SELECTION OF FIRST LINE THERAPY FOR EXON 20 INSERTION

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UNCOMMON EGFR MUTATIONS

Table 2 Uncommon EGFR mutation frequency and their distribution according to predicted sensitivity to oral TKI

Uncommon EGFR mutation types	N=83	%
Uncommon EGFR single mutations		
Exon 18 G719X	8	9.6
Exon 20 insertion	15	19.3
Exon T790M	10	12.0
Exon 20 768I	3	3.6
Exon 21 L861Q	3	3.6

Lung Cancer: Targets and Therapy

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ORIGINAL RESEARCH

Outcome of uncommon EGFR mutation positive newly diagnosed advanced non-small cell lung cancer patients: a single center retrospective analysis

This article was published in the following Dove Medical Press journal:
Lung Cancer: Targets and Therapy

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Background: The significance of uncommon EGFR mutations in newly diagnosed advanced non-small-cell lung cancer (NSCLC) patients is incompletely known. We aimed to analyze the demographic profile, outcome, and treatment attributes of these patients.

Patients and methods: We retrospectively surveyed 5,738 advanced NSCLC patients who underwent EGFR testing in our center from 2013 to 2017 by in-house primer probes on real time PCR platform. Descriptive data were accumulated from electronic medical records. Survival plot was calculated using Kaplan–Meier method and compared between groups using log-rank test.

Results: Out of 1,260 EGFR mutation-positive patients, 83 (6.58%) had uncommon mutations in isolation or in various combinations. Uncommon mutations were more frequent in men, never-smokers, and adenocarcinomas. Overall, exon 18 G719X, exon 20 insertion, exon 20 T790M, exon 20 S768I, and exon 21 (L858R/L861Q) were present in 9.6%, 19.3%, 12%, 3.6%, and 3.6% patients, respectively. Dual mutation positivity was found in 50.6% patients. On classifying

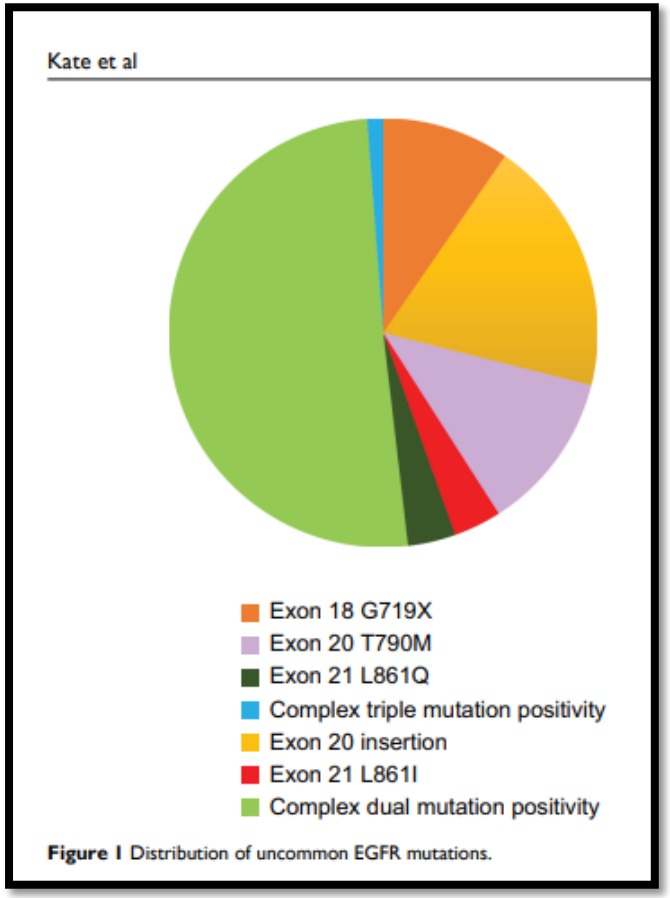
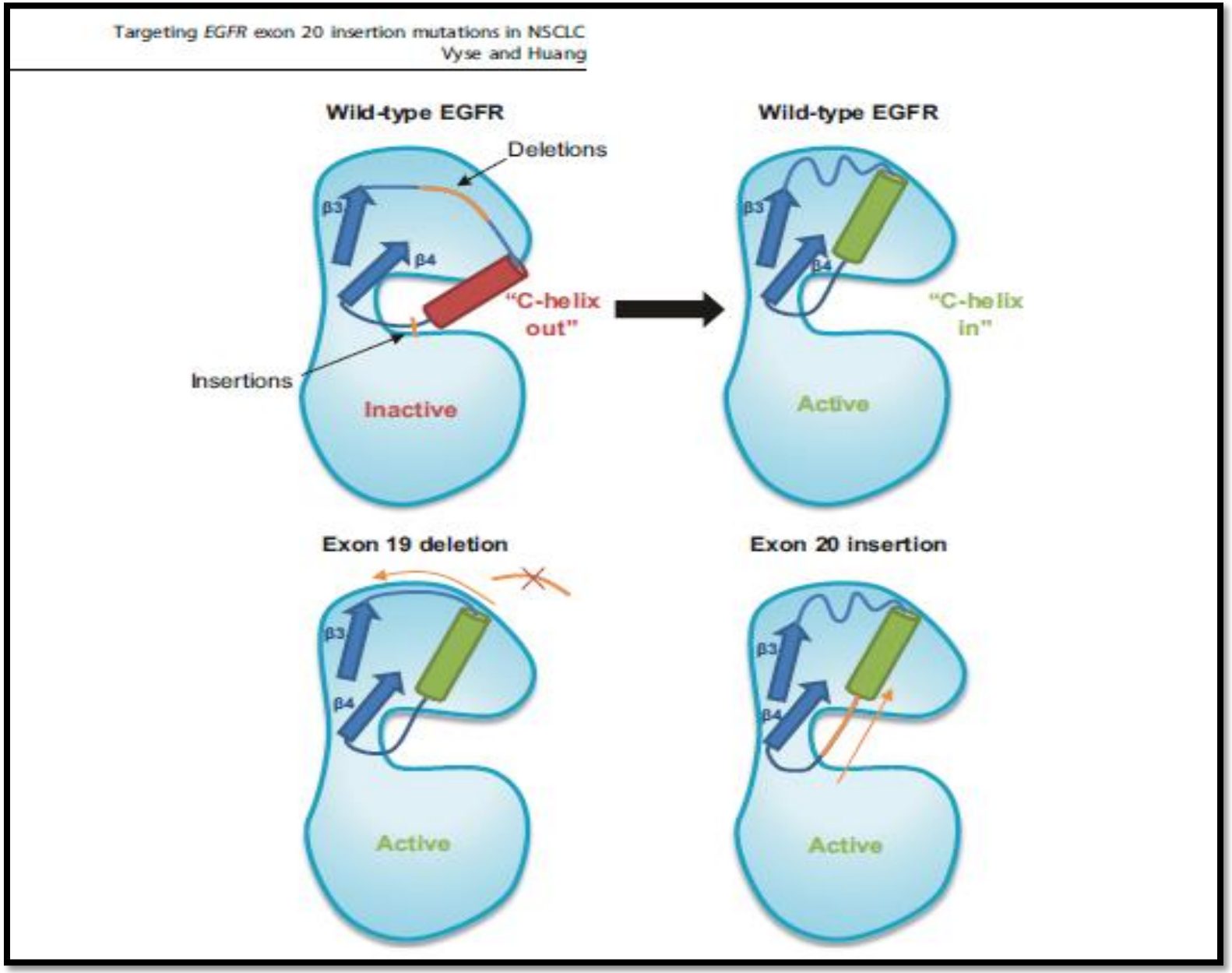


