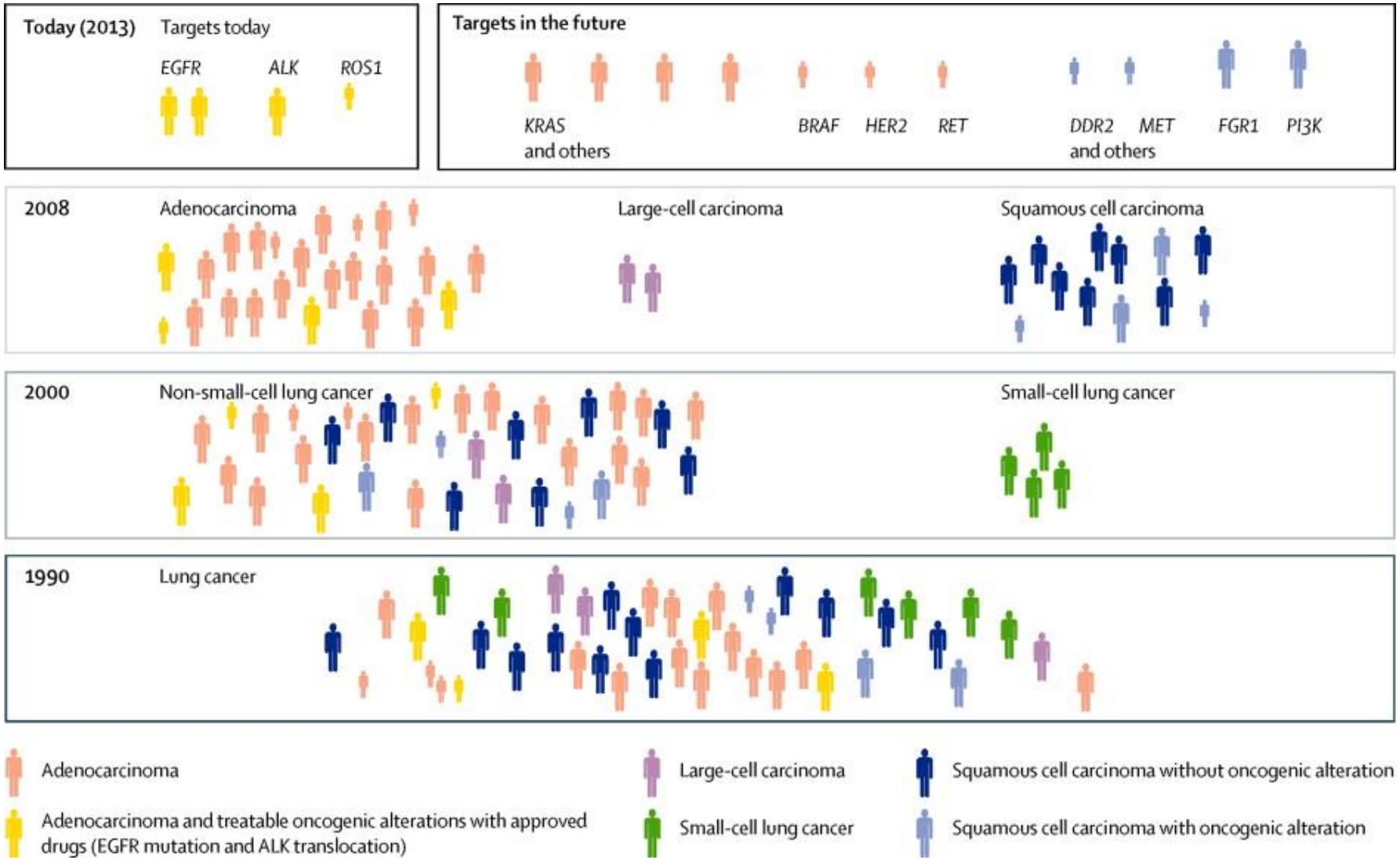
# Rare but critical AE in patients with newly introduced target agents

**Sun Ha Choi**
Department of Internal Medicine, Kyunpook National University
Medical School and Chilgok Hospital

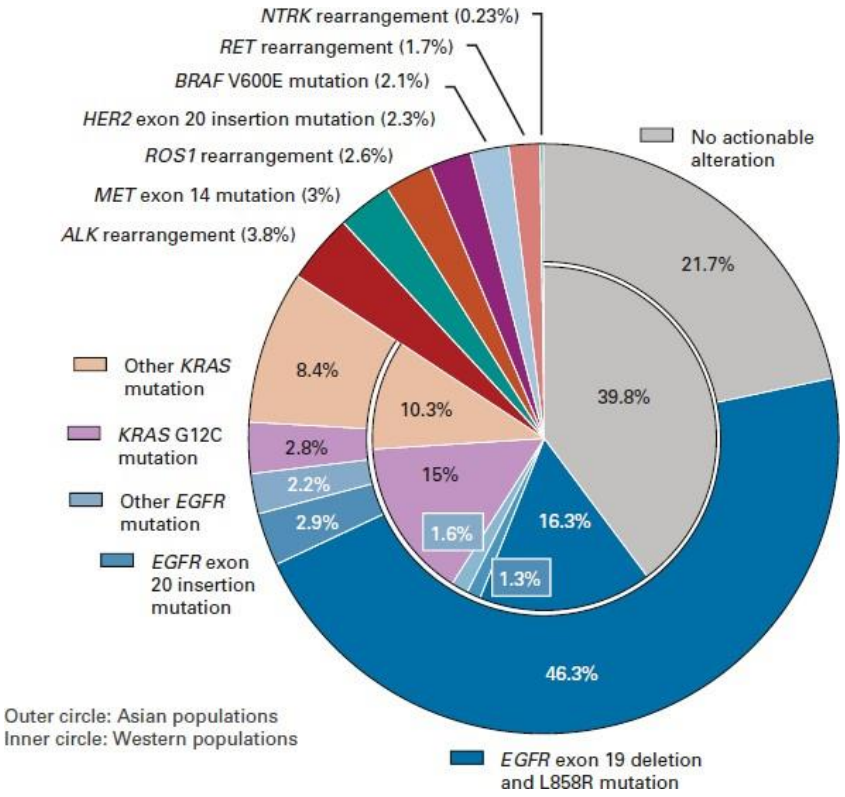
# The concept of lung cancer has changed



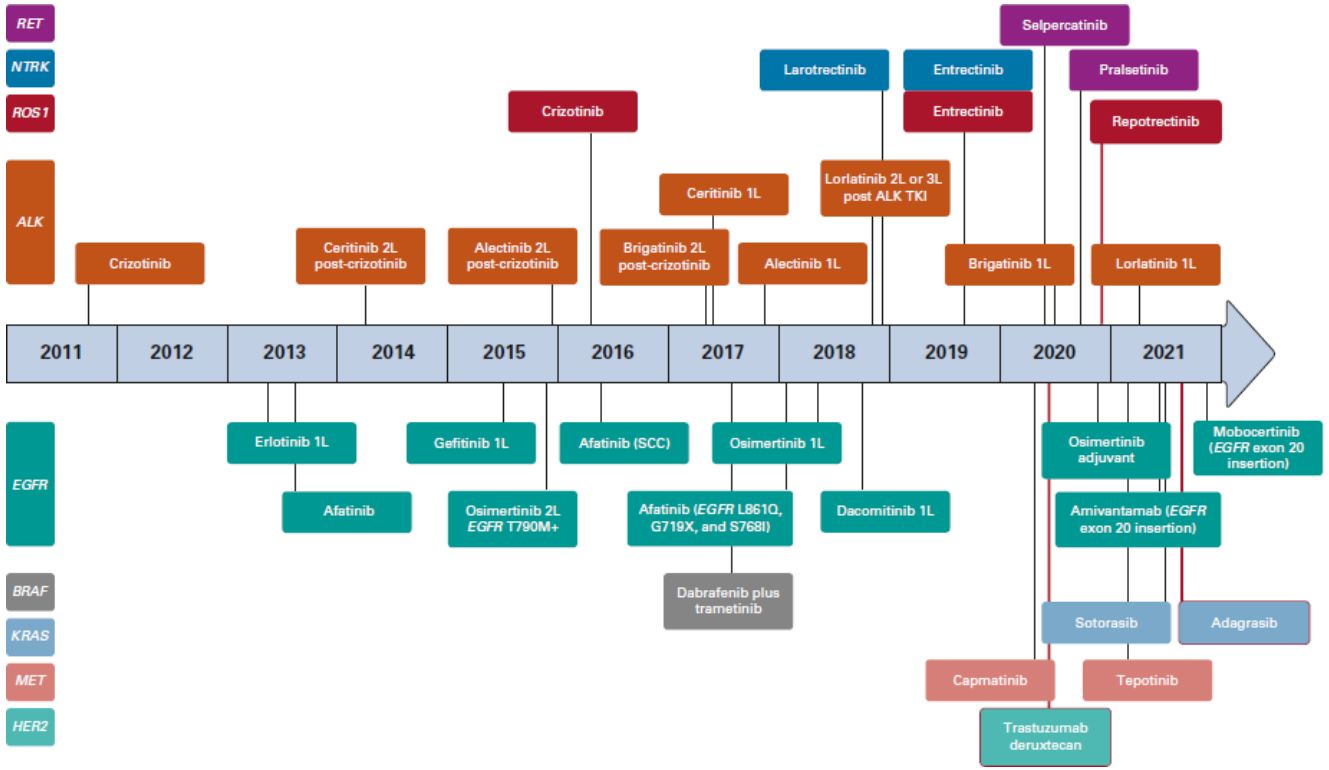

Reck M et al. Lancet. 2013 Aug 24;382(9893):709-19.

# Targetable oncogenic driver molecular alterations in NSCLC

Frequency of targetable oncogenic driver molecular alterations in NSCLC




Timeline of FDA-approved targeted therapies for oncogene-driven NSCLC




Tan AC, Tan DSW. J Clin Oncol 2022;40:611-25

National Comprehensive Cancer Network®

# NCCN Guidelines Version 3.2022
# Non-Small Cell Lung Cancer

NCCN Guidelines Index
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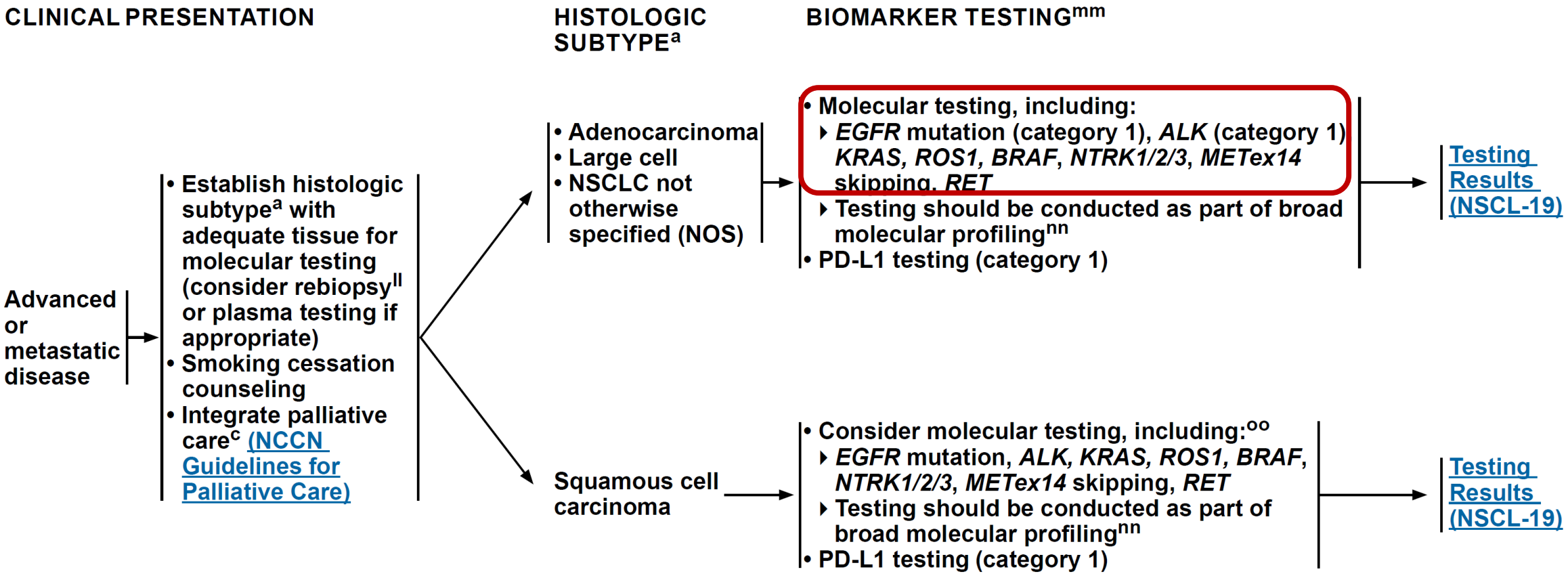
Discussion

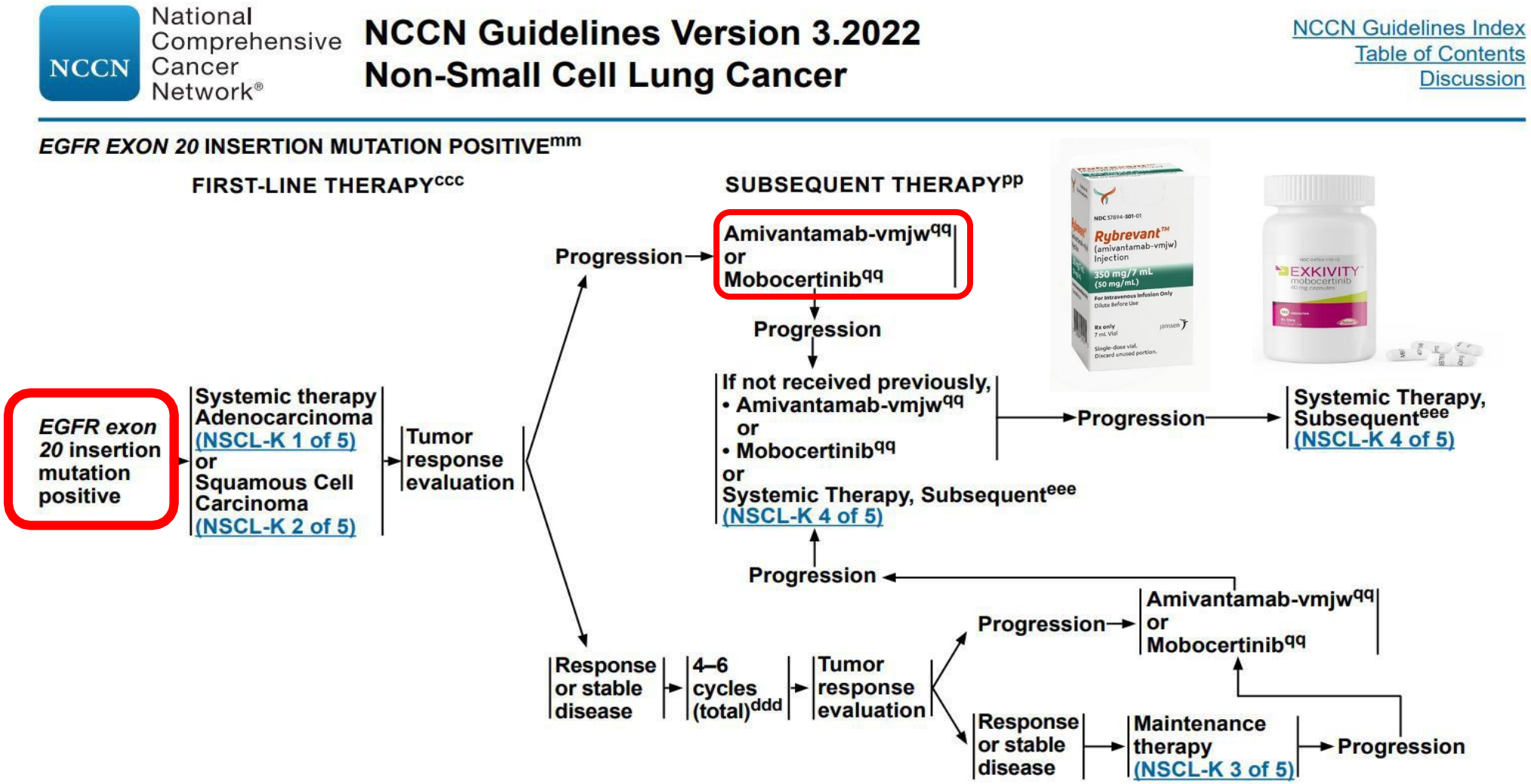


## TESTING RESULTS[ll,mm]

| | |
|---|---|
| *EGFR exon 19* deletion or *L858R* mutation positive | NSCL-20 |
| *EGFR S768I, L861Q,* and/or *G719X* mutation positive | NSCL-23 |
| *EGFR exon 20* insertion mutation positive | NSCL-24 |
| *KRAS G12C* mutation positive | NSCL-25 |
| *ALK* rearrangement positive | NSCL-26 |
| *ROS1* rearrangement positive | NSCL-29 |
| *BRAF* V600E mutation positive | NSCL-31 |
| *NTRK1/2/3* gene fusion positive | NSCL-32 |
| *METex14* skipping mutation positive | NSCL-33 |
| *RET* rearrangement positive | NSCL-34 |
| PD-L1 ≥50% and negative for actionable molecular biomarkers above | NSCL-35 |
| PD-L1 ≥1%–49% and negative for actionable molecular biomarkers above | NSCL-36 |
| PD-L1 <1% and negative for actionable molecular biomarkers above | NSCL-37 |

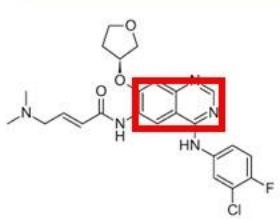
# *EGFR* Exon 20 insertion

# Currently FDA-approved therapy in *EGFR* exon 20 insertion

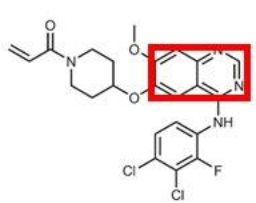


# Targeting *EGFR* exon 20 insertions

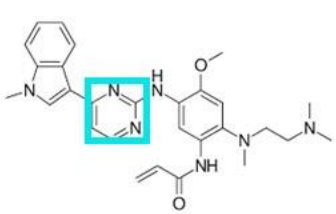
| | Drug | Class | Structure | n | ORR | PFS | DoR |
|---|---|---|---|---|---|---|---|
| | Afatinib[1] (retrospective) | Pan-HER TKI | Quinazoline-based | 70 | 24.3% | - | 11.9 m |
| | Poziotinib[2] | Pan-HER TKI | Quinazoline-based | 115 | 14.8% | 4.2 m | 7.4 m |
| | Osimertinib[3,4,5] | 3G EGFR TKI | Pyrimidine-based | 20 (80 mg)<br>21 (160 mg)<br>24 (160 mg) | 5%<br>24%<br>27% | 3.6 m<br>9.6 m<br>5.5 m | -<br>-<br>8.2 m |
| FDA Accelerated Approval | Mobocertinib[6] | EGFR TKI | Pyrimidine-based | 114 | 28% | 7.3 m | 17.5 m |
| FDA Accelerated Approval | Amivantamab[7] | EGFR-MET Bispecific Ab | Duobody monovalent IgG1 | 81 | 40% | 8.3 m | 11.1 m |
| | Sunvozertinib[8] | EGFR TKI | Pyrimidine-based | 56 | 41.1% | Not mature | Not mature |
| | **CLN-081[9]** | **EGFR TKI** | **Pyrimidine-based** | **73** | **38.4%** | **10 m** | **10 m** |



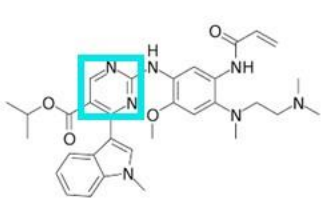
**Afatinib**



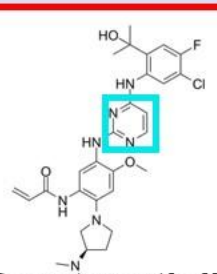
**Poziotinib**



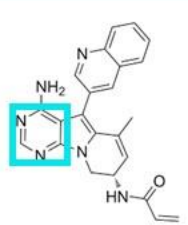
**Osimertinib**



**Mobocertinib**



**Sunvozertinib**

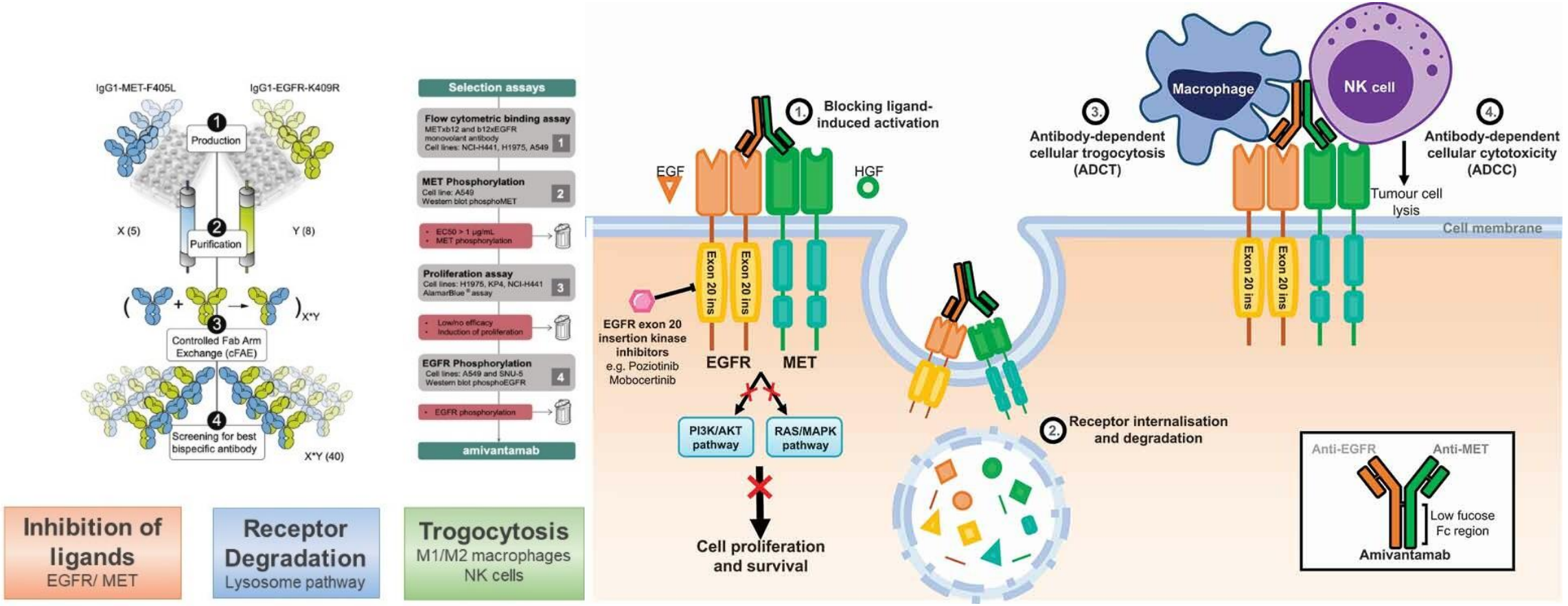


**CLN-081**

[1]Yang JC JTO 2020; [2]Le X et al, AACR 2020; [3]Veggel B et al, Ann Oncol 2018; [4]Piotrowska Z et al, ESMO 2020; [5]Zwierenga et al. ESMO 2021; [7]Zhou C et al, JAMA Onc 2021; [8]Park K et al, JCO 2021; [6]Wang et al, Can Disc 2022; [9]Yu et al ASCO 2022

# Amivantamab: *EGFR-MET* Bispecific Antibody

- Fully human ***EGFR-MET* bispecific antibody** with immune cell-directing activity
- Targets activating and resistance *EGFR* mutations and *MET* mutations and amplifications

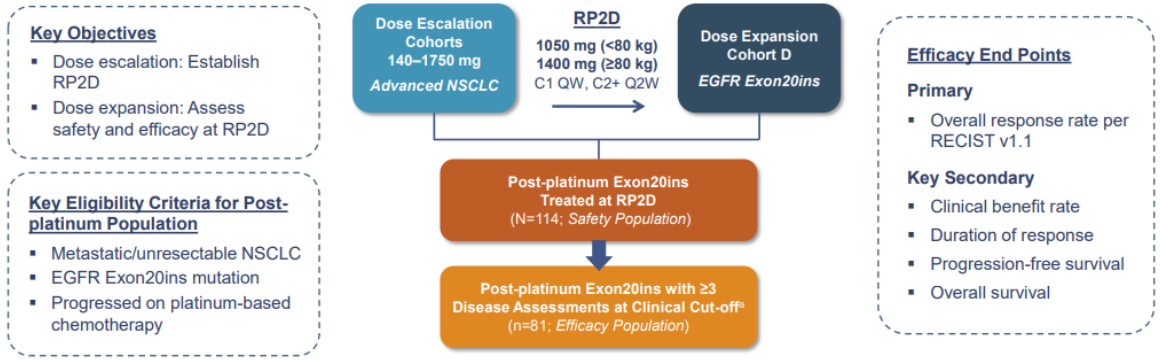




Neijssen J, et al. J Biol Chem. Jan-Jun 2021;296:100641.
Simon Vyse, et al. Expert Rev Anticancer Ther. 2022 Jan;22(1):3-16.