Figure 1 Distribution of uncommon EGFR mutations.



Impact of deletions and insertions on EGFR activation. Upon ligand-binding, the regulatory C-helix pivots from an outward, inactive conformation to an inward, active conformation to form key interactions with the p-loop of the active site located in the cleft between the N-lobe and C-lobe. Oncogenic mutations such as exon 19 deletions can "pull" the C-helix from the N-terminal side whilst exon 20 insertions "push" from the C-terminal side to stabilize the active state of EGFR even in the absence of ligand

- EGFR Exon 20 insertions are **3rd most common EGFR mutations** ,occur in 2% of NSCLC patient & 4 to 12% of patient with EGFR mutations.

- Common Exon 20 insertions- -insASV ,insSVD and insNPH.

- It is preferable to do NGS, PCR based assay may miss some Exon 20 insertions.

- Low response rates to TKIs- 13% ORR across second line treatments, with a median PFS of 3.5 months.

Yasuda H, Kobayashi S, Costa DB. EGFR exon 20 insertion mutations in non-small-cell lung cancer: preclinical data and clinicalimplications. Lancet Oncol 2012;13:e23-31.

Vasconcelos P, Gergis C, Viray H, et al. EGFR-A763_Y764insFQEA Is a Unique Exon 20 Insertion Mutation That Displays Sensitivity to Approved and In-Development Lung Cancer EGFR Tyrosine Kinase Inhibitors. JTO Clin Res Rep

- Pre-clinical in vitro evidence in engineered cell line models has suggested that osimertinib may have some activity against EGFR exon 20 insertions, albeit with a weaker potency than afatinib.
- **However, the evidence to support osimertinib as a candidate inhibitor for EGFR exon 20 insertions in vivo remains unclear.**
- A study of lung cancer patient-derived xenograft (PDX) models harboring EGFR exon 20 insertion mutations showed poor responses to the third-generation EGFR inhibitors osimertinib and rociletinib.
- A phase II clinical trial to assess osimertinib as a treatment for EGFR exon 20 insertion mutant NSCLC (NCT03414814) is ongoing.