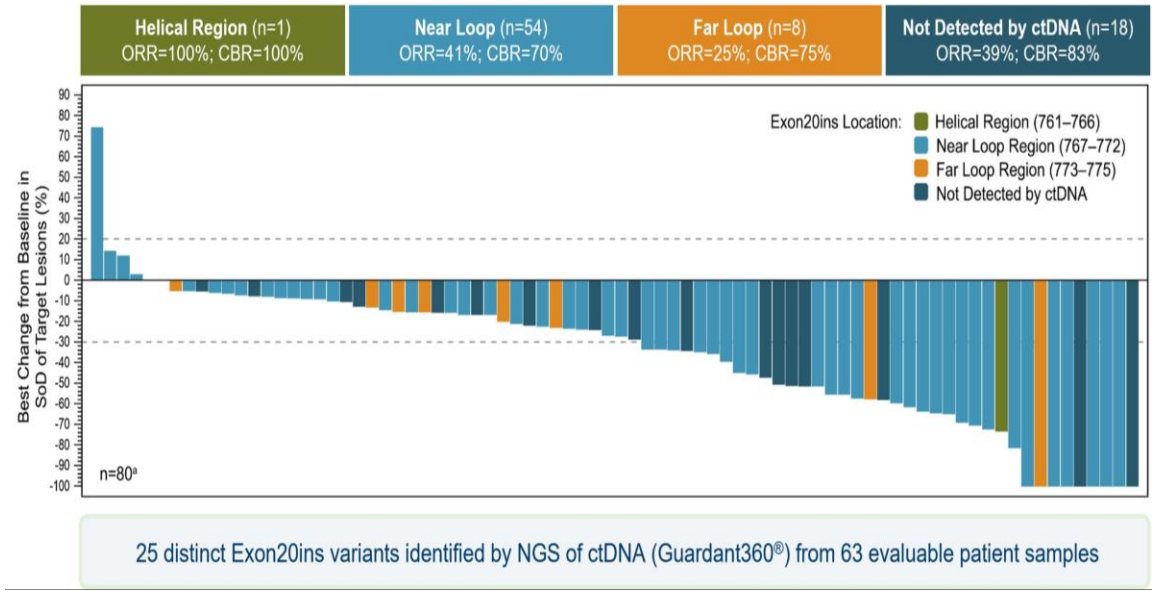
# CHRYSALIS: Amivantamab in Post-platinum Exon20ins Population

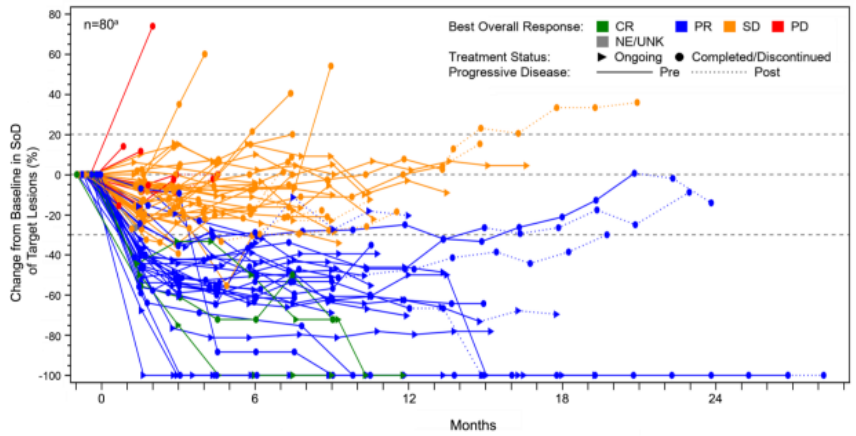
- Dose-escalation/expansion phase I trial of amivantamab, an *EGFR-MET* bispecific antibody




| BICR-assessed Response | Efficacy Population (n=81) |
|---|---|
| Overall response rate | **40%** (95% CI, 29–51) |
| Median duration of response | **11.1 months** (95% CI, 6.9–NR) |
| Best response, n (%) | |
| Complete response | 3 (4) |
| Partial response | 29 (36) |
| Stable disease | 39 (48) |
| Progressive disease | 8 (10) |
| Not evaluable | 1 (1) |
| Clinical benefit rate[a] | 74% (95% CI, 63–83) |

Median follow-up: 9.7 months (range, 1.1–29.3)





Sabari. WCLC 2020. Abstr OA04.04. NCT02609776.
Park K, et al. J Clin Oncol. 2021 Oct 20;39(30):3391-3402.

# CHRYSALIS: Adverse effects regardless of causality

| Adverse Event, n (%) | Safety Population (N=114) | |
|---|---|---|
| | Treatment-emergent AE | Treatment-related AE |
| Any AE | 113 (99) | 112 (98) |
| Grade ≥3 AE | 40 (35) | 18 (16) |
| Serious AE | 34 (30) | 10 (9) |
| AE leading to death | 8 (7) | 0 |
| AE leading to discontinuation | 11 (10) | 5 (4) |
| AE leading to dose reduction | 15 (13) | 15 (13) |
| AE leading to dose interruption[a] | 40 (35) | 24 (21) |

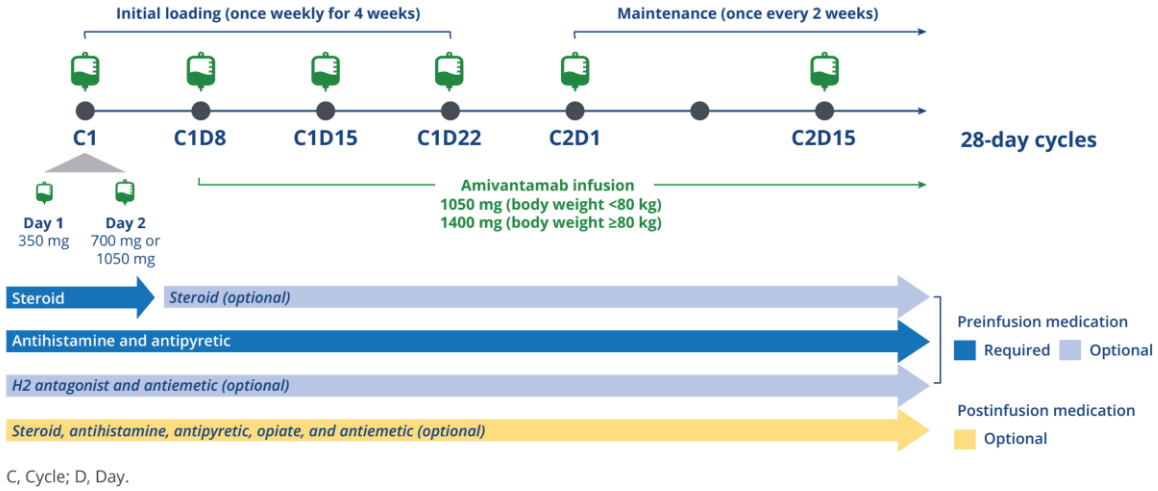
Safety profile consistent with inhibition of *EGFR* and *MET* pathways

- 2% discontinued due to rash
- 12% had diarrhea (10% treatment related)
  — 8.5% grade 1-2, 3.5% grade 3
- 94% of IRRs occurred with the first infusion and rarely impacted ability to continue with subsequent treatments

| | Safety Population (n = 114), No. (%) | | | |
|---|---|---|---|---|
| Most Common AE (≥ 10%) | Total | Grade 1 | Grade 2 | Grade ≥ 3 |
| Rash[b] | 98 (86) | 43 (38) | 51 (45) | 4 (4) |
| Infusion-related reaction | 75 (66) | 9 (8) | 63 (55) | 3 (3) |
| Paronychia | 51 (45) | 28 (25) | 22 (19) | 1 (1) |
| Hypoalbuminemia | 31 (27) | 6 (5) | 22 (19) | 3 (3) |
| Constipation | 27 (24) | 18 (16) | 9 (8) | 0 |
| Nausea | 22 (19) | 17 (15) | 5 (4) | 0 |
| Dyspnea | 22 (19) | 12 (11) | 8 (7) | 2 (2) |
| Stomatitis | 24 (21) | 11 (10) | 13 (11) | 0 |
| Peripheral edema | 21 (18) | 20 (18) | 1 (1) | 0 |
| Pruritus | 19 (17) | 11 (10) | 8 (7) | 0 |
| Fatigue | 21 (18) | 15 (13) | 4 (4) | 2 (2) |
| Cough | 16 (14) | 11 (10) | 5 (4) | 0 |
| Decreased appetite | 16 (14) | 7 (6) | 9 (8) | 0 |
| Dry skin | 18 (16) | 18 (16) | 0 | 0 |
| Increased alanine aminotransferase | 17 (15) | 15 (13) | 1 (1) | 1 (1) |
| Vomiting | 12 (11) | 10 (9) | 2 (2) | 0 |
| Myalgia | 14 (12) | 12 (11) | 2 (2) | 0 |
| Dizziness | 9 (8) | 8 (7) | 0 | 1 (1) |
| Headache | 8 (7) | 4 (4) | 3 (3) | 1 (1) |
| Increased blood alkaline phosphatase | 10 (9) | 8 (7) | 1 (1) | 1 (1) |
| Diarrhea | 14 (12) | 8 (7) | 2 (2) | 4 (4) |
| Back pain | 12 (11) | 6 (5) | 6 (5) | 0 |
| Pyrexia | 15 (13) | 12 (11) | 3 (3) | 0 |
| Hypokalemia | 12 (11) | 5 (4) | 1 (1) | 6 (5) |

Sabari. WCLC 2020. Abstr OA04.04. NCT02609776
Park K, et al. J Clin Oncol. 2021 Oct 20;39(30):3391-3402.

# Infusion related reaction of Amivantamab



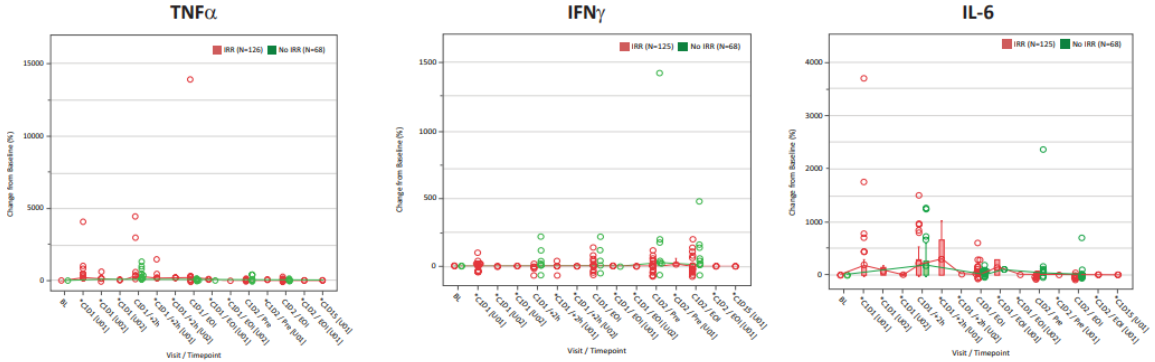

C, Cycle; D, Day.

## Table 2. Most Frequent Symptoms of IRR

| IRR Symptom (≥10%), n (%) | Total (N=380) |
|---|---|
| Chills | 94 (25) |
| Dyspnea | 86 (23) |
| Flushing | 68 (18) |
| Nausea | 69 (18) |
| Chest discomfort | 45 (12) |
| Vomiting | 39 (10) |

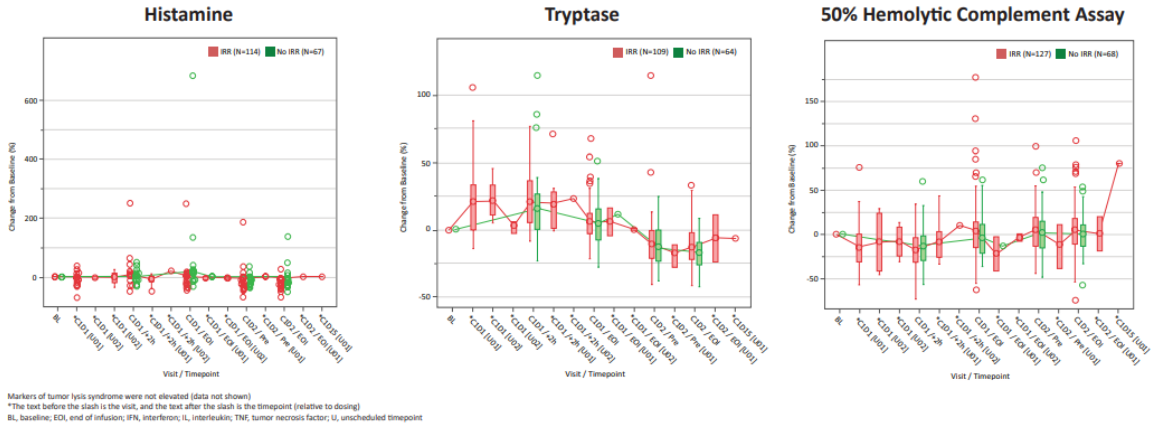
**Figure 4. Key Potential IRR Mechanisms**

*Cytokine Release Markers Not Associated with IRRs*




*Mast Cell Degranulation Markers Not Associated with IRRs*

*Complement Activity Not Increased with IRRs*

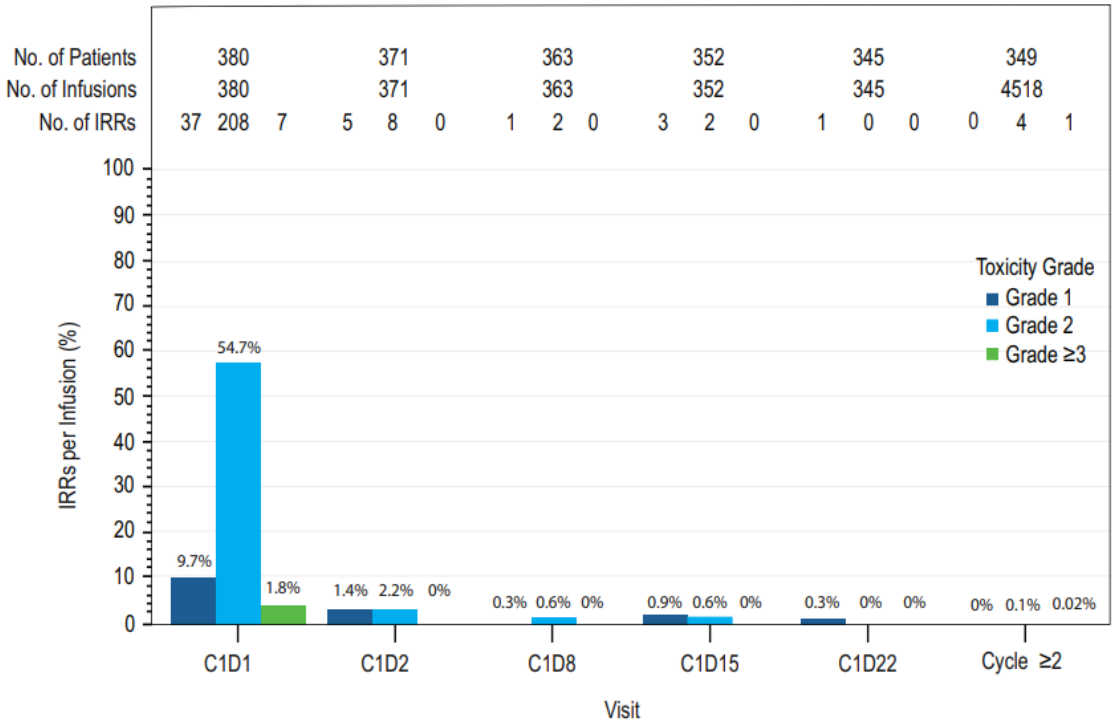



Markers of tumor lysis syndrome were not elevated (data not shown)
*The text before the slash is the visit, and the text after the slash is the timepoint (relative to dosing)
BL, baseline; EOI, end of infusion; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; U, unscheduled timepoint

Studies conducted on a subset of patients to understand the underlying mechanisms contributing to IRRs failed to distinguish a pattern between patients with and without IRR

Annals of Oncology (2021) 32 (suppl_5): S949-S1039. 10.1016/annonc/annonc729

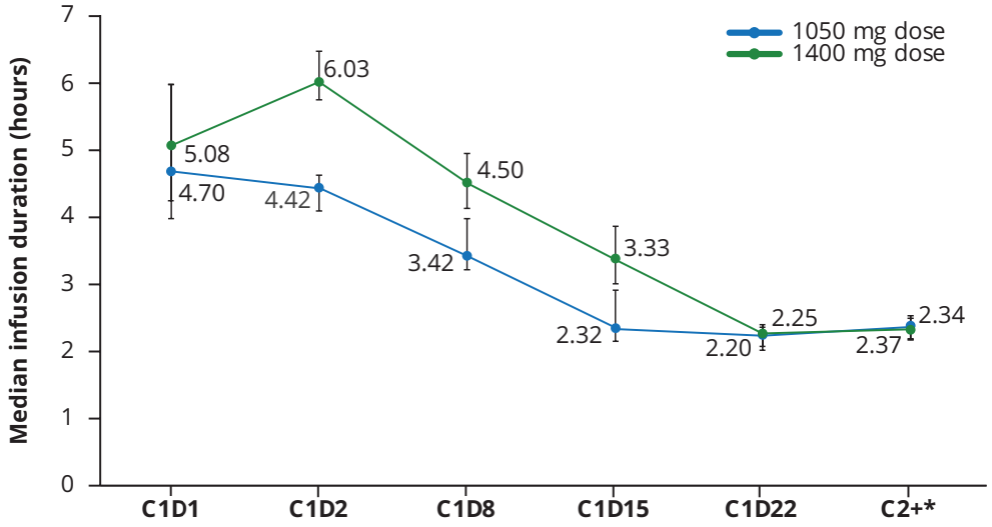
# Rates of IRRs by Amivantamab Infusion Cycle




IRR occurred early, with median time to onset of 45 mins;
98% of events occurred on C1D1, and only 5 events occurred past cycle 2.

The median infusion duration was 4.70 hours for the 1050 mg dose and 5.08 hours for the 1400 mg dose at C1D1, was 4.42 and 6.03 hours at C1D2, and decreased to 2.20 and 2.25 hours, respectively, by C1D22

Annals of Oncology (2021) 32 (suppl_5): S949-S1039. 10.1016/annonc/annonc729




| Duration of infusion (hours; 1050 mg dose) | | | | | | |
|---|---|---|---|---|---|---|
| Mean (SD) | 4.97 (1.623) | 4.39 (0.567) | 3.59 (0.642) | 2.51 (0.516) | 2.26 (0.318) | 2.50 (1.773) |
| Median | 4.70 | 4.42 | 3.42 | 2.32 | 2.20 | 2.37 |
| IQR | (4.25-6.00) | (4.10-4.63) | (3.23-4.00) | (2.17-2.93) | (2.08-2.37) | (2.20-2.50) |
| Range | (0.5-9.7) | (1.5-6.3) | (2.9-8.2) | (1.8-4.8) | (1.9-4.7) | (1.6-28.4) |

| Duration of infusion (hours; 1400 mg dose) | | | | | | |
|---|---|---|---|---|---|---|
| Mean (SD) | 4.80 (2.154) | 6.05 (0.742) | 4.58 (0.585) | 3.45 (0.585) | 2.37 (0.445) | 2.36 (0.234) |
| Median | 5.08 | 6.03 | 4.50 | 3.33 | 2.25 | 2.34 |
| IQR | (4.00-6.00) | (5.77-6.49) | (4.15-4.97) | (3.03-3.87) | (2.03-2.42) | (2.18-2.54) |
| Range | (0.5-9.7) | (4.0-8.0) | (3.0-6.1) | (2.1-5.0) | (1.9-3.9) | (2.0-3.0) |

C, Cycle; D, Day; IQR, interquartile range; SD, standard deviation.
Error bars indicate IQRs.
*For C2+, the maximum infusion duration was used per patient (as study patients may have received multiple infusions).