EGFR EXON 20 INSERTION MUTATION POSITIVE[mm]

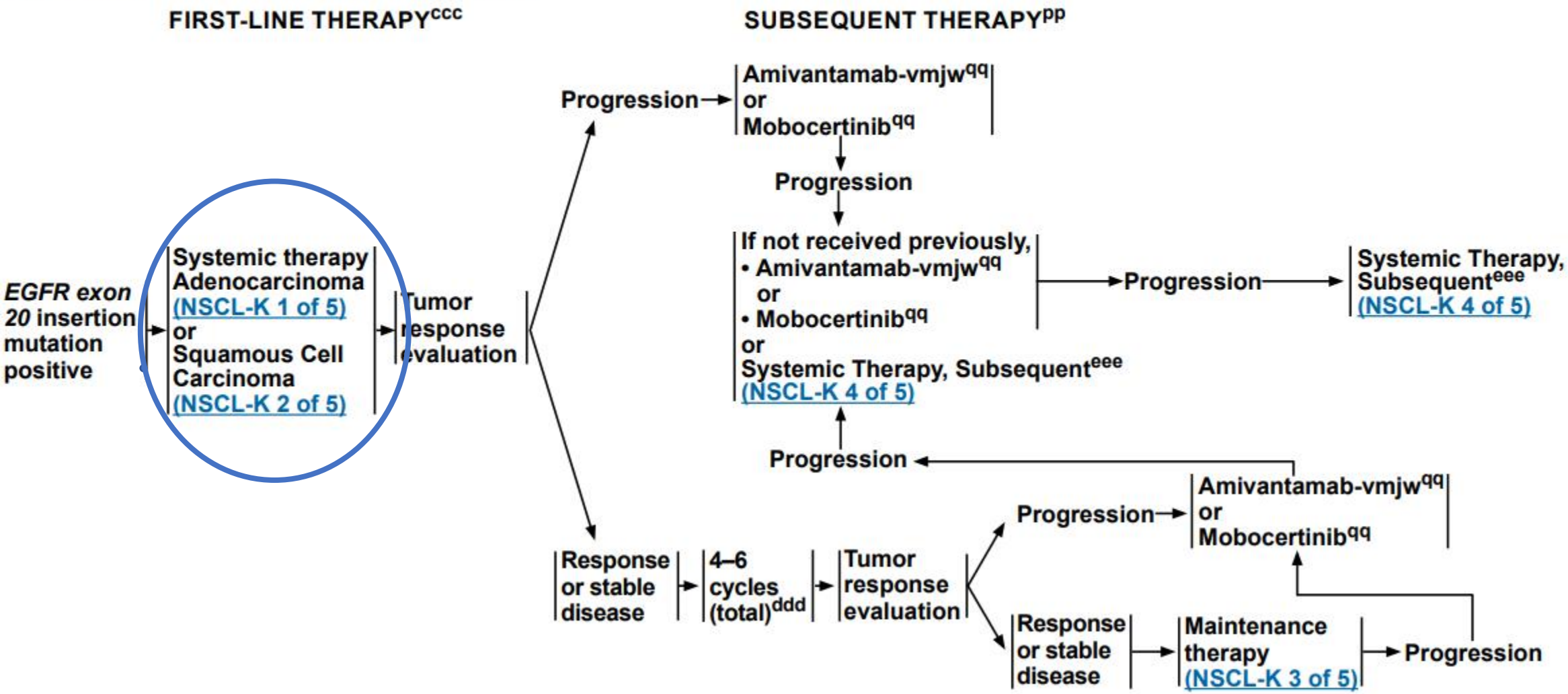


Table 3 mPFS and mOS of the cohort by mutation type and predicted TKI sensitivity

Mutation types	N=83	mPFS (months) first line therapy	95% CI	Log rank (Mantel–Cox)	mOS (months)	95% CI	Log-rank (Mantel–Cox)
Specific mutation types	Entire cohort	6.7	4.7–8.6		15.8	10.1–21.5	
	Exon 18 G719X	8.4	1.8–15.1	0.82	13.5	0–29.9	*P*=0.005
	Exon 20 insertion	6.0	2.4–9.6		15.8	6.2–25.3	
	Exon T790M	8.2	3.4–13.1		12.3	9.4–15.2	
	Exon 20 768I	2.0	NE		2.0	0.9–3.1	
	Exon 21 L861Q	1.0	NE		1.8	0–2.6	
	Exon 18 G719X, exon 20 S768I, and exon 21 L858R	4.8	NE		4.8	NE	
	Dual mutations	6.9	3.2–10.7		22.6	8.2–37.0	
Mutation types by TKI sensitivity	TKI sensitive single mutation (exon 18/20 768I/21 L861Q)	6.5	0.6–12.4	*P*=0.68	12.7	0.0–30.5	*P*=0.039
	TKI insensitive single (exon 20 insertion/T790M)	6.0	5.5–6.5		12.9	11.1–14.7	
	TKI sensitive dual	4.6	0–9.5		9.6	3.6–15.6	
	TKI sensitive + insensitive complex mutation	7.8	3.1–12.4		28.2	15.2–41.2	

Abbreviations: mOS, median overall survival; mPFS, median progression-free survival; NE, not estimable; TKI, tyrosine kinase inhibitor.