# Guidelines for Monitoring and Management of IRR

- **Diphenhydramine** 25 to 50mg (IV or Oral)
- **Acetaminophen** 650mg to 1000mg (IV or Oral)
- **Dexamethasone** 10mg or Methylprednisolone 40mg or equivalent IV

- Required at initial dose (Week 1, Day 1 and 2) : optional for subsequent doses

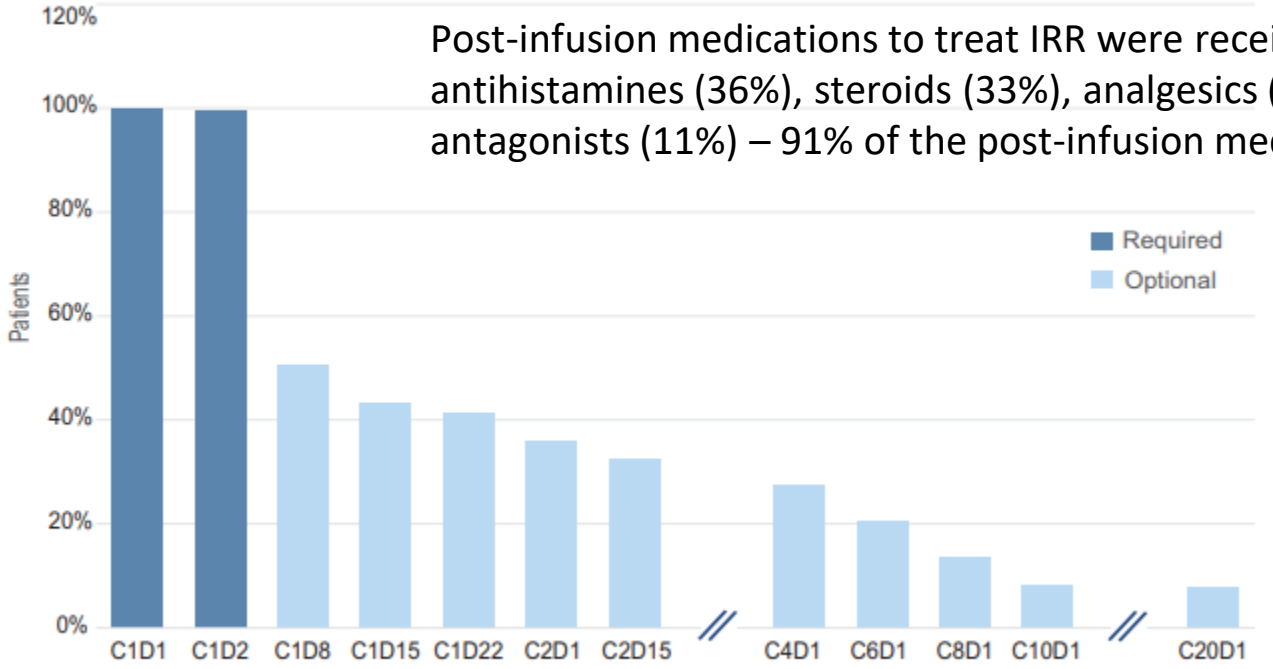
- During cycle 1, a peripheral line rather than a central line is recommended to allow for slower infusion of amivantamab thereby reducing risk of IRR; use of central line catheter was permitted at C2D1 and beyond in clinical trials

| Toxicity Grade | Treatment/Intervention | Premedication and Treatments at Subsequent Dosing |
|---|---|---|
| **General** | • Patients were informed of the symptoms of IRR and instructed to alert site staff as soon as they were experienced | |
| **Grade 1**<br>*Mild reaction* | • If occurring with initial dose, consider infusion interruption | • Antihistamine, antipyretic, and steroid |
| **Grade 2**<br>*Mild to moderate reaction* | • Interrupt infusion, monitor until symptoms recover<br>• 1st interruption: restart at 50% the rate<br>• 2nd interruption:<br>– Restart at 50% the rate at time of the 2nd interruption or consider discontinuation at that visit<br>– If no evidence of recurring IRR symptoms after 30 mins, rate can be increased to the prior rate<br>– Further rate escalation can resume after another 30 mins if no evidence of recurring signs and symptoms | • Antihistamine, antipyretic, and steroid<br>• Consider meperidine for chills and rigor |
| **Grade 3**<br>*Severe reaction* | • Stop infusion | • Based on the severity of symptoms, consider discontinution of treatment with amivantamab<br>• Discontinue treatment with amivantamab for recurrent Grade 3 IRR |
| **Grade 4**<br>*Life-threatening* | • Stop infusion | • Discontinue treatment with amivantamab |

Annals of Oncology (2021) 32 (suppl_5): S949-S1039. 10.1016/annonc/annonc729

# Infusion related reaction of Amivantamab

## Receipt of Pre-infusion Steroid Medications by Cycle




Early protocol amendment required steroid premedication with each amivantamab dose, which was reversed with subsequent protocol amendments when declining IRR risk was recognized

Post-infusion medications to treat IRR were received by 208 patients (55%) and included antihistamines (36%), steroids (33%), analgesics (21%), oxygen (12%), and histamine H2- receptor antagonists (11%) – 91% of the post-infusion medications were given on C1D1 and 5% on C1D2

**Table 3. Treatment Modifications Due to IRR**

| | Total (N=380) |
|---|---|
| Patients with IRR | 256 (67) |
| C1D1 infusion interrupted | 214 (56) |
| C1D1 infusion rate decreased | 202 (53) |
| C1D1 infusion not completed | 53 (14)* |
| Discontinued treatment | 4 (1) |

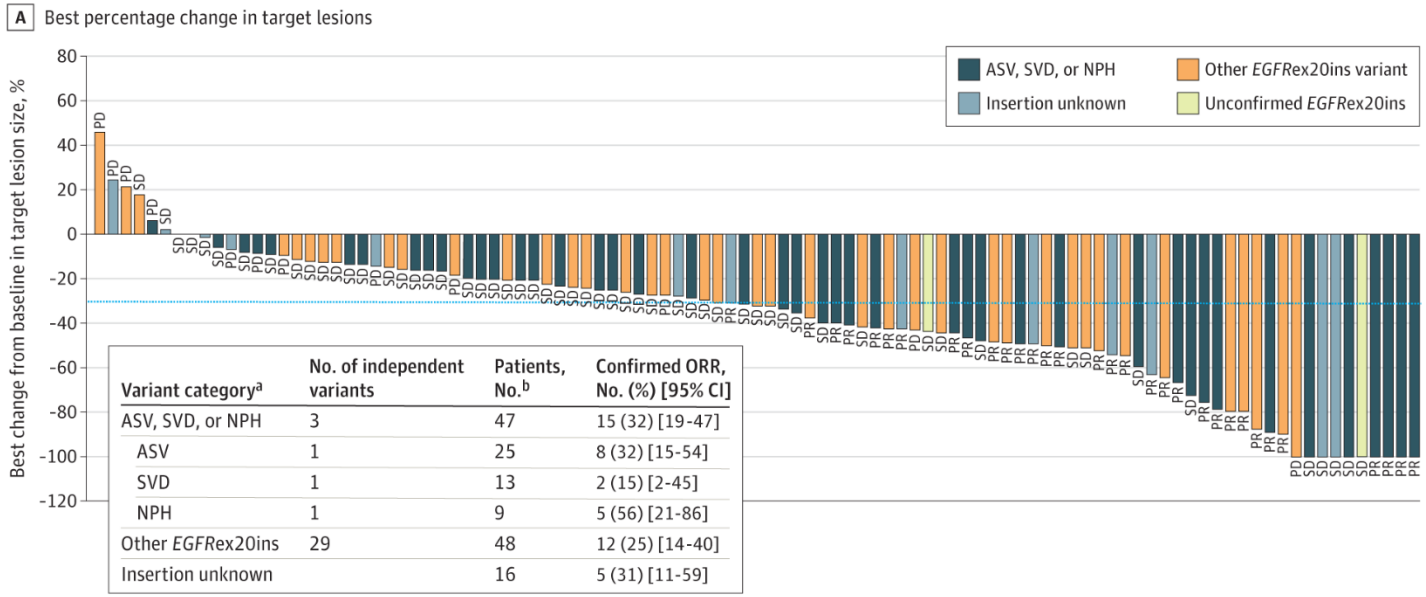
*Of the 53 patients who did not complete the C1D1 infusion, 45 went on to complete C1D2 infusions

While all patients received required pre-infusion steroids, 51% of patients received optional steroids on C1D8; optional steroid use decreased with subsequent cycles

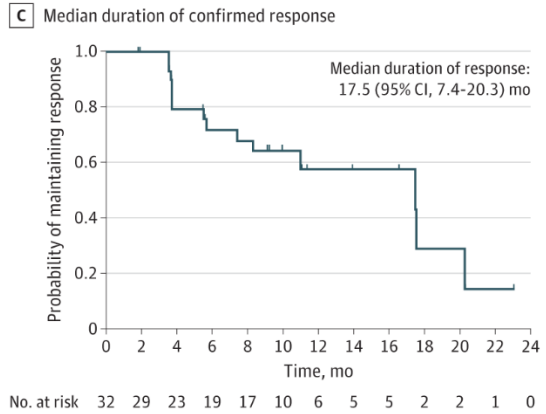
Annals of Oncology (2021) 32 (suppl_5): S949-S1039. 10.1016/annonc/annonc729

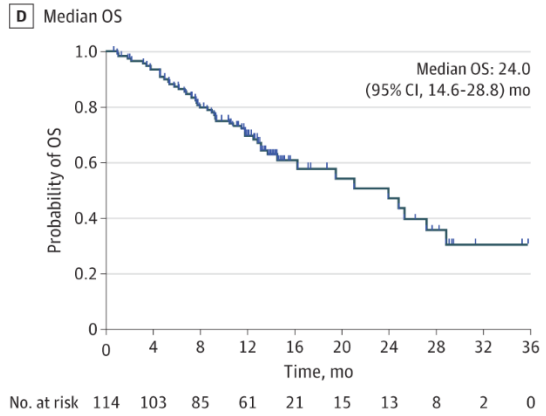
# Phase I/II Trial: Mobocertinib in Platinum-Pretreated *EGFR* Exon 20 Insertion Advanced NSCLC

- **Mobocertinib:** oral, first-in-class, irreversible *EGFR* TKI that targets *EGFR* ex20ins mutations




| Variant category[a] | No. of independent variants | Patients, No.[b] | Confirmed ORR, No. (%) [95% CI] |
|---|---|---|---|
| ASV, SVD, or NPH | 3 | 47 | 15 (32) [19-47] |
| ASV | 1 | 25 | 8 (32) [15-54] |
| SVD | 1 | 13 | 2 (15) [2-45] |
| NPH | 1 | 9 | 5 (56) [21-86] |
| Other *EGFR*ex20ins | 29 | 48 | 12 (25) [14-40] |
| Insertion unknown | | 16 | 5 (31) [11-59] |




96% pts had a reduction from baseline in the sum of target lesions;
Median time to response: 1.9months
Responses observed across all *EGFR* exon 20 insertion mutation subtypes

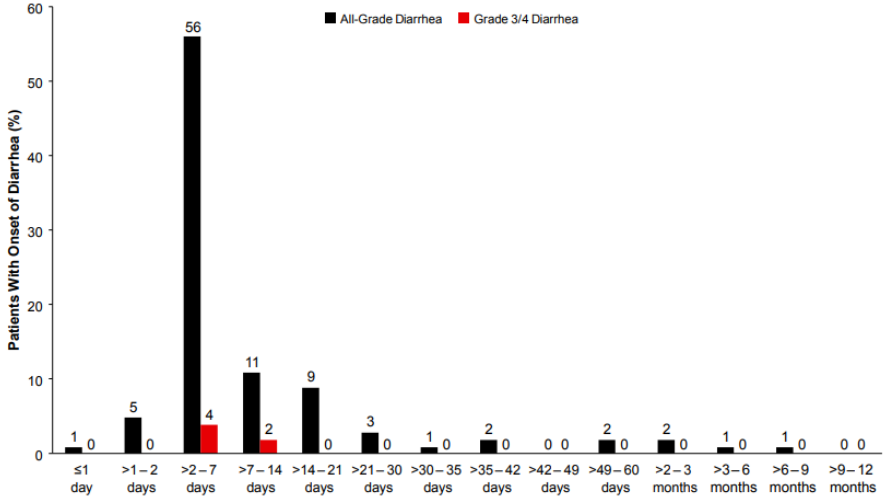
Zhou C. et al, JAMA Oncol. 2021;7:e214761.

# TRAEs With Mobocertinib in ≥20% of Patients

Table 3. Safety Overview and Treatment-Related Adverse Events (AEs) of Any Grade Reported in 10% or More or Grade 3 or Higher AEs Reported in 3% or More Among All Patients in the EXCLAIM and PPP Cohorts

| | Patients, No. (%) | | | |
|---|---|---|---|---|
| | PPP cohort (n = 114) | | EXCLAIM cohort (n = 96) | |
| Adverse event | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Overview of AEs | | | | |
| Any | 114 (100) | 79 (69) | 96 (100) | 63 (66) |
| Any treatment-related | 113 (99) | 54 (47) | 95 (99) | 40 (42) |
| Serious | 56 (49) | 52 (46) | 45 (47) | 42 (44) |
| Leading to dose reduction | 29 (25) | NA[a] | 21 (22) | NA[a] |
| Leading to treatment discontinuation | 19 (17) | NA[a] | 10 (10) | NA[a] |

Figure 2. Onset of Diarrhea Over Time in PPP Cohort




## Table 1. Summary of GI Treatment-Emergent Adverse Events (N=114)[a]

| GI AEs, n (%) | All-Grade | Grade 3 | Grade 4 | Serious | Led to Dose Reduction | Led to Discontinuation |
|---|---|---|---|---|---|---|
| Diarrhea | 106 (93) | 24 (21) | 1 (1) | 9 (8) | 12 (11) | 5 (4) |
| Nausea | 46 (40) | 5 (4) | 0 | 3 (3) | 6 (5) | 4 (4) |
| Vomiting | 47 (41) | 3 (3) | 0 | 6 (5) | 3 (3) | 2 (2) |

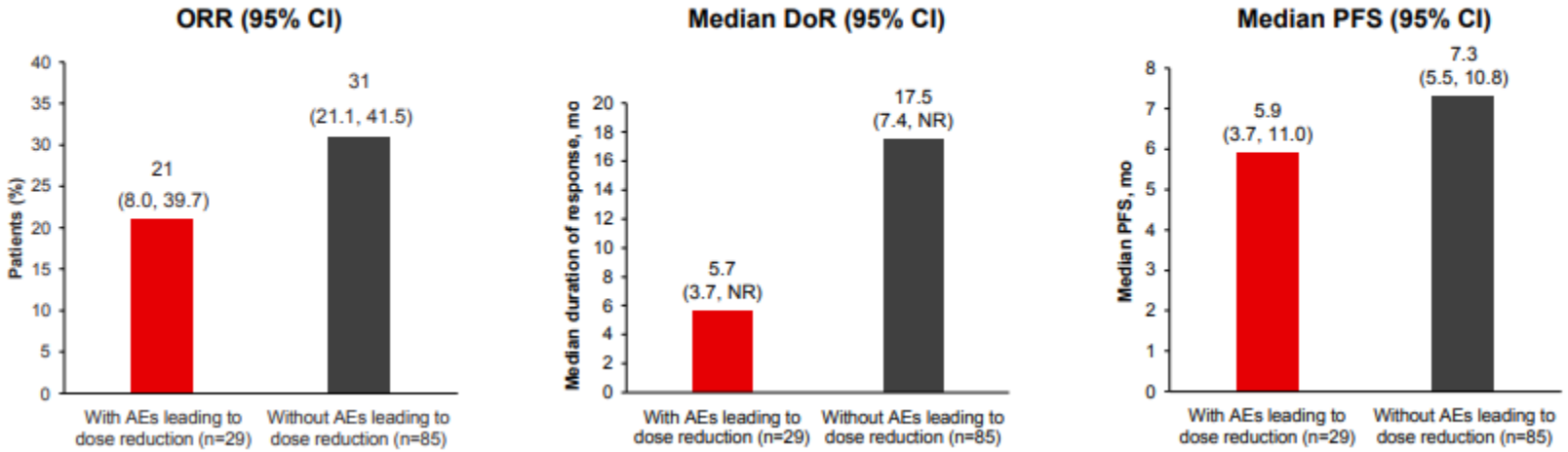
[a] Treatment-related GI AEs included diarrhea (all-Grade: 91%; Grade 3/4: 21%), nausea (all-Grade: 34%; Grade 3/4: 4%), and vomiting (all-Grade: 30%; Grade 3/4: 3%)

Diarrhea was managed with antidiarrheal medication in 74% of patients, most commonly loperamide-containing medications

Zhou C. et al, JAMA Oncol. 2021;7:e214761.
Nguyen D, et al. Annals of Oncology (2021) 32 (suppl_5): S949-S1039. 10.1016/annonc/annonc729

# Mobocertinib: Dose Reductions Due to Adverse Events

**Figure 6. Clinical Outcomes in Patients With and Without AEs Leading to Mobocertinib Dose Reductions in PPP Cohort (N=114)**




- AEs led to dose reductions in 25% of PPP (29/114) – GI toxicities were the most common AEs leading to dose reductions, including diarrhea in 11% of patients, nausea in 5%, and vomiting in 3%
- Efficacy outcomes were affected by dose reductions due to AEs, which were primarily due to GI toxicity

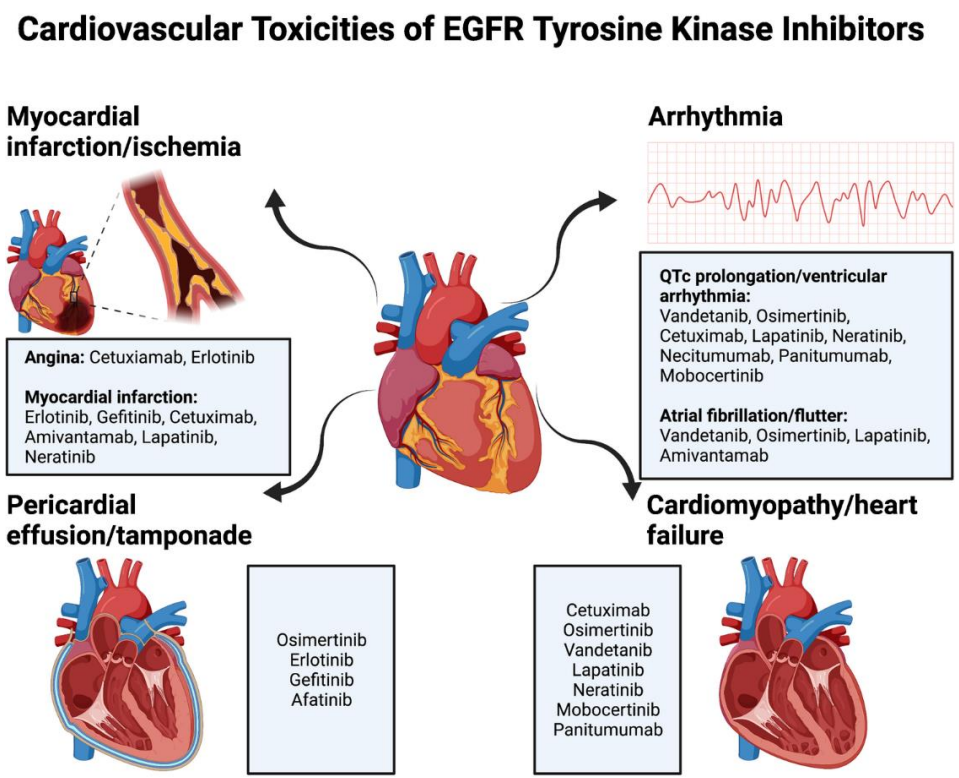
Nguyen D, et al. Annals of Oncology (2021) 32 (suppl_5): S949-S1039. 10.1016/annonc/annonc729

# Mobocertib: QTc prologation and Torsade de ointes

| Adverse Reaction | EXKIVITY (N = 114) | |
|---|---|---|
| | All Grades* (%) | Grade 3 or 4 (%) |
| **Cardiac Disorders** | | |
| QTc interval prolongation[k] | 10 | 3.5 |
| Hypertension[l] | 10 | 4.4** |

**WARNING: QTc PROLONGATION AND TORSADES DE POINTES**

- **EXKIVITY can cause life threatening heart rate-corrected QT (QTc) prolongation, including Torsades de Pointes, which can be fatal, and requires monitoring of QTc and electrolytes at baseline and periodically during treatment. Increase monitoring frequency in patients with risk factors for QTc prolongation *[see Warnings and Precautions (5.1)]*.**
- **Avoid use of concomitant drugs which are known to prolong the QTc interval and use of strong or moderate CYP3A inhibitors with EXKIVITY, which may further prolong the QTc *[see Warnings and Precautions (5.1), Drug Interactions (7.1, 7.3)]*.**
- **Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity of QTc prolongation *[see Dosage and Administration (2.3)]*.**




Ongoing phase III trials are evaluating the CV safety profile of mobocertinib

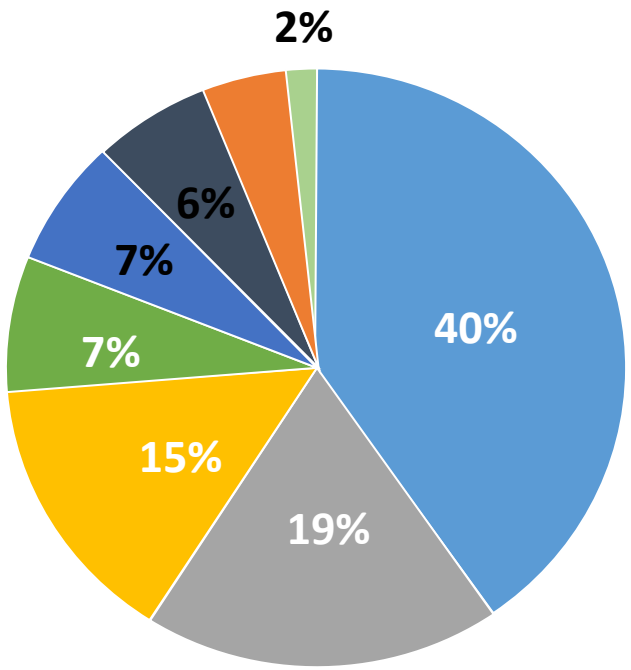
Mobocertinib PI

Chitturi KR, et al. Curr Oncol Rep. 2022 Apr;24(4):475-491.

# *KRAS* G12C Mutations

# *KRAS* mutations in advanced NSCLC

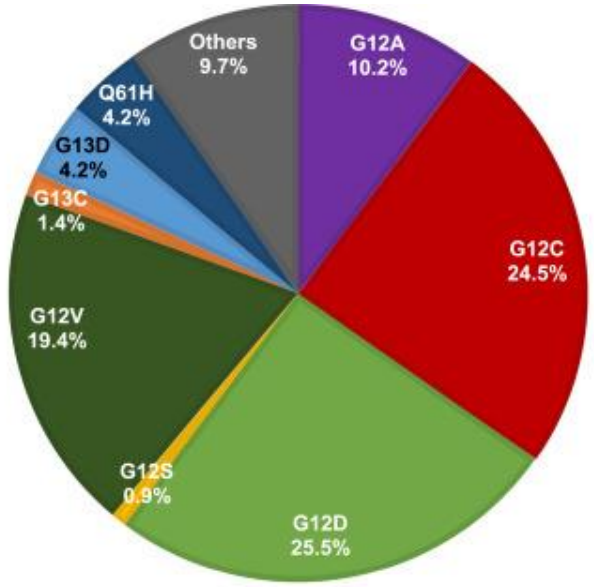
## Incidence of *KRAS* Mutation Variants in Advanced NSCLC




| *KRAS* Categories | N |
|---|---|
| G12C | 1882 |
| G12V | 915 |
| G12D | 684 |
| G13 Any | 327 |
| Q61 Any | 313 |
| G12A | 298 |
| G12 Other | 210 |
| Other | 77 |

- Most common oncogenic driver in NSCLC
- KRAS G12C most common variant
  - Comprise 40% of KRAS mutations overall
  - ~15% incidence in adenocarcinoma

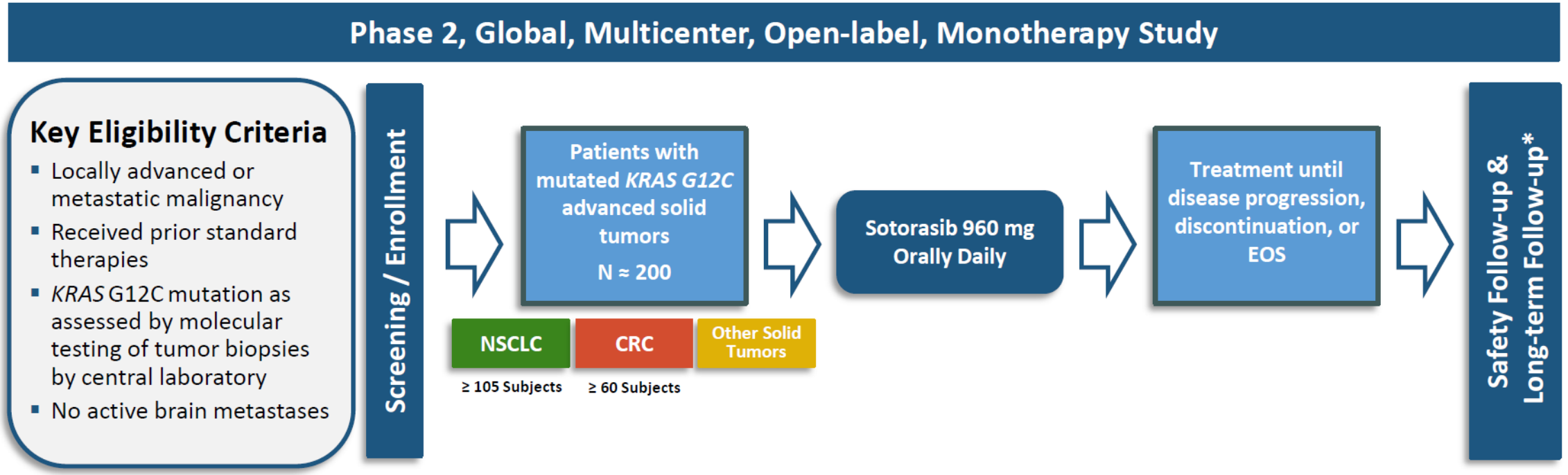
## Asia (Korea, Singapore, China, Japan, India)




| Subtypes | Frequency, N (%) Total population N = 216 (%) | Current/former smoker n = 142 (%) | Never smoker n = 74 (%) |
|---|---|---|---|
| G12D | 55 (25.5) | 22 (15.5) | 33 (44.6) |
| G12C | 53 (24.5) | 46 (32.4) | 7 (9.5) |
| G12V | 42 (19.4) | 27 (19.0) | 15 (20.3) |
| G12A | 22 (10.2) | 13 (9.2) | 9 (12.2) |
| G13D | 9 (4.2) | 9 (6.3) | 0 (0.0) |
| Q61H | 9 (4.2) | 4 (2.8) | 5 (6.8) |
| G13C | 3 (1.4) | 2 (1.4) | 1 (1.4) |
| G12S | 2 (0.9) | 1 (0.7) | 1 (1.4) |
| Others | 21 (9.7) | 18 (12.7) | 3 (4.1) |

Liu. ASCO 2020. Abstr 9544. Lee J, et al. JTO Clin Res Rep 2022;3(1):100261

# CodeBreaK100: Sotorasib in Pretreated Advanced *KRAS* G12C Mutation–Positive NSCLC



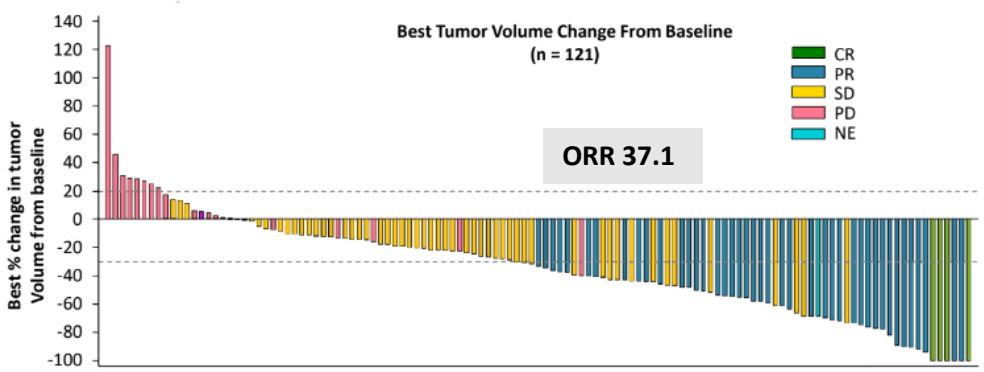

**Primary endpoint:** ORR†

**Secondary endpoints include:** DOR; DCR; TTR; PFS; OS; PK; Safety and Tolerability

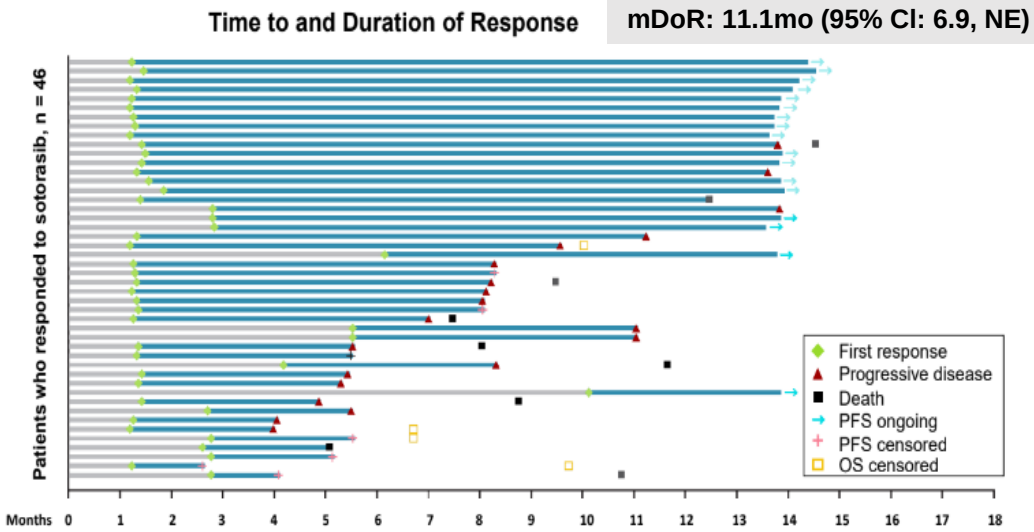
**Exploratory endpoints include**: PRO,‡ Biomarker Testing

Hong DS, et al. N Engl J Med. 2020;383:1207-1217. Supplementary material: Protocol.

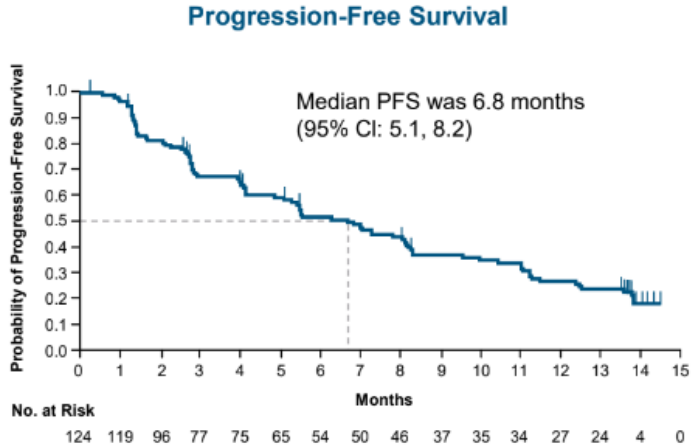
# CodeBreaK100: Sotorasib in Pretreated Advanced *KRAS* G12C Mutation–Positive NSCLC

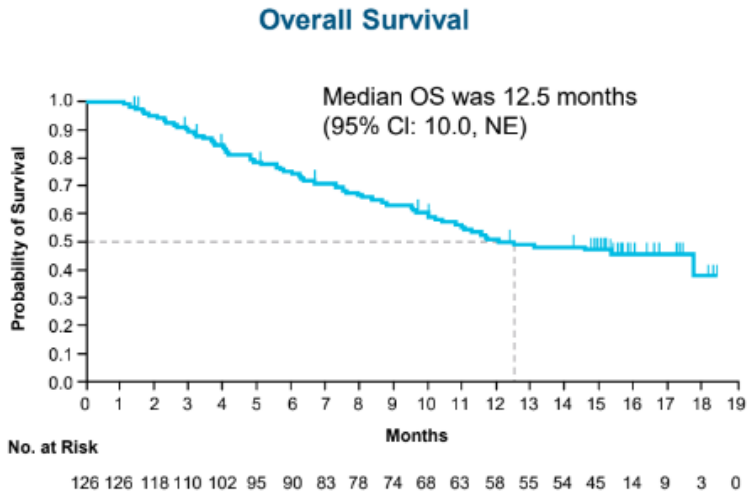



**ORR 37.1**



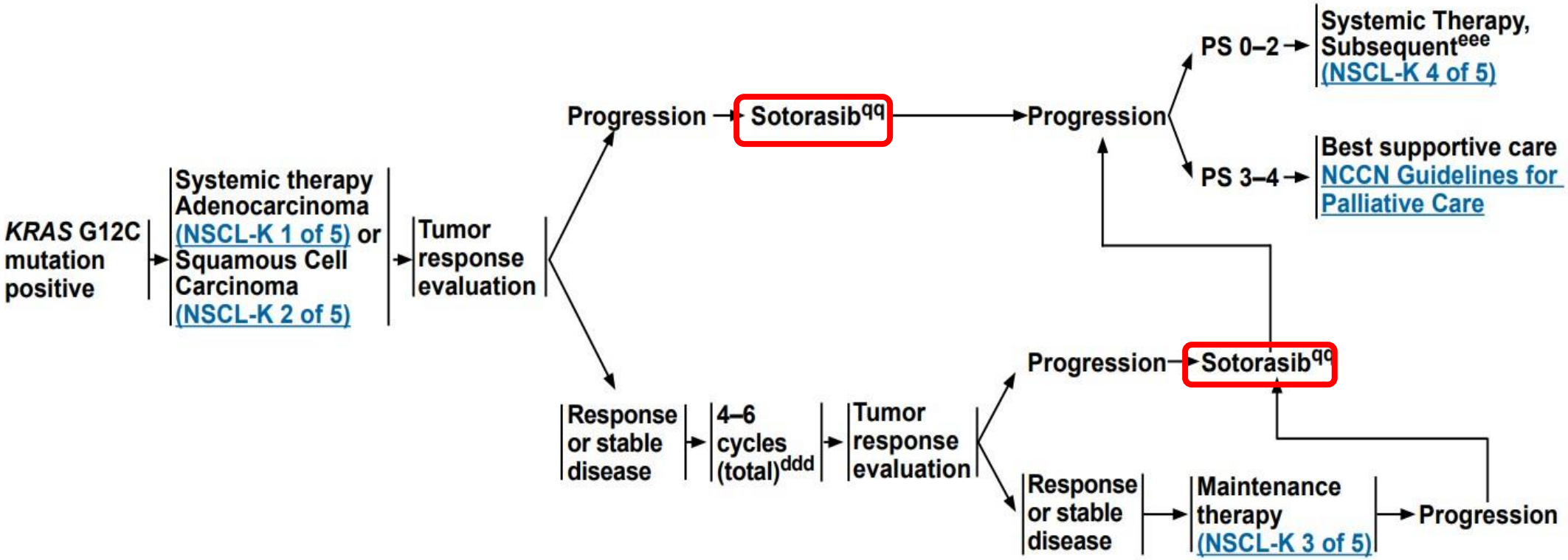

**mDoR: 11.1mo (95% CI: 6.9, NE)**




Skoulidis F, et al. N Engl J Med. 2021;384:2371-2381.

## *KRAS* G12C MUTATION POSITIVE[mm]



# Sotorasib: Treatment-related Adverse Events

**Table 3. Adverse Events.***

| Event | All Patients (N = 126) | | | | |
|---|---|---|---|---|---|
| | Any Grade | Grade 1 or 2 | Grade 3 | Grade 4 | Fatal |
| | *number of patients (percent)* | | | | |
| Adverse event | 125 (99.2) | 48 (38.1) | 53 (42.1) | 4 (3.2) | 20 (15.9) |
| Treatment-related adverse event | 88 (69.8) | 62 (49.2) | 25 (19.8) | 1 (0.8) | 0 |
| Treatment-related adverse event leading to dose modification | 28 (22.2) | 8 (6.3) | 20 (15.9) | 0 | 0 |
| Treatment-related adverse event leading to discontinuation of therapy | 9 (7.1) | 4 (3.2) | 4 (3.2) | 1 (0.8) | 0 |

**Table 1. Treatment-Related Adverse Events (TRAEs) in Patients with Advanced Solid Tumors Treated with Sotorasib at 960 mg QD (N = 357)**

| | Any grade, % | Grade ≥ 3, % |
|---|---|---|
| **Total TRAEs** | 57.7 | 14.6 |
| **TRAEs occurring in >5% of subjects** | | |
| Diarrhea | 22.4 | 3.4 |
| Nausea | 12.0 | 0.3 |
| AST increase | 11.2 | 3.6 |
| ALT increase | 10.9 | 4.5 |
| Fatigue | 8.1 | 0.6 |
| Vomiting | 5.6 | 0.3 |
| ALP increase | 5.3 | 0.6 |

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment related adverse event

**Table 3. Adverse Events.***

| Event | All Patients (N = 126) | | | | |
|---|---|---|---|---|---|
| | Any Grade | Grade 1 or 2 | Grade 3 | Grade 4 | Fatal |
| | *number of patients (percent)* | | | | |
| Treatment-related adverse event of any grade occurring in >5% of the patients or that was grade ≥3 | | | | | |
| 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 |

No fatal TRAEs occurred
TRAEs led to treatment dose interruption and/or reduction in 22.2% of patients
TRAEs led to treatment discontinuation in 7.1% of patients

LUMAKRAS™(Sotorasib). Full prescribing information 2021
Skoulidis F, et al.N Engl J Med. 2021;384:2371-2381

# Sotorasib: Treatment-related Adverse Events

*Gastrointestinal TRAEs, Time to First Onset†*

**Gastrointestinal disorders**
All grade median onset (n = 120):
**13 days (3.0–50.5)**
Grade 3 median onset (n = 13):
**37 days (12.0–51.0)**

**Diarrhea**
All grade median onset (n = 80):
**30 days (4.0–70.0)**
Grade 3 median onset (n = 12):
**40 days (20.5–52.5)**

**Nausea**
All grade median onset (n = 43):
**15 days (3.0–65.0)**
Grade 3 median onset (n = 1):
**12 days (NA)**

**Vomiting**
All grade median onset (n = 20):
**21 days (9.5–71.0)**
Grade 3 median onset (n = 1):
**11 days (NA)**

† Data is presented as: median (interquartile range)

- Treatment related diarrhea led to dose reduction or interruptions in 5.9% of overall patients, nausea in 2.5% and vomiting in 0.8%.
- There was one subject who discontinued sotorasib due to a GI related TRAE, which was attributed to vomiting.

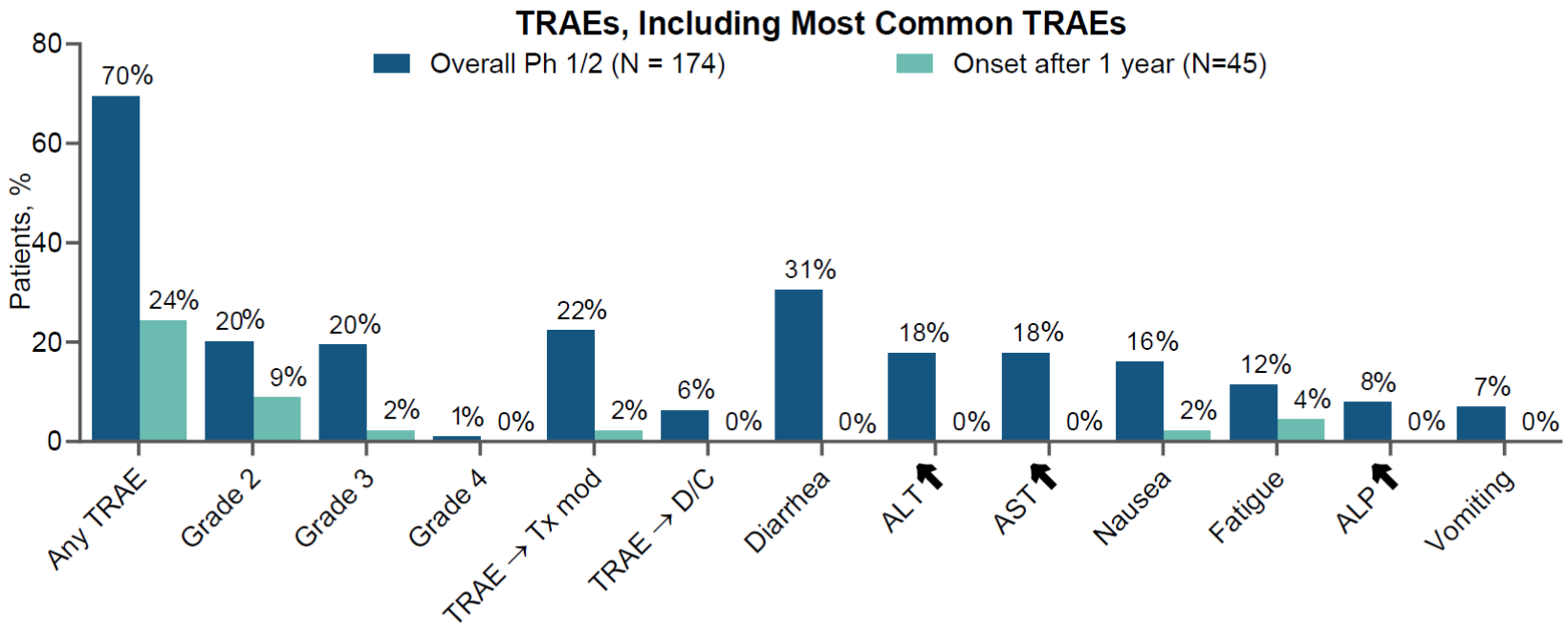
*Gastrointestinal TRAEs, Duration*

| | Subjects with event (%) | Resolved events/total events (resolution rate)^ | Median duration, days (IQR)†‡ |
|---|---|---|---|
| Gastrointestinal disorders | | | |
| All grade | 120 (33.6%) | 208/273 (76.2%) | 15.5 (4–44) |
| Grade ≥ 3 | 13 (3.6%) | 22/22 (100%) | 9.0 (6–20) |
| Diarrhea | | | |
| All grade | 80 (22.4%) | 102/126 (81%) | 20.0 (4–50) |
| Grade ≥ 3 | 12 (3.4%) | 19/19 (100%) | 8.5 (6–22) |
| Nausea | | | |
| All grade | 43 (12.0%) | 44/59 (74.6%) | 12.0 (3–26) |
| Grade ≥ 3 | 1 (0.3%) | 1/1 (100%) | 3.0 (NA) |
| Vomiting | | | |
| All grade | 20 (5.6%) | 24/27 (88.9%) | 2.5 (2–4) |
| Grade ≥ 3 | 1 (0.3%) | 1/1 (100%) | 2.0 (NA) |

^Resolution rates are based on event outcomes/end dates reported as of the data cutoff
† Data is presented as: median (interquartile range [IQR])
‡ Duration was estimated for subset of subjects with available TRAE resolution data

LUMAKRAS™(Sotorasib). Full prescribing information 2021
Hong DS, et al. N Engl J Med. 2020;383:1207-1217
https://ons.confex.com/ons/2022/industry/eposterview.cgi?eposterid=2239

# Sotorasib: Treatment-related Adverse Events




- Grade 3 or 4 TRAEs occurred in 21% of patients
  - One patient with new onset Grade 3 TRAE after 1 year (hemolytic anemia)
- No fatal TRAEs occurred
  - No TRAE leading to discontinuation after 1 year

**Well-tolerated in the long-term: late-onset TRAEs were mild and manageable**

Sotorasib PI.

Grace K. Dy, et al. Presented at American Association for Cancer Research (AACR) Annual Meeting, April 8-13, 2022; New Orleans.