Kate et al

Lung Cancer: Targets and Therapy 2019:10

original reports

Amivantamab in EGFR Exon 20 Insertion–Mutated Non–Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study

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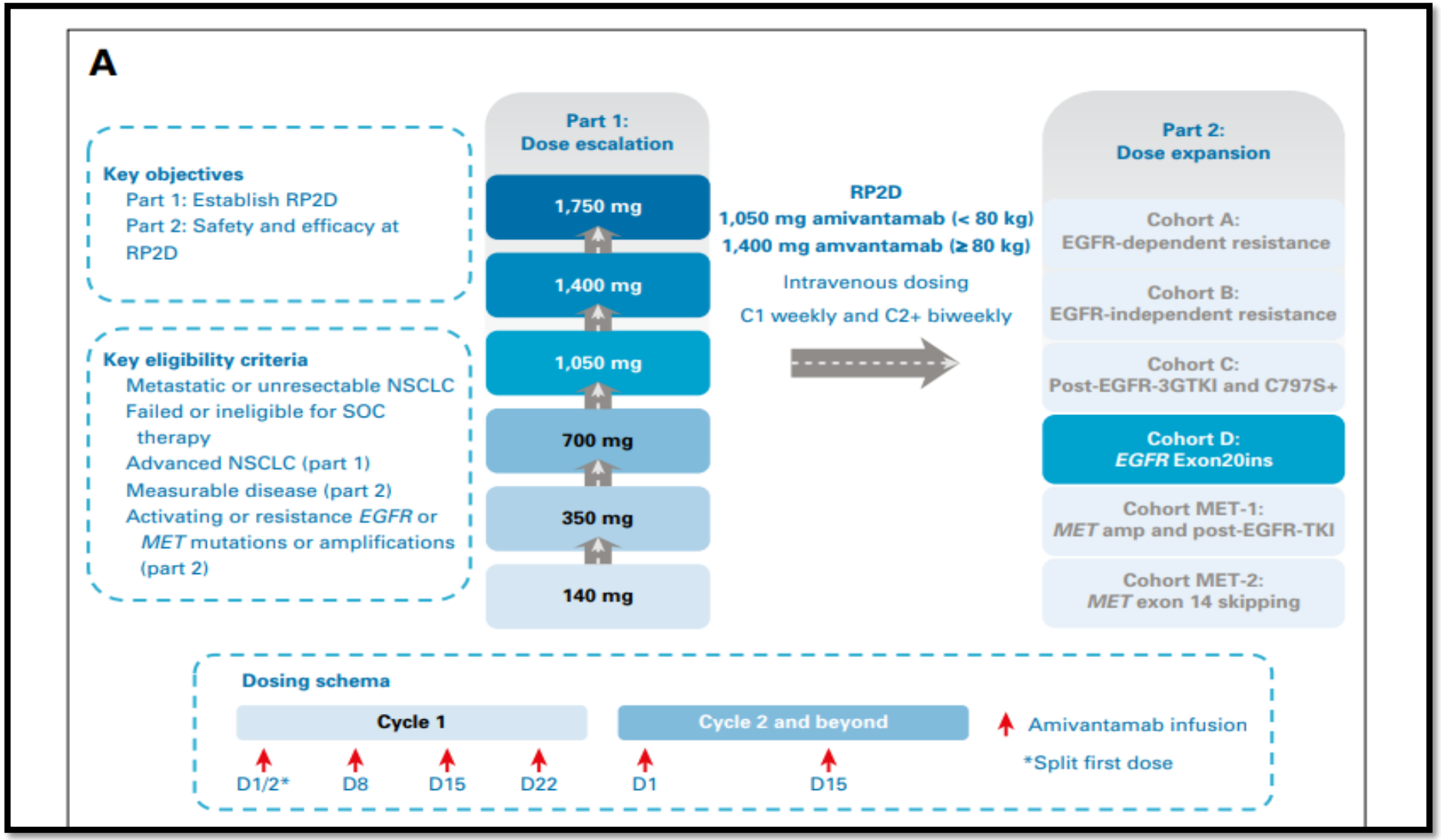
- Amivantamab (JNJ-61186372) is a fully human EGFR MET bispecific antibody with immune cell–directing activity designed to engage two distinct driver pathways in NSCLC.

- By binding to each receptor’s extracellular domain, amivantamab can inhibit ligand binding, promote receptor-antibody complex endocytosis and degradation, and induce Fc-dependent trogocytosis by macrophages and antibody-dependent cellular cytotoxicity by NK cells.