# CodeBreaK 201 Study Schema:

## *Phase 2 study in First-Line advanced NSCLC – Sotorasib Monotherapy*

CodeBreaK 201

**Screening**

**Key Eligibility**

- Untreated stage IV NSCLC
- *KRAS* G12C mutation
- PD-L1 TPS score < 1% and/or *STK11* mutation
- ECOG ≤ 1
- No active brain metastases

**N = ~170**

**R**

**Sotorasib 240 mg once daily**

**Sotorasib 960 mg once daily**

**Stratified by:**
Known presence of *STK11* mutation

**Primary Endpoint**

**ORR**

**Key Secondary Endpoints:**

Disease control, DOR, TTR, PFS, OS, safety and toxicity, and PK parameters of sotorasib


※ 해당 이미지는 실제 알약의 크기가 아닙니다. 루마크라스®는 8정이 포함된 블리스터 30판 포장으로 제공됩니다(240정/상자(8정/PTPx30)).

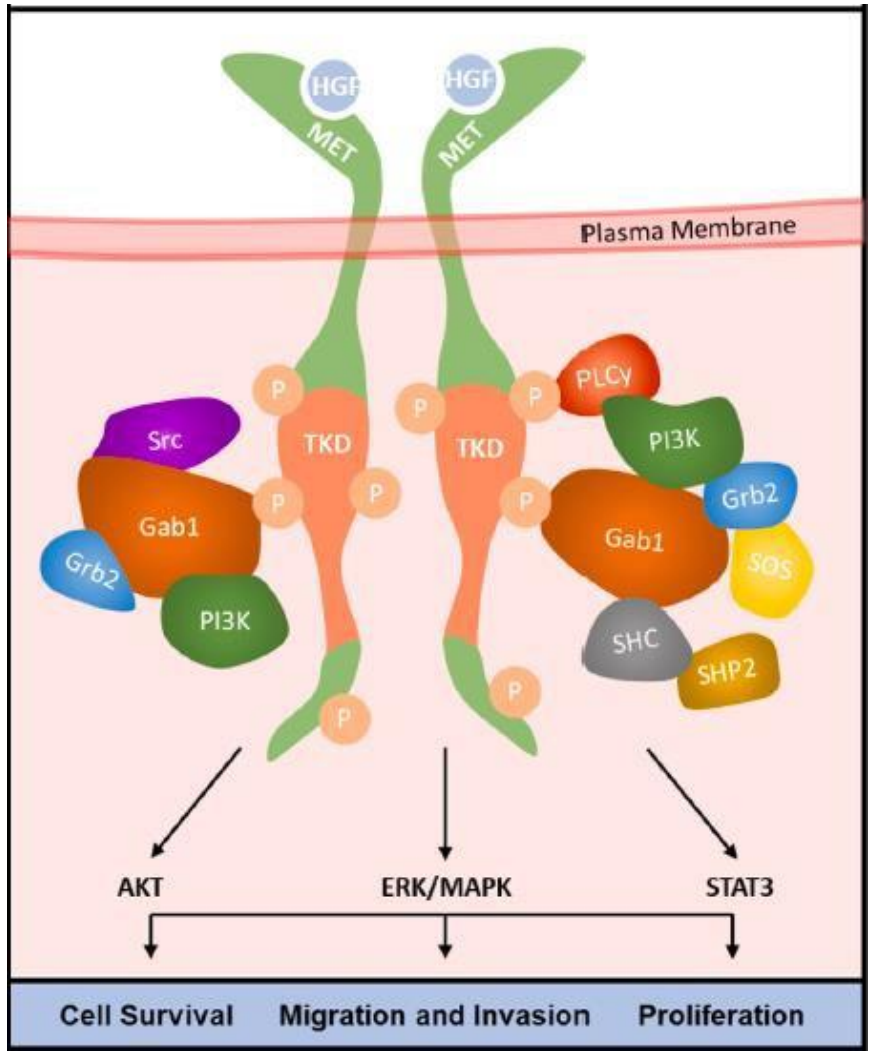
# *MET*ex14 skipping mutation

# *MET*ex14-Skipping Mutations in NSCLC

- HGF –only natural ligand –Dimerization

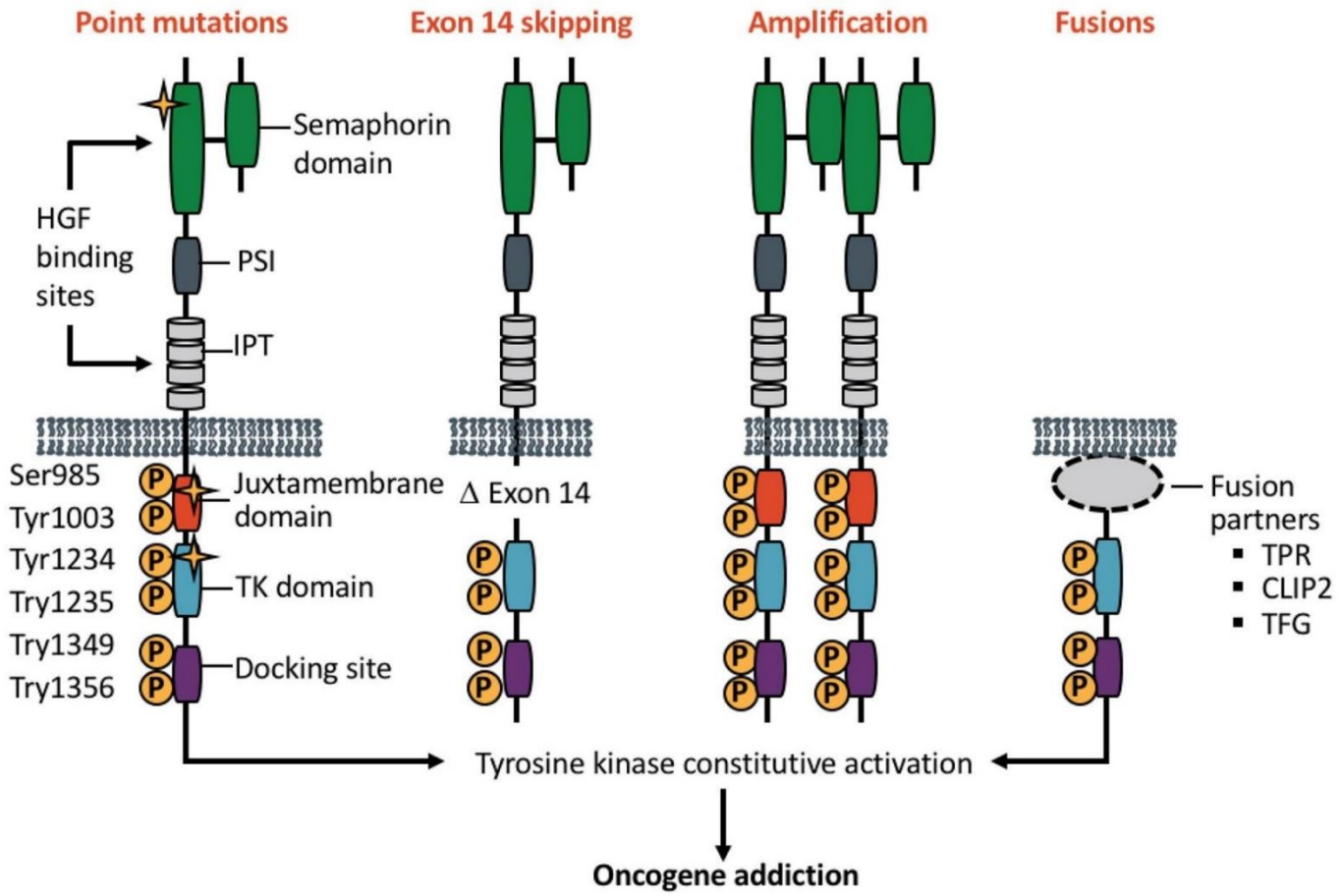
- Epithelial cells, Endothelial cells, neurons and hepatocytes.
- Normal role in embryogenesis and wound healing

- In cancer, METex14-skipping mutations cause in-frame deletion of juxtamembrane domain, resulting in increased stability and constitutive kinase activation
  - 3% to 4% of nonsquamous NSCLC
  - 20% to 30% of sarcomatoid cancers



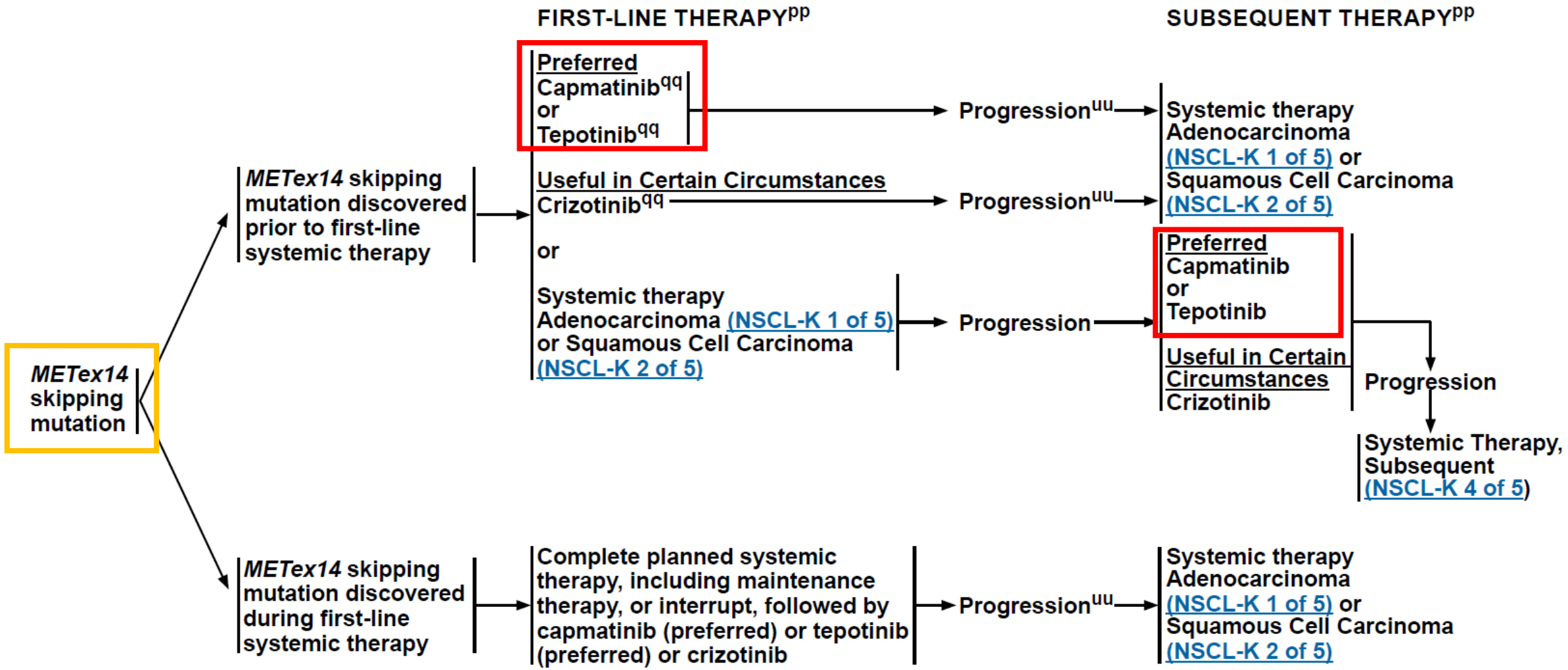

Drilon A et al. Clin Cancer Res. 2016;22:2832. Awad MM et al. JCO. 2016;34:721. Tong JH et al. Clin Cancer Res. 2016;22:3048. Coleman N et al. Lung Cancer. 2022 Feb;164:56-68

# Different mechanisms of aberrant MET activation and signaling : primary or secondary/co-driver



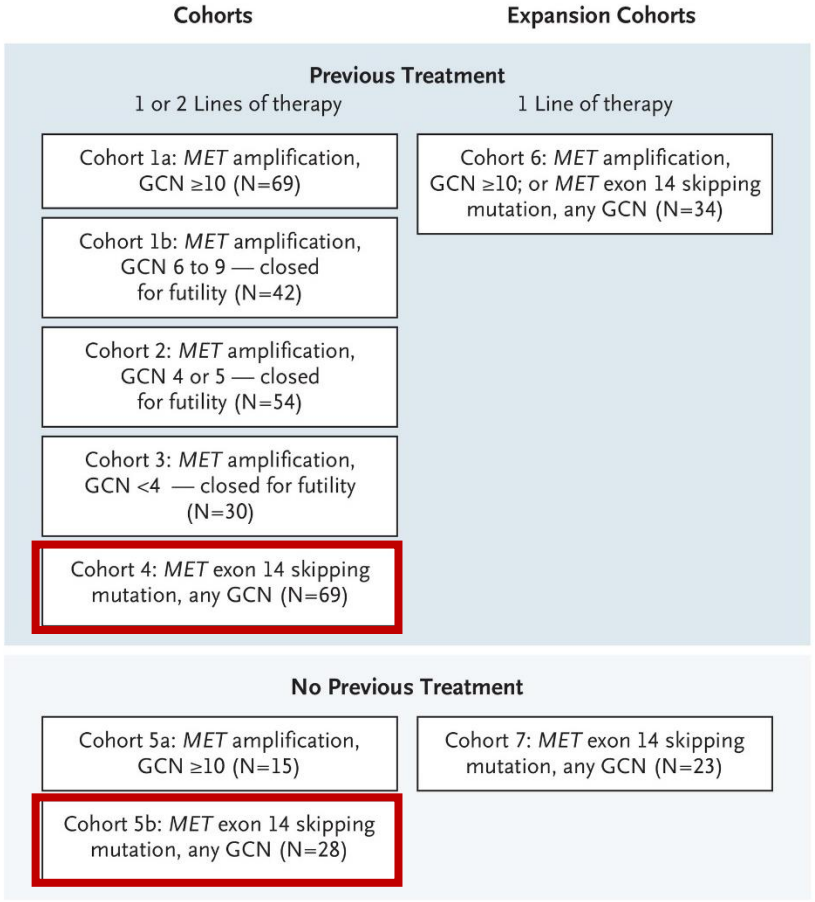

Coleman N. Lung Cancer. 2022 Feb;164:56-68

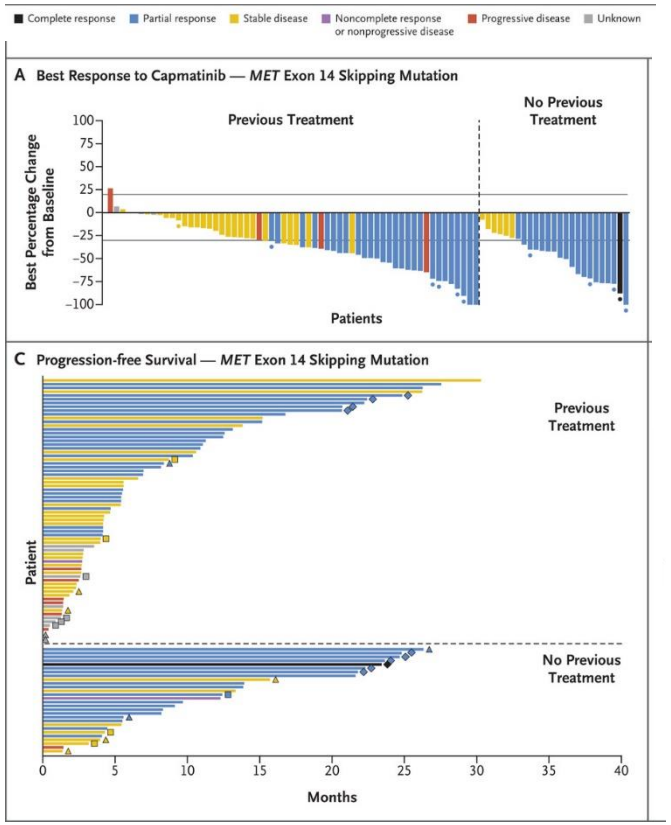
## *METex14* SKIPPING MUTATION[mm]

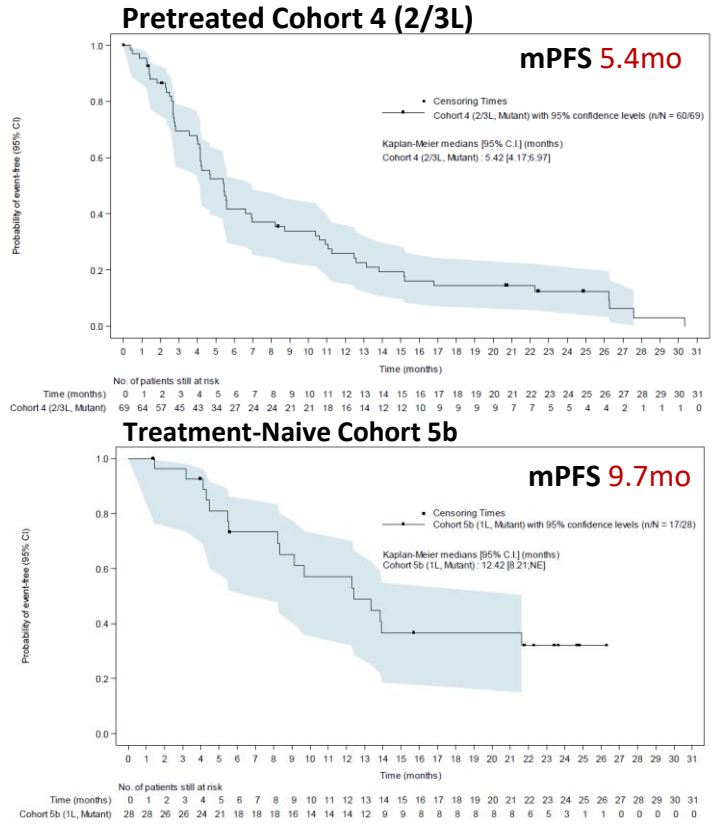


# GEOMETRY mono-1 (Capmatinib)
# MET Exon 14–Mutated or MET-Amplified NSCLC

- Multicenter, open-label, phase 2 trial evaluation the efficacy and safety of single agent capamatinib in adults




Wolf J et al. N Engl J Med. 2020 Sep 3;383(10):944-957

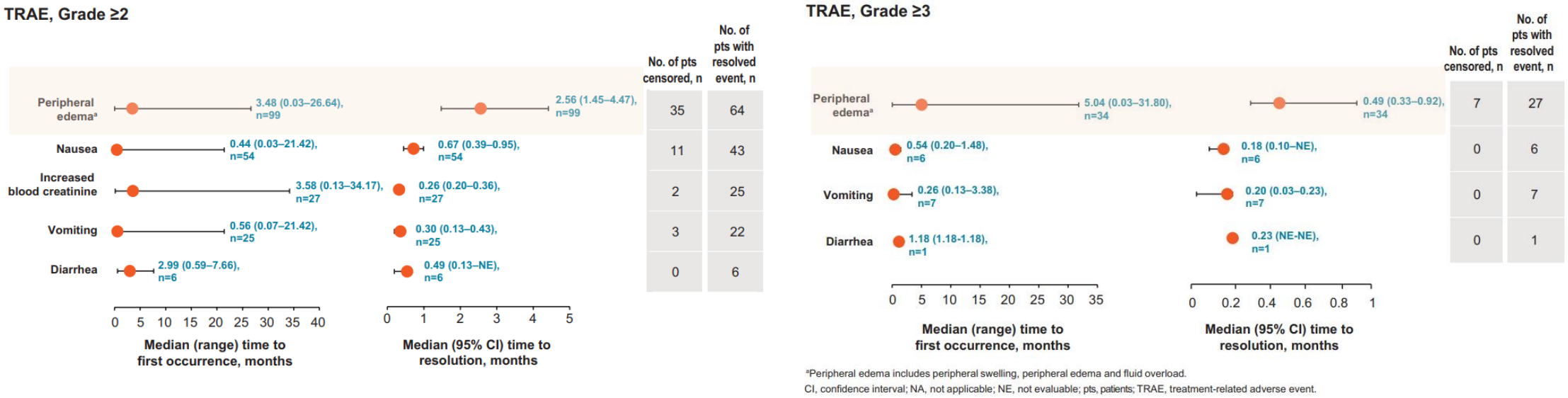
# GEOMETRY mono-1: AEs regardless of causality

| | Treatment-naive | | Pretreated | | | | All patients[a] | |
|---|---|---|---|---|---|---|---|---|
| | Cohort 5b N=28 | | Cohort 4 (2/3L) N=69 | | Cohort 6 (2L) N=31 | | N=373 | |
| | All grades | Grade 3/4 | All grades | Grade 3/4 | All grades | Grade 3/4 | All grades | Grade 3/4 |
| Any event, n (%) | 28 (100) | 21 (75.0) | 68 (98.6) | 52 (75.4) | 31 (100) | 18 (58.1) | 367 (98.4) | 256 (68.6) |
| Most common events, n (%) | | | | | | | | |
| Peripheral edema | 21 (75.0) | 3 (10.7) | 37 (53.6) | 10 (14.5) | 22 (71.0) | 4 (12.9) | 202 (54.2) | 36 (9.7) |
| Nausea | 13 (46.4) | 0 | 32 (46.4) | 0 | 10 (32.3) | 1 (3.2) | 168 (45.0) | 9 (2.4) |
| Vomiting | 7 (25.0) | 0 | 19 (27.5) | 0 | 8 (25.8) | 0 | 105 (28.2) | 9 (2.4) |
| Increased blood creatinine | 10 (35.7) | 0 | 23 (33.3) | 0 | 9 (29.0) | 0 | 99 (26.5) | 0 |
| Dyspnea | 6 (21.4) | 2 (7.1) | 19 (27.5) | 7 (10.1) | 3 (9.7) | 0 | 87 (23.3) | 25 (6.7) |
| Fatigue | 4 (14.3) | 1 (3.6) | 18 (26.1) | 6 (8.7) | 9 (29.0) | 0 | 83 (22.3) | 16 (4.3) |
| Decreased appetite | 8 (28.6) | 0 | 15 (21.7) | 1 (1.4) | 5 (16.1) | 0 | 79 (21.2) | 4 (1.1) |

[a]All patients with *MET*-dysregulated advanced NSCLC in the trial (includes *MET*ex14 and *MET* amplification)
2/3L, second-/third-line treatment; *MET*ex14, *MET* exon 14 skipping mutation; NSCLC, non-small cell lung cancer

Wolf J et al. J Clin Oncol 39, 2021 (suppl 15; abstr 9020)

# GEOMETRY mono-1: Time to first occurrence and duration of first occurrence of TRAE




[a]Peripheral edema includes peripheral swelling, peripheral edema and fluid overload.
CI, confidence interval; NA, not applicable; NE, not evaluable; pts, patients; TRAE, treatment-related adverse event.