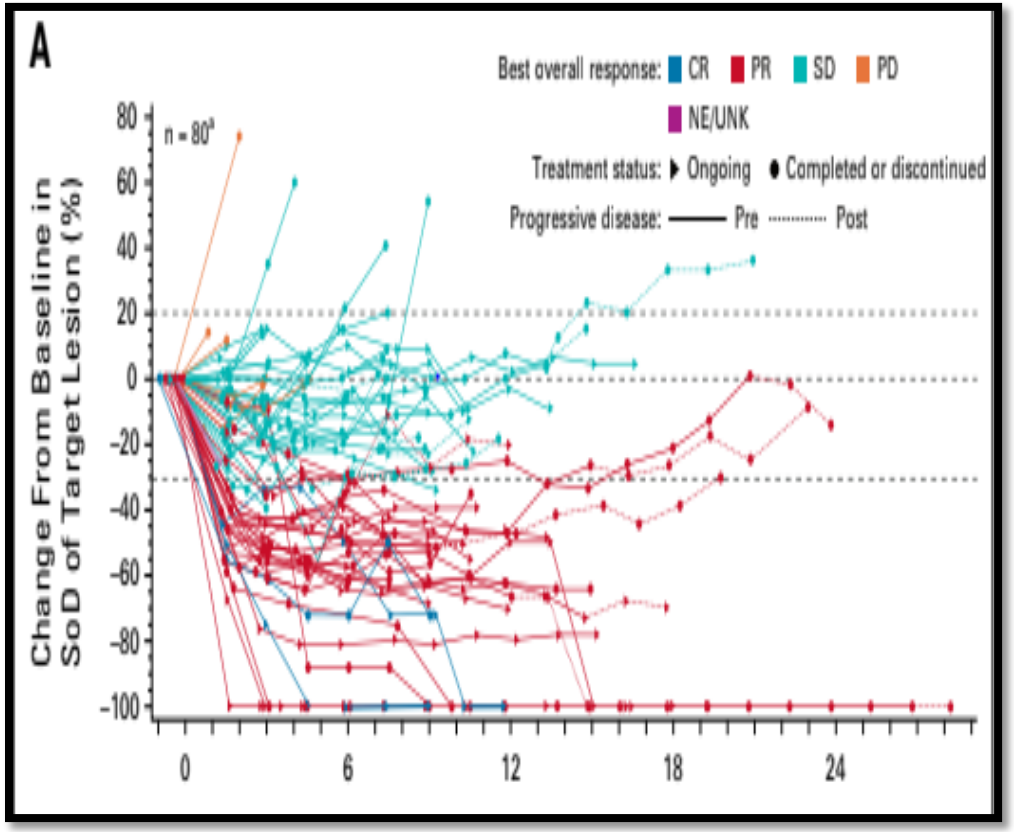

A
Key objectives
Part 1: Establish RP2D
Part 2: Safety and efficacy at RP2D
Key eligibility criteria
Metastatic or unresectable NSCLC
Failed or ineligible for SOC therapy
Advanced NSCLC (part 1)
Measurable disease (part 2)
Activating or resistance EGFR or MET mutations or amplifications (part 2)
Part 1: Dose escalation
1,750 mg
1,400 mg
1,050 mg
700 mg
350 mg
140 mg
RP2D
1,050 mg amivantamab (< 80 kg)
1,400 mg amvantamab (≥ 80 kg)
Intravenous dosing
C1 weekly and C2+ biweekly
Part 2: Dose expansion
Cohort A: EGFR-dependent resistance
Cohort B: EGFR-independent resistance
Cohort C: Post-EGFR-3GTKI and C797S+
Cohort D: EGFR Exon20ins
Cohort MET-1: MET amp and post-EGFR-TKI
Cohort MET-2: MET exon 14 skipping
Dosing schema
Cycle 1
Cycle 2 and beyond
Amivantamab infusion
*Split first dose
D1/2*
D8
D15
D22
D1
D15

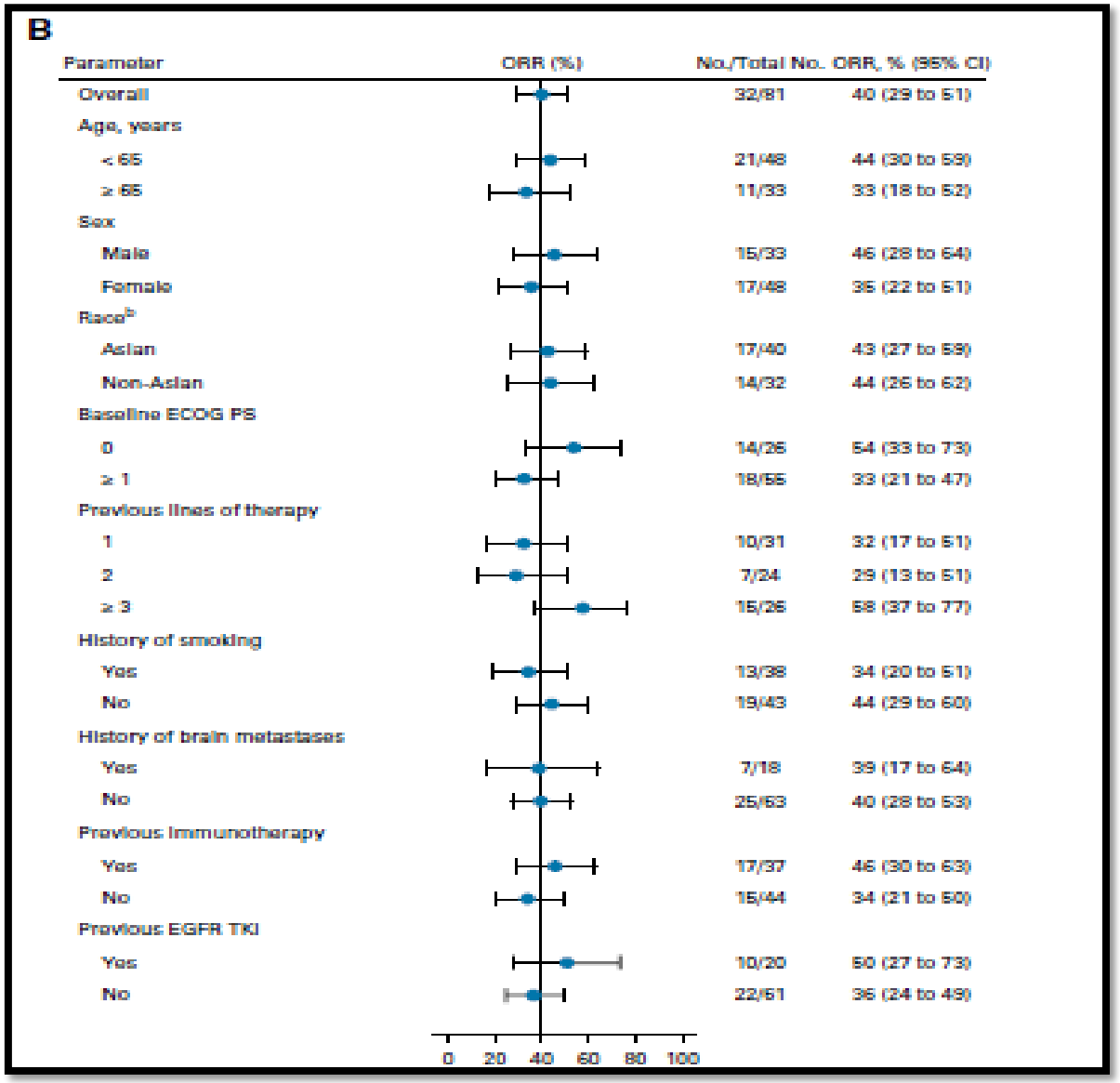
RESULTS

- OVERALL RR - 40%
- CBR (SD AT ATLEAST 11 WEEKS/RESPONSE)- 74%
- MEDIAN DOR -11.1 months.
- MEDIAN PFS- 8.3 Months.
- MEDIAN OS 23 Months.

TABLE 3. Response as Assessed by Blinded Independent Central Review

Response per RECIST	Efficacy Population (n = 81)
ORR, % (95% CI)[a]	40 (29 to 51)
CBR, % (95% CI)[b]	74 (63 to 83)
Best response, No. (%)	
CR	3 (4)
PR	29 (36)
SD	39 (48)
PD	8 (10)
NE	2 (2)


A
Best overall response: CR PR SD PD
NE/UNK
Treatment status: Ongoing Completed or discontinued
Progressive disease: Pre Post
n = 80[a]
Change From Baseline in SoD of Target Lesion (%)
80
60
40
20
0
-20
-40
-60
-80
-100
0
6
12
18
24


B
Parameter
ORR (%)
No./Total No.
ORR, % (95% CI)
Overall 32/81 40 (29 to 51)
Age, years
< 65 21/48 44 (30 to 59)
≥ 65 11/33 33 (18 to 52)
Sex
Male 15/33 46 (28 to 64)
Female 17/48 35 (22 to 51)
Race[b]
Asian 17/40 43 (27 to 59)
Non-Asian 14/32 44 (26 to 62)
Baseline ECOG PS
0 14/26 54 (33 to 73)
≥ 1 18/55 33 (21 to 47)
Previous lines of therapy
1 10/31 32 (17 to 51)
2 7/24 29 (13 to 51)
≥ 3 15/26 58 (37 to 77)
History of smoking
Yes 13/38 34 (20 to 51)
No 19/43 44 (29 to 60)
History of brain metastases
Yes 7/18 39 (17 to 64)
No 25/63 40 (28 to 53)
Previous immunotherapy
Yes 17/37 46 (30 to 63)
No 15/44 34 (21 to 50)
Previous EGFR TKI
Yes 10/20 50 (27 to 73)
No 22/61 36 (24 to 49)
0
20
40
60
80
100