- The median (range) time to first occurrence of Grade ≥2 symptoms was 3.48 (0.03–26.64; n=99) and 0.44 (0.03–21.42; n=54) months, respectively
- The median (range) time to occurrence of grade 3/4 symptoms was 5.04 (0.03–31.80; n=34) and 0.54 (0.20–1.48; n=6) months, respectively.
- The median (95% CI) time to resolution of first grade 3/4 symptoms (recovered/resolved or return to grade ≤2) of treatment-related peripheral edema and nausea was 0.49 (0.33, 0.92) and 0.18 (0.10, NE) months, respectively

Wolf J et al. Annals of Oncology (2021) 32 (suppl_5): S949-S1039. 10.1016/annonc/annonc729

# GEOMETRY mono-1: TRAEs leading to dose adjustment, dose interruption or permanent discontinuation

- TRAEs leading to permanent discontinuation were reported in 42 patients (11.3%).

- **Peripheral edema**
  dose adjustment in 9.7%
  dose interruptionin 10.5%
  permanent discontinuation in 2.1%

- In patients with brain metastasis at baseline,
  TRAEs led to dose adjustment in 5 patients (17.2%)
  dose interruption in 16 patients (55.2%)
  permanent discontinuation in 3 patients (10.3%).

Wolf J et al. Annals of Oncology (2021) 32 (suppl_5): S949-S1039. 10.1016/annonc/annonc729

# GEOMETRY mono-1: fatal AEs

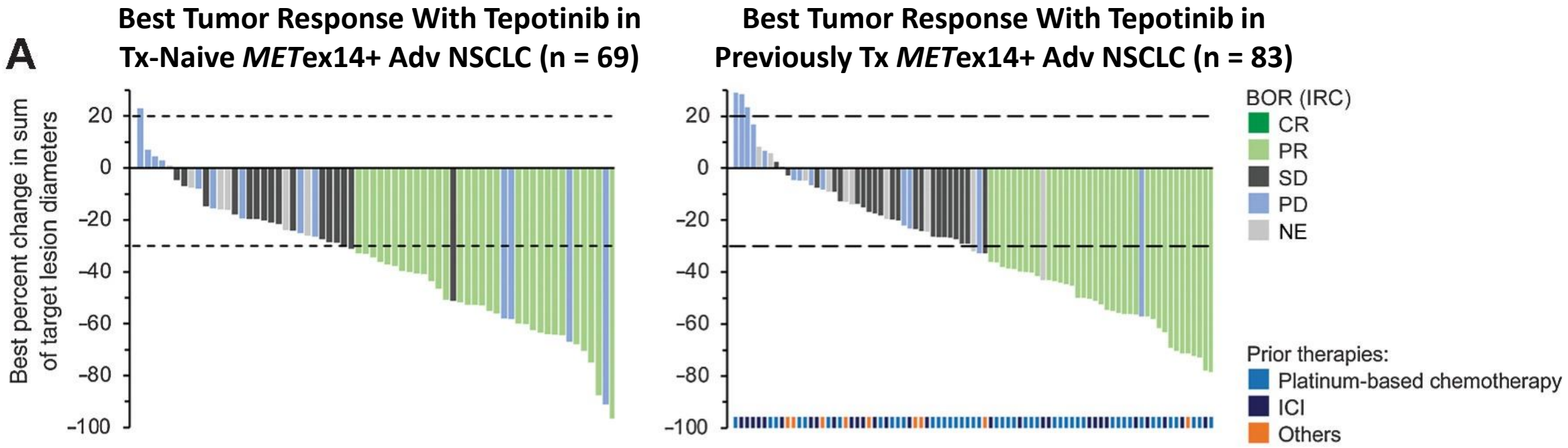
- Death from causes other than advanced NSCLC occurred during treatment in 14 patients (3.8%)

- Only 1 death (pneumonitis) was suspected to be related to capmatinib according to a review by the investigator and the medical review by the sponsor.

Wolf J et al. Annals of Oncology (2021) 32 (suppl_5): S949-S1039. 10.1016/annonc/annonc729

# VISION (NCT02864992)
# Tepotinib in advanced NSCLC harboring METex14 skipping

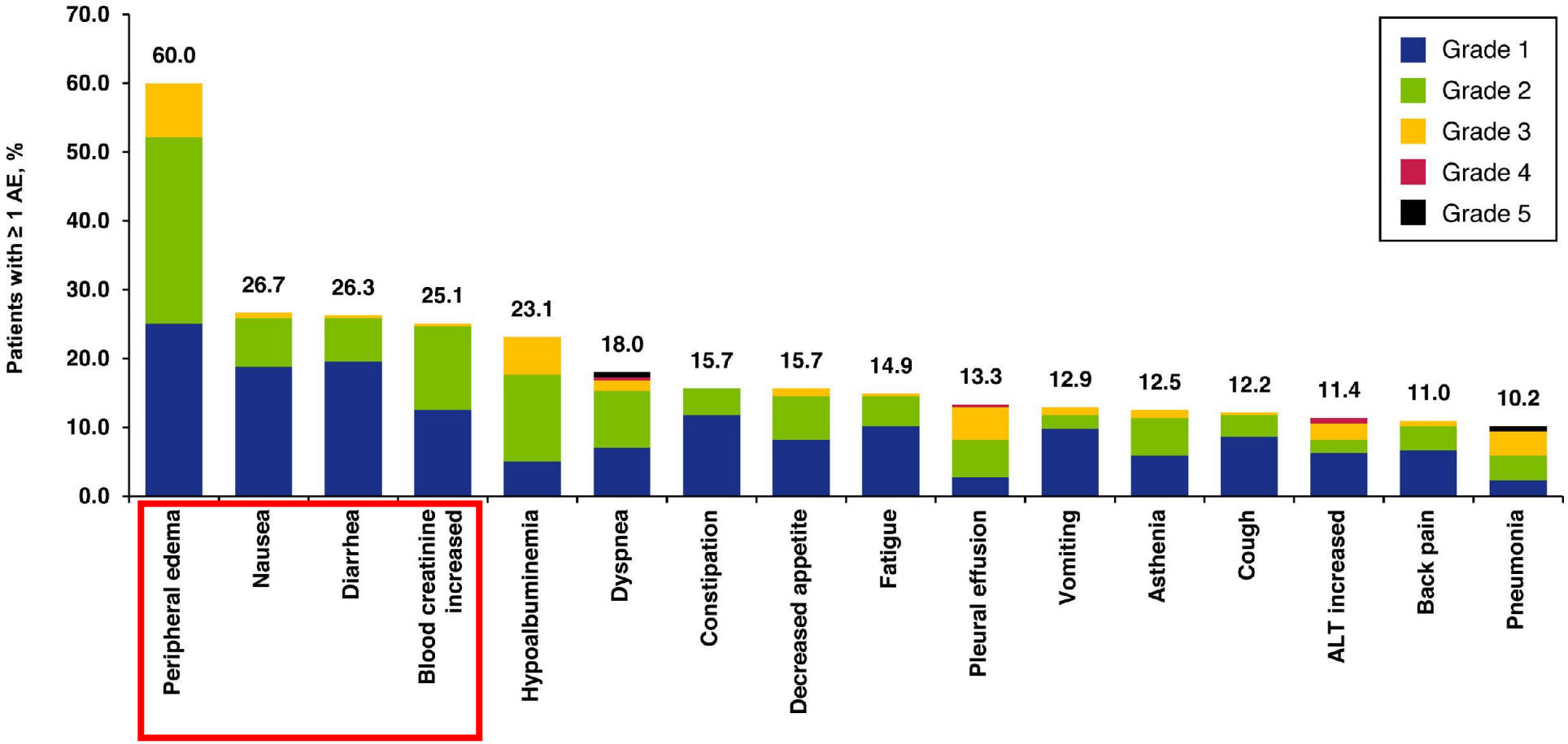
- Phase II, ***MET*ex14Δ** or ***de novo MET*amp**, **NGS** (**tissue**- Oncomine Focus Assay, **ctDNA**-Guardant360)
- ***MET*ex14Δ** : ORR 46%(IRC), 56%(IARR), mDoR 11.1m
- ORR 47%, molecular response 67%




Paik PK et al. N Engl J Med 2020;383:931-43

# Tepotinib

## Time to first onset and time to resolution of AEs of clinical interest




Veillon et al. 2022 Jun;23(4):320-332

# **Tepotinib:** Time to first onset and time to resolution of AEs of clinical interest

| | Patients, n | Total events, n | Events resolved, n | Time to first onset<br>Weeks since treatment initiation, median (range)<br>0 20 40 60 80 100 120 140 160 | Time to resolution<br>Weeks since onset of AE, median (range)<br>0 20 40 60 80 100 120 140 160 180 200 |
|---|---|---|---|---|---|
| Edema | 178 | 337 | 115 | 7.9 weeks (0.1–58.3) | Not described due to low proportion of resolved events |
| Hypo-albuminemia | 61 | 74 | 25 | 9.4 weeks (0.1–150.3) | Median not reached |
| Pleural effusion | 34 | 39 | 15 | 16.6 weeks (0.1–88.9) | 56.1 weeks (0.6–84.4+) |
| Creatinine increase | 66 | 96 | 67 | 3.1 weeks (0.1–78.4) | 12.1 weeks (0.4+–104.3) |
| Nausea | 68 | 87 | 67 | 4.0 weeks (0.1–89.0) | 5.9 weeks (0.1+–88.6+) |
| Diarrhea | 67 | 112 | 102 | 2.4 weeks (0.1–48.0) | 1.8 weeks (0.1–37.4) |
| Vomiting | 33 | 47 | 44 | 5.1 weeks (0.1–61.7) | 0.3 weeks (0.1–25.4) |
| ALT and/or AST increase | 31 | 56 | 46 | 6.1 weeks (0.1–34.0) | 5.0 weeks (0.1–31.1) |

Veillon et al. 2022 Jun;23(4):320-332

# TRAEs for METex14 Skipping Inhibitors in NSCLC

| | Tepotinib[21] N = 152% All-grade / ≥3 (Unless Stated) | Capmatinib[27] N = 151[a]% All-grade / ≥3 (Unless Stated) | Savolitinib[32] N = 70% All-grade / ≥3 (Unless Stated) | Crizotinib[36] N = 69% All-grade / ≥3 (Unless Stated) |
|---|---|---|---|---|
| AEs | 98 | 97/66 | 100/64 | |
| TRAEs | 89/28 | 88/46 | 100/46 | 94/29 |
| TRAEs Leading to Dose Reduction | 33/NR | NR | NR | 38/NR |
| TRAEs Leading to Discontinuation | 11/NR | 12/8 | 14/NR | 7/NR |
| Serious TRAEs | 15/NR | 15/13 | 24/14 | NR |
| Deaths (Related or Potentially Related to Treatment) | Respiratory failure and dyspnea | Pneumonitis | Tumor lysis syndrome | Interstitial lung disease |
| *Most Frequently Reported TRAEs in ≥ 10% of Patients* | | | | |
| TRAEs Presented in Original Publication | TRAEs in ≥5% Patients/Treatment | TRAEs in ≥10% Patients in Any Cohort | All-cause AEs in ≥25% Patients | TRAEs in ≥10% Patients |
| Peripheral Edema | 63/7 | 50/11 | 54/9 | 51/1[b,c] |
| Nausea | 26/1 | 36/1 | 46/0 | 41/0 |
| Diarrhea | 22/1 | 9/0 | NR | 39/0 |
| Increased Creatinine | 18/1 | 19/0 | NR | NR |
| Hypoalbuminemia | 16/2 | NR | 23/0 | NR |
| Increased Amylase | 11/3 | 8/4 | NR | NR |
| Increased Lipase | 9/3 | 9/7 | NR | NR |
| Decreased Appetite | 8/1 | 13/1 | 20/0 | 19/0 |
| Fatigue | 7/1 | 13/3 | NR | 23/0 |
| Increased AST | 7/2 | 6/3 | 37/13 | 17/4[b,d] |
| Increased ALT | 7/3 | 11/7 | 39/10 | 17/4[b,d] |
| Vomiting | 6/0 | 17/1 | 26/0 | 29/0 |

Cortot et al. Clin Lung Cancer . 2022 May;23(3):195-207

# Peripheral Edema in METex14 Skipping Inhibitors

- Across the studies reviewed here, peripheral edema was the most reported TRAE (50%-63% patients [grade ≥3: 1%-11%]).

- Prophylactic measures, such as support stockings, bed elevation, and reduction in dietary salt intake, should be considered, along with lymphedema massage.

- *MET* TKI dose reduction, interruption or intermittent dosing schedules should be considered; data from patients with dose reductions of tepotinib show that they remained on treatment for prolonged periods.

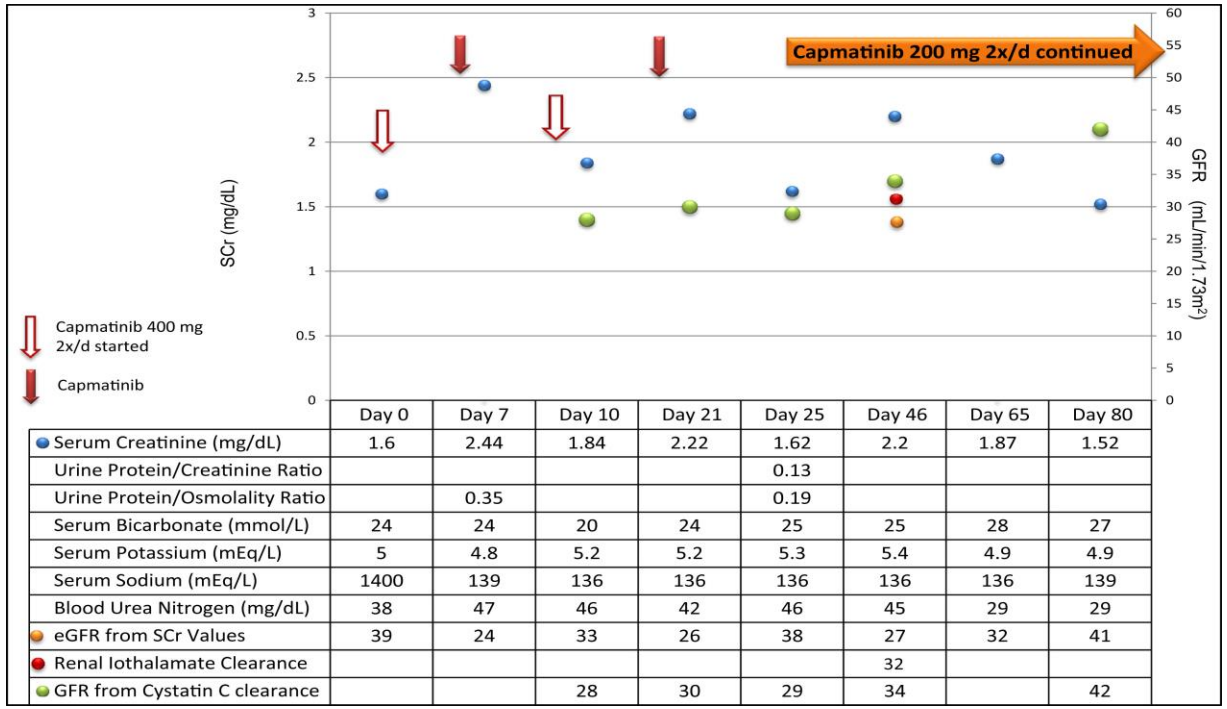
Cortot et al. Clin Lung Cancer . 2022 May;23(3):195-207
Coodwin et al. Journal of Thoracic Oncology; 2021 Supplement, Vol. 16 Issue 1, pS16-S17, 2p

# GI disturbances in METex14 Skipping Inhibitors

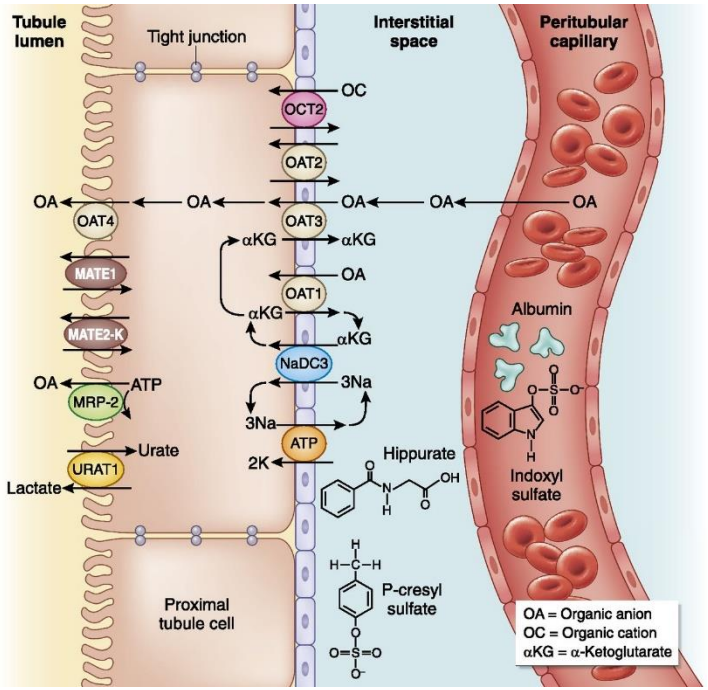
- Of the 177 patients in GEOMETRY mono-1 who experienced nausea and/or vomiting, 21.5% received an antiemetic as management.
- Nausea or vomiting could occur acutely (within 30 minutes to 2 hours after dosing) or at any time throughout the day.
- Ondansetron, granisetron, and prochlorperazine were the most commonly (≥5%) administered antiemetics.
- Some other patients experienced reduced vomiting after reducing capmatinib dosage to 300 mg twice daily

Goodwin K et al. Journal of Thoracic Oncology; 2021 Supplement, Vol. 16 Issue 1, pS16-S17, 2p

# Increased blood creatinine in METex14 Skipping Inhibitors




| | Day 0 | Day 7 | Day 10 | Day 21 | Day 25 | Day 46 | Day 65 | Day 80 |
|---|---|---|---|---|---|---|---|---|
| Serum Creatinine (mg/dL) | 1.6 | 2.44 | 1.84 | 2.22 | 1.62 | 2.2 | 1.87 | 1.52 |
| Urine Protein/Creatinine Ratio | | | | | 0.13 | | | |
| Urine Protein/Osmolality Ratio | | 0.35 | | | 0.19 | | | |
| Serum Bicarbonate (mmol/L) | 24 | 24 | 20 | 24 | 25 | 25 | 28 | 27 |
| Serum Potassium (mEq/L) | 5 | 4.8 | 5.2 | 5.2 | 5.3 | 5.4 | 4.9 | 4.9 |
| Serum Sodium (mEq/L) | 1400 | 139 | 136 | 136 | 136 | 136 | 136 | 139 |
| Blood Urea Nitrogen (mg/dL) | 38 | 47 | 46 | 42 | 46 | 45 | 29 | 29 |
| eGFR from SCr Values | 39 | 24 | 33 | 26 | 38 | 27 | 32 | 41 |
| Renal Iothalamate Clearance | | | | | | 32 | | |
| GFR from Cystatin C clearance | | | 28 | 30 | 29 | 34 | | 42 |

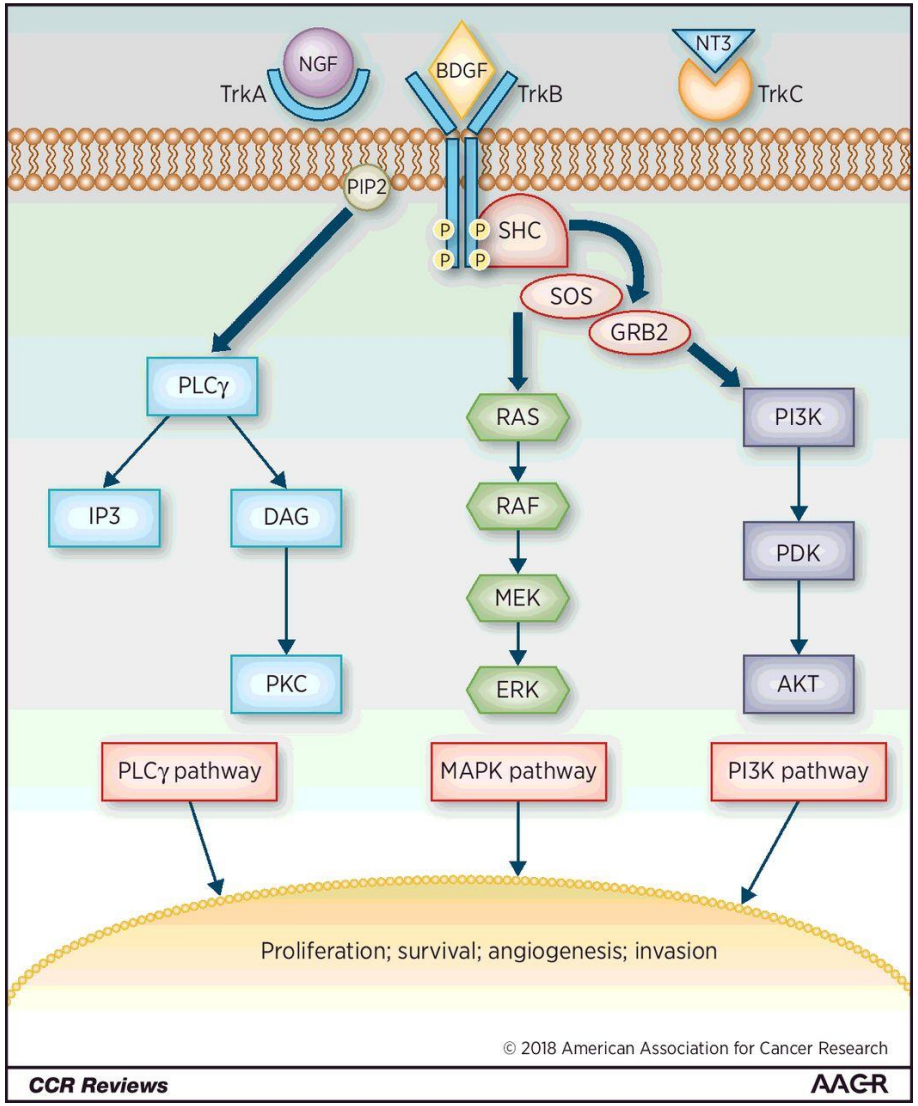


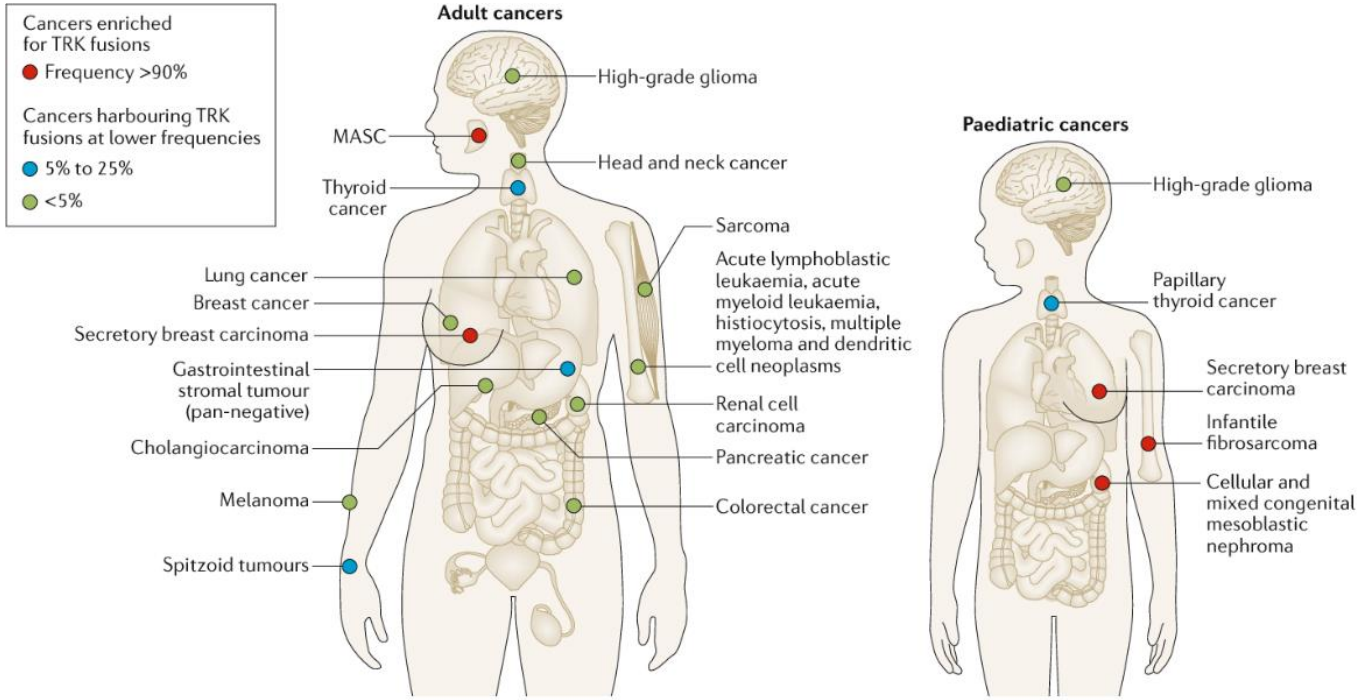

- *MET* TKIs are known to inhibit creatinine transporters, causing creatinine levels to rise by approximately 20% to 25%
- Increased blood creatinine is likely due to renal transporter (MATE1 and MATE2K) inhibition.
- Alternative markers for measuring GFR can help determine whether creatinine elevation in fact reflects renal impairment.