ADVERSE EVENTS

TABLE 2. Summary of AEs

Event	Safety Population (n = 114), No. (%)	Patients Treated at the RP2D (n = 258), No. (%)
Any AE	113 (99)	257 (100)
Grade ≥ 3 AE	40 (35)	101 (39)
Serious AE	34 (30)	79 (31)
AE leading to death	8 (7)	13 (5)
AE leading to discontinuation	11 (10)	17 (7)
AE leading to dose reduction	15 (13)	26 (10)
AE leading to dose interruption[a]	40 (35)	88 (34)

Most Common AE (≥ 10%)	Safety Population (n = 114), No. (%)				Patients Treated at the RP2D (n = 258), No. (%)			
	Total	Grade 1	Grade 2	Grade ≥ 3	Total	Grade 1	Grade 2	Grade ≥ 3
Rash[b]	98 (86)	43 (38)	51 (45)	4 (4)	202 (78)	101 (39)	94 (36)	7 (3)
Infusion-related reaction	75 (66)	9 (8)	63 (55)	3 (3)	167 (65)	21 (8)	140 (54)	6 (2)
Paronychia	51 (45)	28 (25)	22 (19)	1 (1)	104 (40)	50 (19)	51 (20)	3 (1)
Hypoalbuminemia	31 (27)	6 (5)	22 (19)	3 (3)	63 (24)	21 (8)	38 (15)	4 (2)
Constipation	27 (24)	18 (16)	9 (8)	0	58 (23)	36 (14)	22 (9)	0
Nausea	22 (19)	17 (15)	5 (4)	0	55 (21)	40 (16)	14 (5)	1 (0.4)
Dyspnea	22 (19)	12 (11)	8 (7)	2 (2)	52 (20)	28 (11)	13 (5)	11 (4)
Stomatitis	24 (21)	11 (10)	13 (11)	0	50 (19)	33 (13)	17 (7)	0
Peripheral edema	21 (18)	20 (18)	1 (1)	0	50 (19)	43 (17)	5 (2)	2 (1)
Pruritus	19 (17)	11 (10)	8 (7)	0	49 (19)	40 (16)	9 (4)	0
Fatigue	21 (18)	15 (13)	4 (4)	2 (2)	47 (18)	29 (11)	16 (6)	2 (1)
Cough	16 (14)	11 (10)	5 (4)	0	40 (16)	25 (10)	15 (6)	0
Decreased appetite	16 (14)	7 (6)	9 (8)	0	39 (15)	23 (9)	16 (6)	0
Dry skin	18 (16)	18 (16)	0	0	33 (13)	32 (12)	1 (0.4)	0
Increased alanine aminotransferase	17 (15)	15 (13)	1 (1)	1 (1)	30 (12)	22 (9)	5 (2)	3 (1)
Vomiting	12 (11)	10 (9)	2 (2)	0	29 (11)	22 (9)	6 (2)	1 (0.4)
Myalgia	14 (12)	12 (11)	2 (2)	0	28 (11)	23 (9)	5 (2)	0
Dizziness	9 (8)	8 (7)	0	1 (1)	28 (11)	24 (9)	3 (1)	1 (0.4)
Headache	8 (7)	4 (4)	3 (3)	1 (1)	28 (11)	17 (7)	8 (3)	3 (1)
Increased blood alkaline phosphatase	10 (9)	8 (7)	1 (1)	1 (1)	28 (11)	22 (9)	4 (2)	2 (1)
Diarrhea	14 (12)	8 (7)	2 (2)	4 (4)	27 (11)	16 (6)	6 (2)	5 (2)
Back pain	12 (11)	6 (5)	6 (5)	0	26 (10)	13 (5)	11 (4)	2 (1)
Pyrexia	15 (13)	12 (11)	3 (3)	0	26 (10)	21 (8)	5 (2)	0
Hypokalemia	12 (11)	5 (4)	1 (1)	6 (5)	21 (8)	11 (4)	3 (1)	7 (3)

MOBOCERTINIB

- Oral TKI approved for patients progressed on or after platinum – based chemotherapy.

- RR 28% , Median DOR- 17.5 months.