Mohan A, Am J Kidney Dis. 2022 Jan;79(1):120-124.
Cortot A et al. Clin Lung Cancer. 2022 May;23(3):195-207.

# *NTRK*

# *NTRK* gene fusion and TRK activation

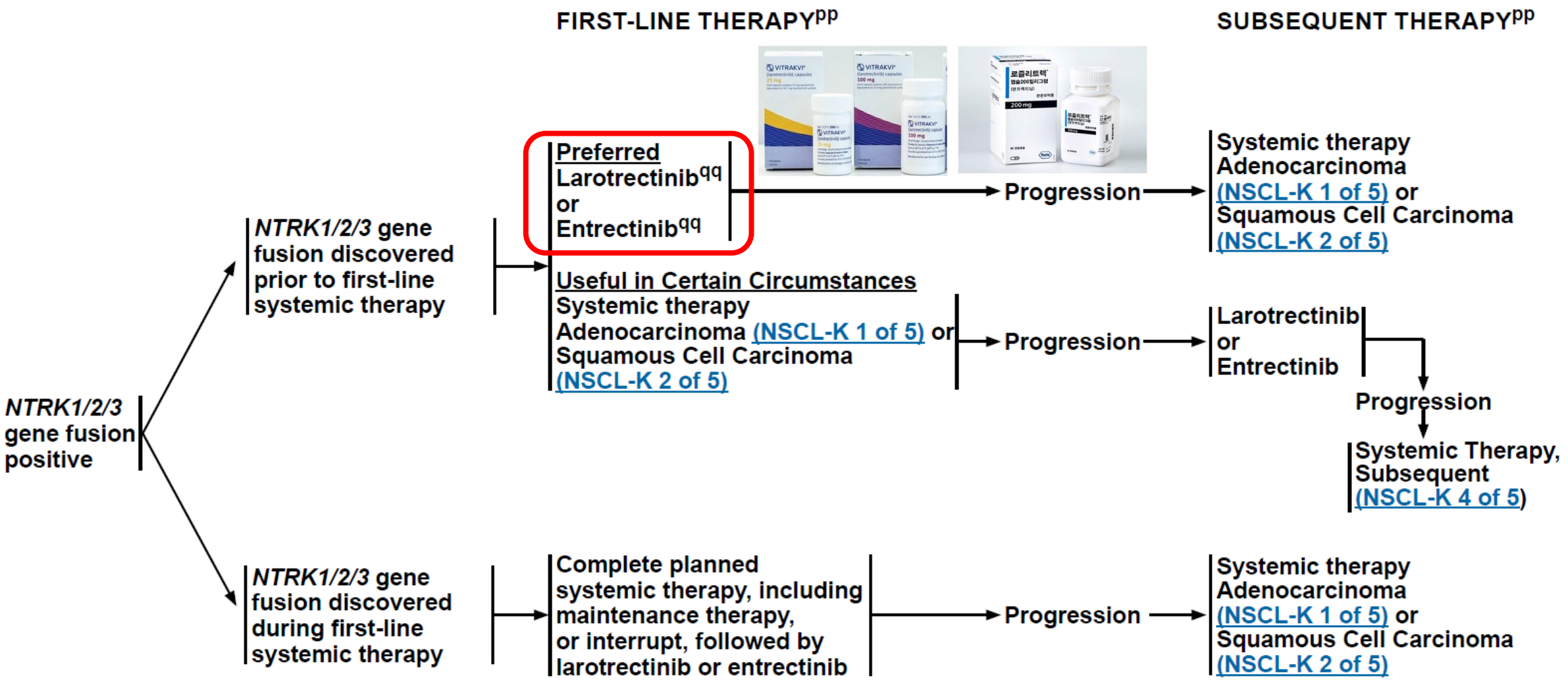



- Neurotrophic receptor tyrosine kinase ( *NTRK* ) gene fusions including *NTRK*1 , *NTRK*2 , and *NTRK*3 are known oncogenic drivers across a range of tumor types.
- Present in <1% NSCLC (detected across solid tumor)

[1].Kheder ES et al. Clin Cancer Res 2018 [2]. Drilon A. Ann Oncol 2019;30(Suppl_8):viii23 viii30 [3]. Cocco E et al. Nature reviews Clinical oncology 2018;15(12):731 47. [4]. Amatu A et al. Ann Oncol 2019;30 Suppl 8:viii5 viii15

## *NTRK* GENE FUSION POSITIVE[mm]



# Larotrectinib

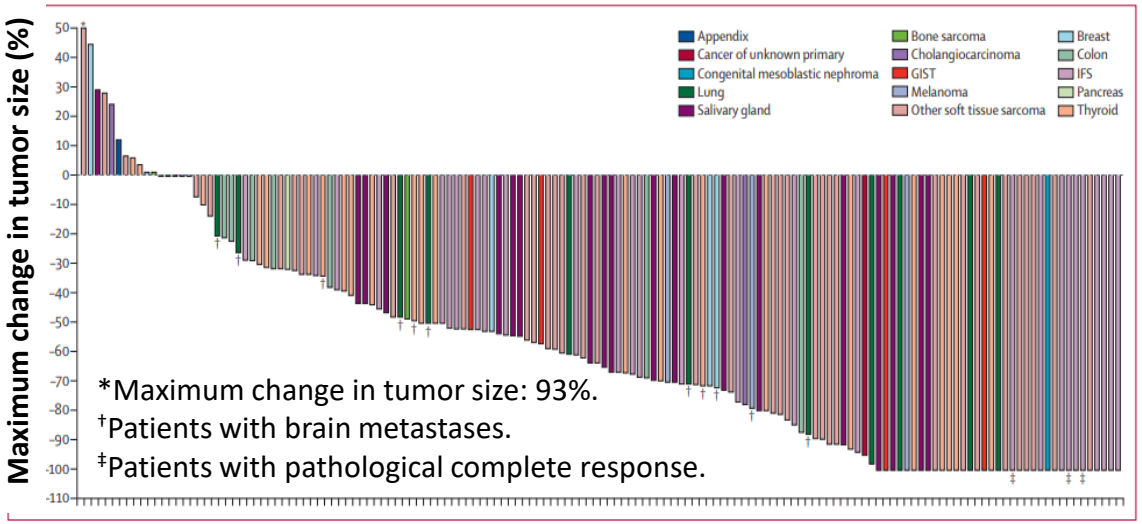
the first FDA-approved pan-TRK inhibitor

| | Patients | Patients with response | Median duration of response, months* |
|---|---|---|---|
| Overall | 153 | 121 (79%, 72–85) | 35·2 (22·8–NE) |
| Soft tissue sarcoma | | | |
| Infantile fibrosarcoma | 28 | 27 (96%, 82–100) | NE (NE–NE) |
| Gastrointestinal stromal tumour | 4 | 4 (100%, 40–100) | 26·3 (7·6–26·3) |
| Other | 36 | 29 (81%, 64–92) | NE (10·1–NE) |
| Thyroid | 24 | 19 (79%, 58–93) | NE (14·8–NE) |
| Salivary gland | 20 | 18 (90%, 68–99) | 35·2 (13·3–NE) |
| Lung | 12 | 9 (75%, 43–95) | NE (NE–NE) |
| Colon | 8 | 4 (50%, 16–84) | 3·7 (3·7–NE) |
| Melanoma | 7 | 3 (43%, 10–82) | NE (3·7–NE) |
| Breast | 4 | 3 (75%, 19–99) | NE (NE–NE) |
| Bone sarcoma | 2 | 1 (50%, 1–99) | 7·7 (NE–NE) |
| Cholangiocarcinoma | 2 | 1 (50%, 1–99) | 7·3 (NE–NE) |
| Pancreas | 2 | 1 (50%, 1–99) | 3·5 (NE–NE) |
| Appendix | 1 | 0 (NC) | .. |
| Congenital mesoblastic nephroma | 1 | 1 (100%, 3–100) | NE (NE–NE) |
| Hepatocellular | 1 | 0 (NC) | .. |
| Unknown primary | 1 | 1 (100%, 3–100) | NE (NE–NE) |

Data are n, n (%, 95% CI), or median (95% CI). NC=not calculable. NE=not estimable. *In patients with confirmed responses (n=108).

***Table 3:*** **Proportion of patients with response and duration of responses by tumour type according to investigator assessment**

**Change in Tumor Size With Larotrectinib**



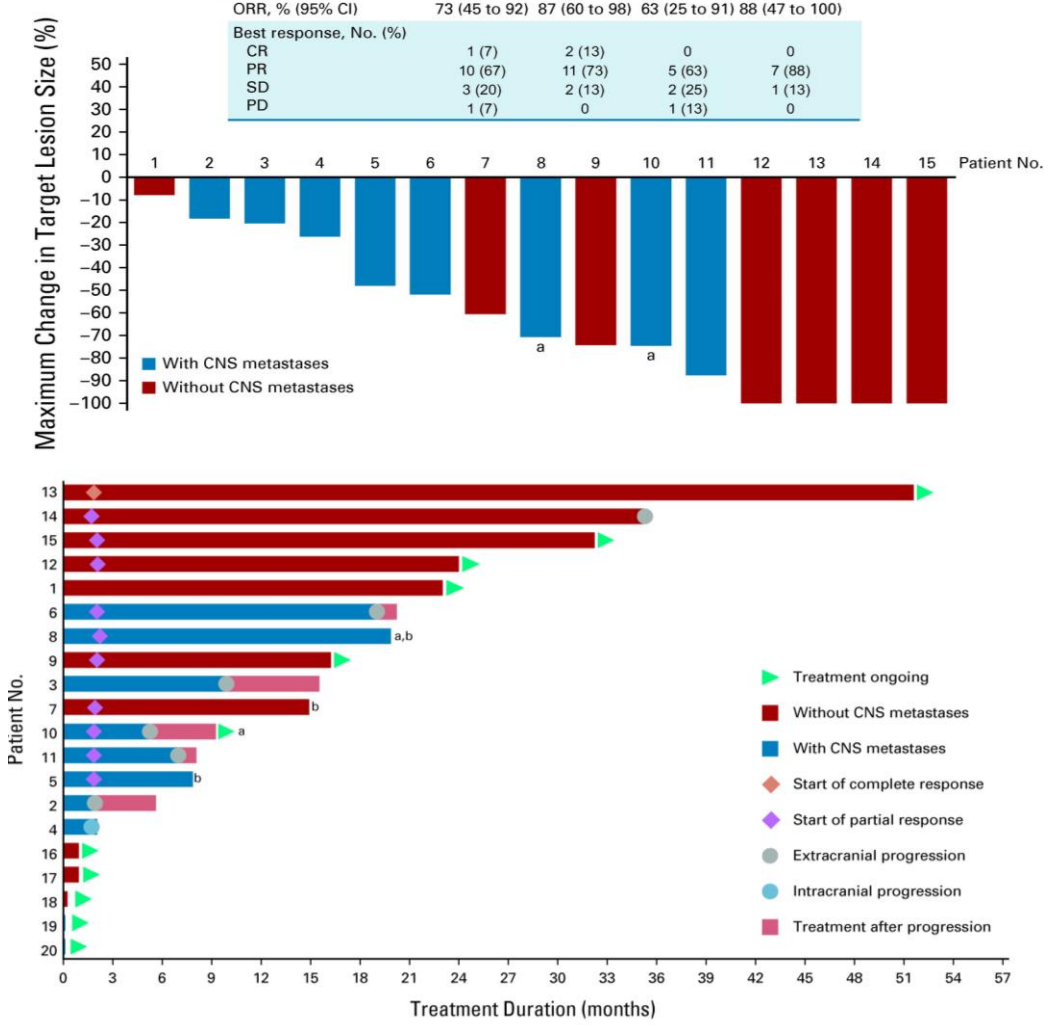

| Larotrectinib | N = 159* |
|---|---|
| ORR, % (95% CI) | 79 (72-85) |
| Median DoR, mo | 35.2 |
| Median PFS, mo | 28.3 |
| Median follow-up, mo | 12.9 |

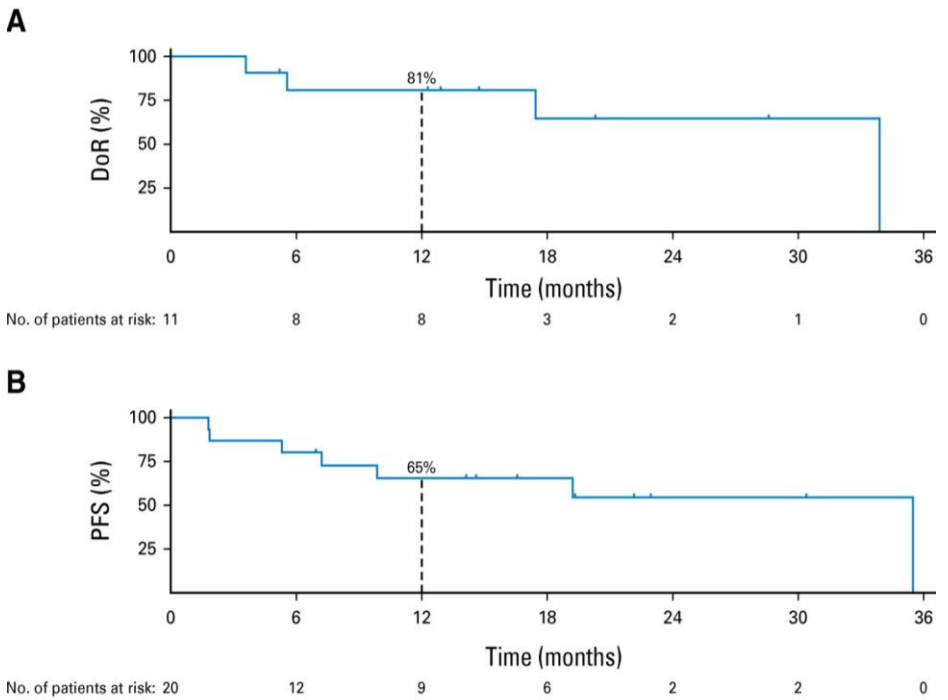
*exclude 6 patients awaiting an initial response assessment

DS Hong et al. Lancet Oncol. 2020;21:531.

# Larotrectinib in Patients With TRK Fusion+Lung Cancers

| | All Patients (N = 20) | | Patients With CNS Metastases (n = 10) | |
|---|---|---|---|---|
| | INV | IRC | INV | IRC |
| Evaluable patients, No. | 15 | 15 | 8 | 8 |
| ORR, % (95% CI) | 73 (45 to 92) | 87 (60 to 98) | 63 (25 to 91) | 88 (47 to 100) |
| Best response, No. (%) | | | | |
| CR | 1 (7) | 2 (13) | 0 | 0 |
| PR | 10 (67) | 11 (73) | 5 (63) | 7 (88) |
| SD | 3 (20) | 2 (13) | 2 (25) | 1 (13) |
| PD | 1 (7) | 0 | 1 (13) | 0 |

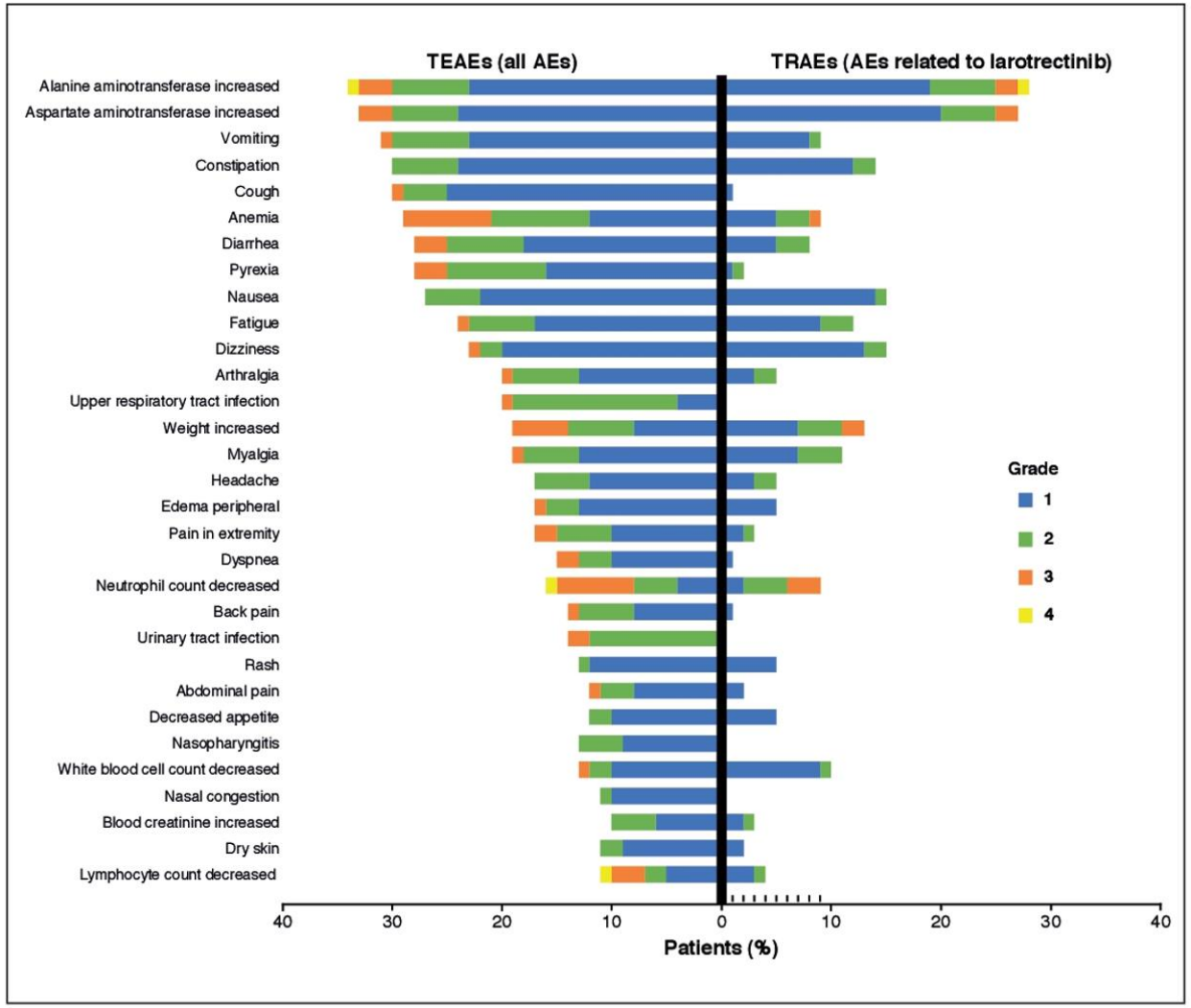



| Larotrectinib | N = 15 |
|---|---|
| ORR, % (95% CI) | 73 (45 – 92) |
| Median DoR, mo | 33.9(5.6 – 33.9) |
| Median PFS, mo | 35.4 (5.3 – 35.4) |
| Median follow-up, mo | 16.2 |

Drilon A., et al. JCO precision oncology 6 (2022): e2100418.