- Serious adverse events-46% patients(diarrhoea , dyspnea , vomiting ,pyrexia , AKI, nausea, pleural effusion and cardiac failure)

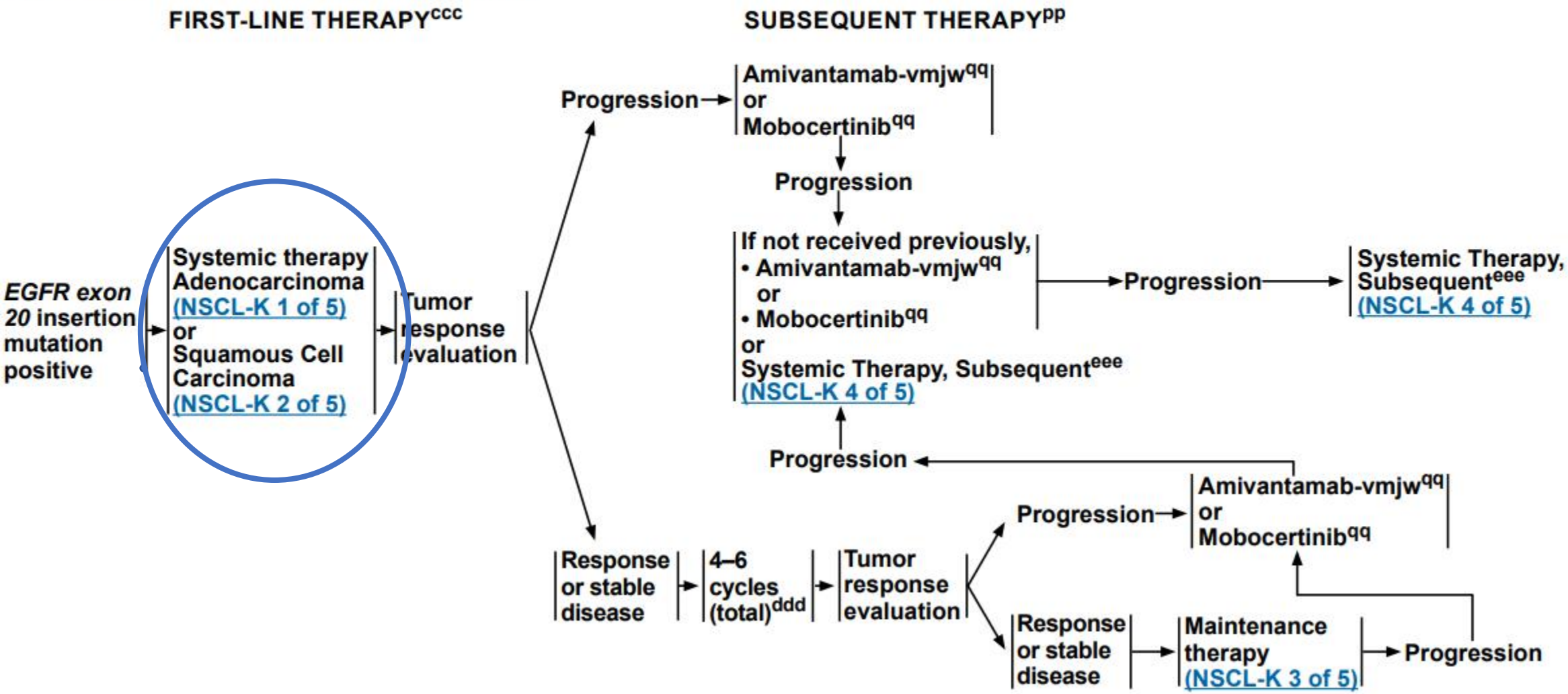
Subscribe

Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with *EGFR* mutations or baseline liver metastases in a randomised, open-label phase 3 trial

Martin Reck, MD • Tony S K Mok, MD • Makoto Nishio, MD • Robert M Jotte, MD • Federico Cappuzzo, MD • Francisco Orlandi, MD • et al. Show all authors • Show footnotes

- In EGFR-mt patients, the median OS was not reached in arm B(ABCP) versus 18.7 months in arm C (BCP) (HR, 0.61; 95% CI, 0.29-1.28); in EGFR-mts patients, the median OS was not reached versus 17.5 months, respectively (HR, 0.31; 95% CI, 0.11-0.83); and in patients receiving prior TKIs, the median OS was not reached versus 17.5 months (HR, 0.39; 95% CI, 0.14-1.07).

EGFR EXON 20 INSERTION MUTATION POSITIVE[mm]



PAPILLON STUDY-ONGOING

A Randomised Open Label Phase 3 Study Of Combination Amivantamab And Carboplatin – Pemetrexed Therapy,ompared With Carboplatin-Pemetrexed ,In Patients With EGFR Exon 20 Ins Mutated Locally Advanced Or Metastatic NSCLC.

SUMMARY

- The preferred first-line treatment for Exon 20 insertion patients is platinum-based chemotherapy, carboplatin and pemetrexed.

- 2 approved targeted therapies for these patients, neither of them is approved in the frontline setting.

- The role of immunotherapy for these patients is still an open question about whether we should be giving them first-line chemotherapy and immunotherapy combinations, or whether perhaps patients with EGFR exon 20 insertions may have less benefit from immunotherapy.

- Role for sequencing mobocertinib and amivantamab?