# Long-Term Efficacy and Safety of Larotrectinib in a Pooled Analysis of Patients With Tropomyosin Receptor Kinase (TRK) Fusion Cancer




AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

- TRAEs were mainly Grade 1-2
- 53 patients (20%) had Grade 3-4 TRAEs
- 5 patients (2%) discontinued treatment due to TRAEs
  - Emotional poverty
  - Hypoventilation
  - Neutropenia
  - decrease in neutrophil count
  - increase in ALT/AST increase

Drilon A. et al, J Clin Oncol 40, 2022 (suppl 16; abstr 3100)

# Entrectinib : Ph I (ALKA-372-001 or STARTRK-1) or ph II STARTRK-2

**Table 2.** Overall efficacy (BICR assessed) of entrectinib in patients with *NTRK* fusion-positive solid tumors, by baseline investigator-assessed CNS metastases status.

| Efficacy parameter | Efficacy-evaluable population ($n = 121$) | Baseline CNS metastases[a] ($n = 26$) | No baseline CNS metastases[a] ($n = 95$) |
|---|---|---|---|
| ORR, *n* (%) | 74 (61.2) | 15 (57.7) | 59 (62.1) |
| (95% CI) | (51.9–69.9) | (36.9–76.7) | (51.6–71.9) |
| CR | 19 (15.7) | 2 (7.7) | 17 (17.9) |
| PR | 55 (45.5) | 13 (50.0) | 42 (44.2) |
| Stable disease | 13 (10.7) | 4 (15.4) | 9 (9.5) |
| Progressive disease | 13 (10.7) | 2 (7.7) | 11 (11.6) |
| Non-CR/non-PD[b] | 6 (5.0) | 0 | 6 (6.3) |
| Missing or unevaluable[c] | 15 (12.4) | 5 (19.2) | 10 (10.5) |
| DoR | $n = 74$ | $n = 15$ | $n = 59$ |
| Median, mo (95% CI) | 20.0 (13.0–38.2) | 17.2 (6.0–29.4) | 29.0 (12.9–NE) |
| PFS | | | |
| Median, mo (95% CI) | 13.8 (10.1–19.9) | 11.7 (4.7–30.2) | 13.8 (10.2–20.8) |
| OS | | | |
| Median, mo (95% CI) | 33.8 (23.4–46.4) | 19.9 (7.9–NE) | 37.1 (23.9–NE) |

Note: Data cut-off August 31, 2020.

[a]CNS metastases status determined by investigator.

[b]Patients with nonmeasurable lesions.

[c]Missing or unevaluable included patients with unevaluable on-study scans or who discontinued prior to obtaining adequate scans to evaluate or confirm response.

1. Doebele RC et al. Lancet Oncol. 2020 Feb;21(2):271-282. 2.Demetri GD. Clin Cancer Res. 2022 Apr 1;28(7):1302-1312.

# Entrectinib demonstrated efficacy regardless of number of prior lines of therapy and was well tolerated

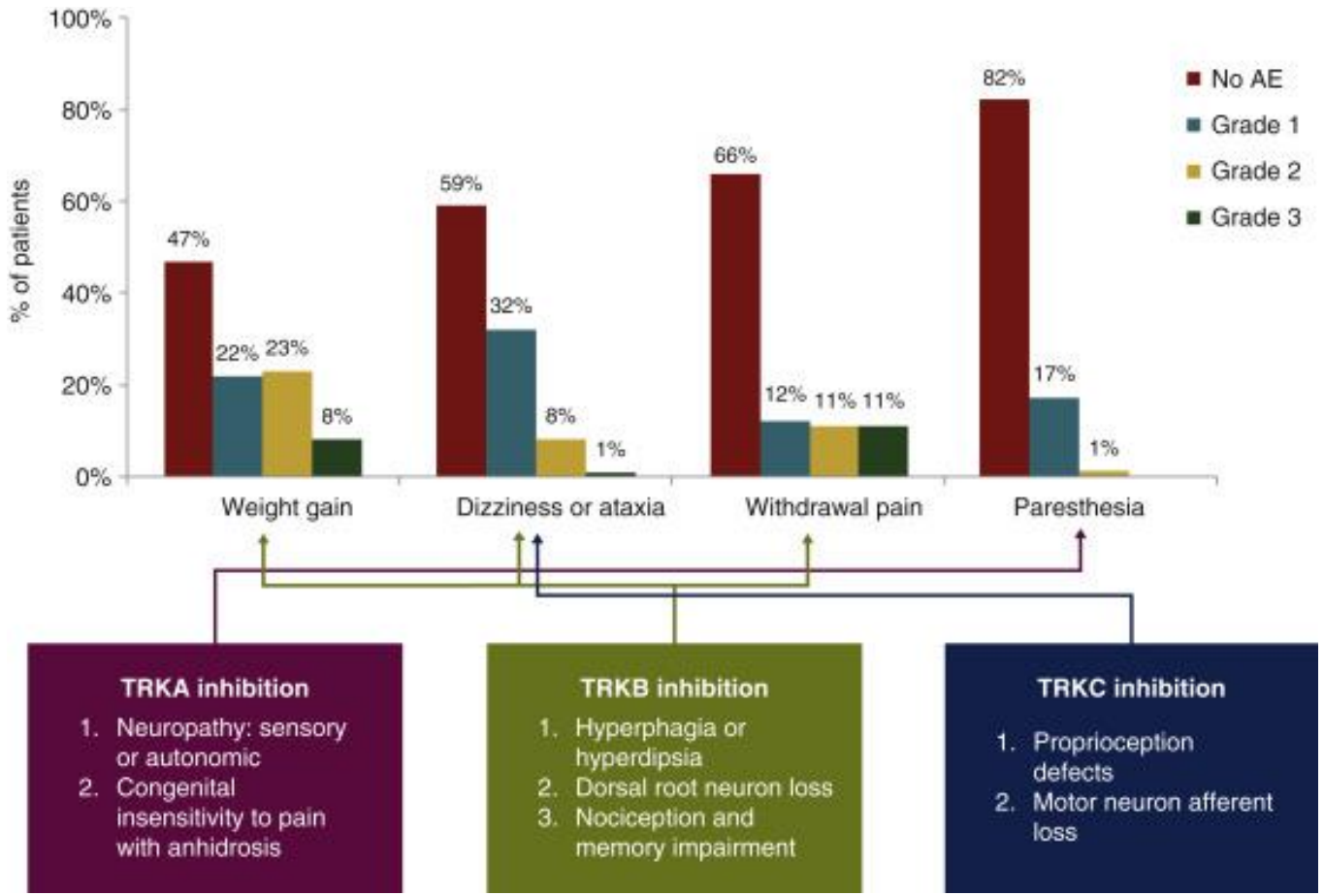
| Parameter | Prior lines of systemic therapy* | | | | | |
|---|---|---|---|---|---|---|
| | 0 (N=51) | 1 (N=44) | 2 (N=29) | 3 (N=12) | 4 (N=10) | >4 (N=4) |
| **ORR**, n (%) [95% CI] | 39 (**76.5**) [62.5–87.2] | 24 (**54.4**) [38.9–69.6] | 19 (**65.5**) [45.7–82.1] | 6 (**50.0**) [21.1–78.9] | 4 (**40.0**) [12.2–73.8] | 0 [0.0–60.2] |
| **Median DoR** months [95% CI] | **NE** [18.4–NE] | **17.2** [10.4–31.1] | **15.0** [9.3–29.4] | **12.0** [9.0–NE] | **NE** [2.8–NE] | – |

- **Safety data** were **consistent with the known safety profile of entrectinib** in patients with *NTRK* fusion-positive solid tumors: the **most frequent TRAEs** were **dysgeusia** (36.6%), **diarrhea** (29.8%) and **weight increase** (28.5%).
- **TRAEs** led to **dose interruption, reduction** or **discontinuation** in **32.8%, 24.3%** and **7.2%** of patients, respectively.

*Systemic therapy in the metastatic setting.
CI, confidence interval; DoR, duration of response; NE, not estimable; ORR, objective response rate; TRAE, treatment-related adverse event

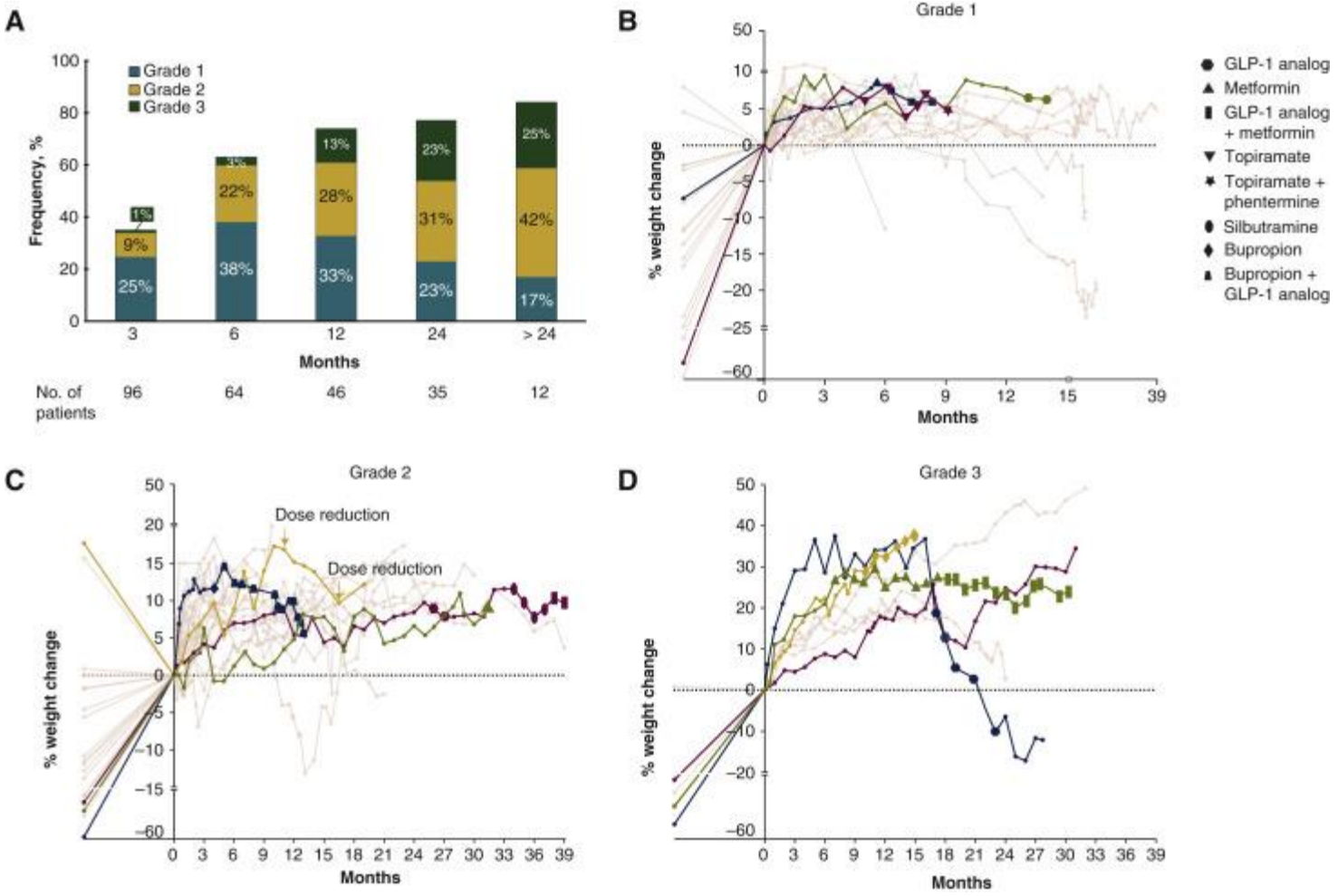

PRESENTED BY: Prof Maciej Krzakowski, MD

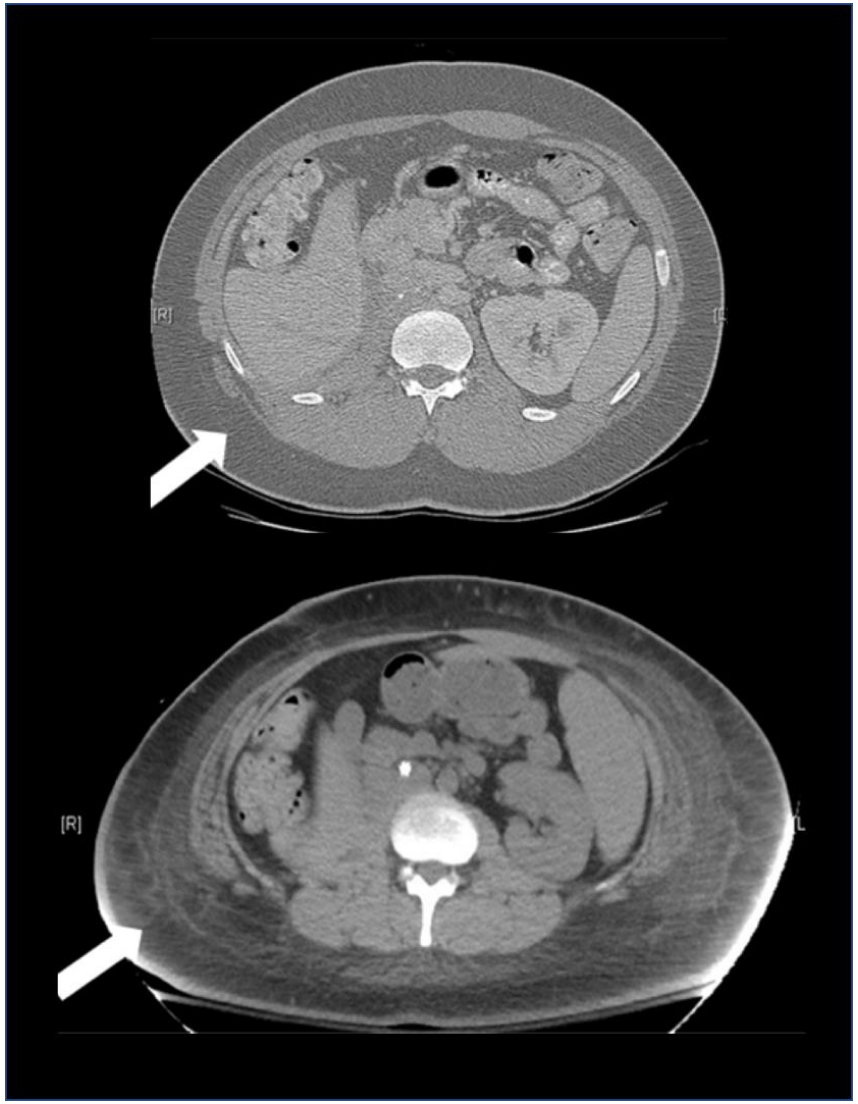
# TRK inhibitors have on-target side effect




Liu D et al. Ann Oncol. 2020;S0923-7534(20)39820

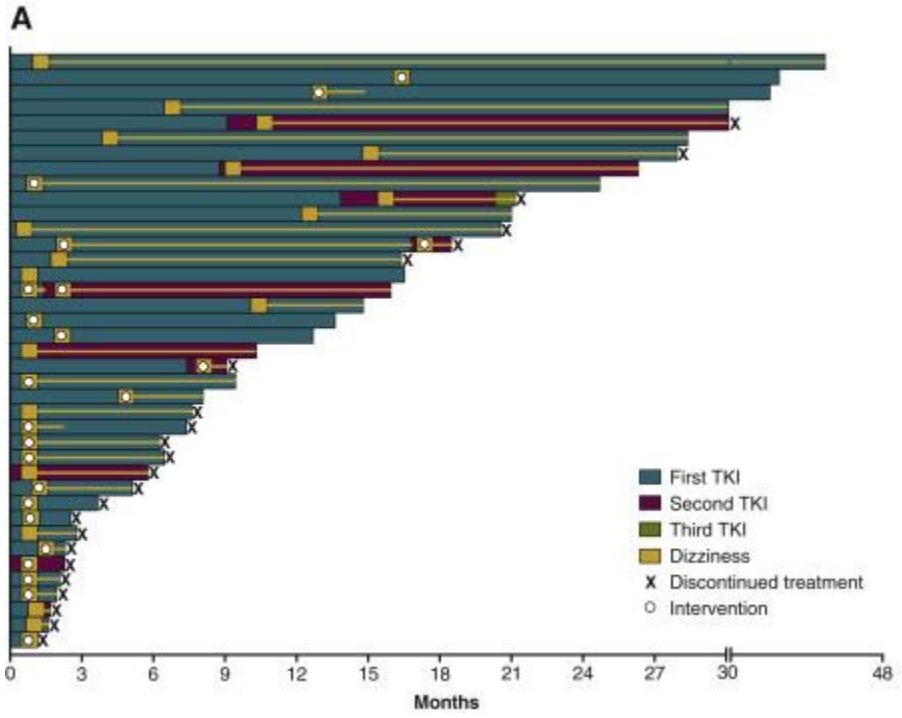
# TRK inhibitors: Weight gain

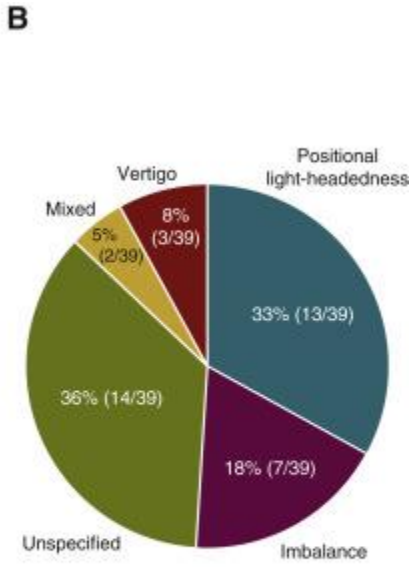



Liu D et al. Ann Oncol. 2020;S0923-7534(20)39820

# TRK inhibitors: Dizziness with ataxia

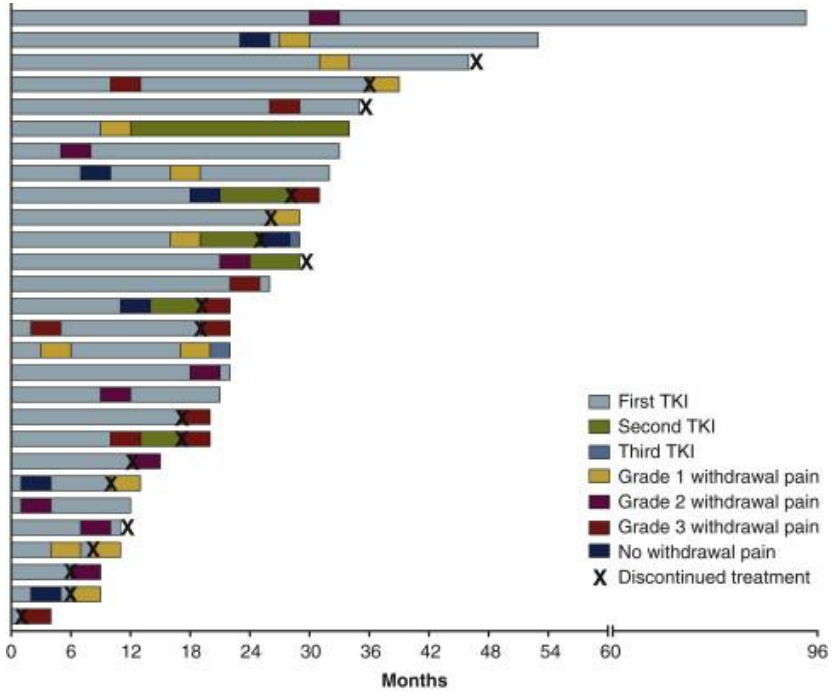



- Dizziness 41% (39 of 96; 95% CI, 31%–51%)
- 6 patients with dizziness developed ataxia concurrently.
- The median time to onset was 2 weeks (range, 3 days to 16 months).
- The median duration of dizziness was 5 months (range, 1 day to 40 months) from symptom onset.

Liu D et al. Ann Oncol. 2020;S0923-7534(20)39820

# TRK inhibitors: Withdrawal pain




Molecular basis of congenital insensitivity to pain with anhidrosis (CIPA): Mutations and polymorphisms in *TRKA (NTRK1)* gene encoding the receptor tyrosine kinase for nerve growth factor

Yasuhiro Indo

First published: 13 November 2001 | https://doi.org/10.1002/humu.1224 | Citations: 115

Symptoms were described as full-body ache, muscle pain, and/or allodynia, occasionally accompanied by a headache

Median time to onset:2 days (range, 1–6 days).

Liu D et al. Ann Oncol. 2020;S0923-7534(20)39820

# Agents approved by the FDA or recommended in clinical guidelines for the management of weight gain, dizziness, and pain.

**Table 2. Supportive medication**

| Adverse event | Agent(s) | Mechanism of action | Dose and schedule |
|---|---|---|---|
| Weight gain | Liraglutide | GLP-1 analog | 0.6–3.0 mg once/day |
| | Orlistat | Inhibits fat absorption | 60–120 mg three times/day |
| | Phentermine/topiramate combination | Increases norepinephrine release; GABA receptor agonist | 3.75/23–15/92 mg once/day |
| | Lorcaserin | 5-$HT_{2C}$ receptor agonist | 10 mg twice/day |
| | Naltrexone/bupropion combination | μ-Opioid receptor antagonist; dopamine and norepinephrine reuptake inhibitor | 8/90–16/180 mg once or twice/day |
| | Metformin | Modulates hypothalamic appetite regulatory centers | 500–2000 mg once/day |
| Dizziness (ataxia or vertigo) | Meclizine | $H_1$ histamine receptor antagonist, suppresses vestibular stimulation, anticholinergic | 25–50 mg once/day |
| | Scopolamine | Antagonizes histamine and serotonin | 1 Patch every 3 days |
| Dizziness (orthostasis) | Midodrine | $\alpha_1$ Adrenergic receptor agonist, increases vascular tone | 5–10 mg three times/day |
| | Fludrocortisone | Mineralocorticoid | 0.05–0.2 mg once/day |
| | Droxidopa | Metabolized to norepinephrine, induces vasoconstriction | 100 mg three times/day (1.8 g/day maximum) |
| Withdrawal pain | Nonsteroidal anti-inflammatory agents | COX-1/COX-2 inhibitors | Per agent/label |
| | Opioids | Opioid receptor agonists | Per label |
| | Gabapentin/pregabalin | GABA analog | Per label |

Agents approved by the US Food and Drug Administration or recommended in clinical guidelines for the management of weight gain, dizziness, and pain.[24–27,30–34]
COX, cyclooxygenase; GABA, gamma-aminobutyric acid; GLP-1, glucagon-like peptide 1; 5-HT, 5-hydroxytryptamine.

Liu D et al. Ann Oncol. 2020;S0923-7534(20)39820

# NTRK inhibitor: summary

- TRK inhibitors have a unique on-target side-effect profile.
- Weight gain, dizziness/ataxia, and paresthesias should be monitored on therapy.
- In addition, withdrawal pain can occur in patients who temporarily or permanently discontinue treatment.
- These side-effects are manageable with pharmacologic intervention and/or dose modification.

# Thank you for your attention

sunha20@knu.ac.kr