Selection of 1st Line therapy for MET Amplification and MET EXON 14 Mutation in NSLC

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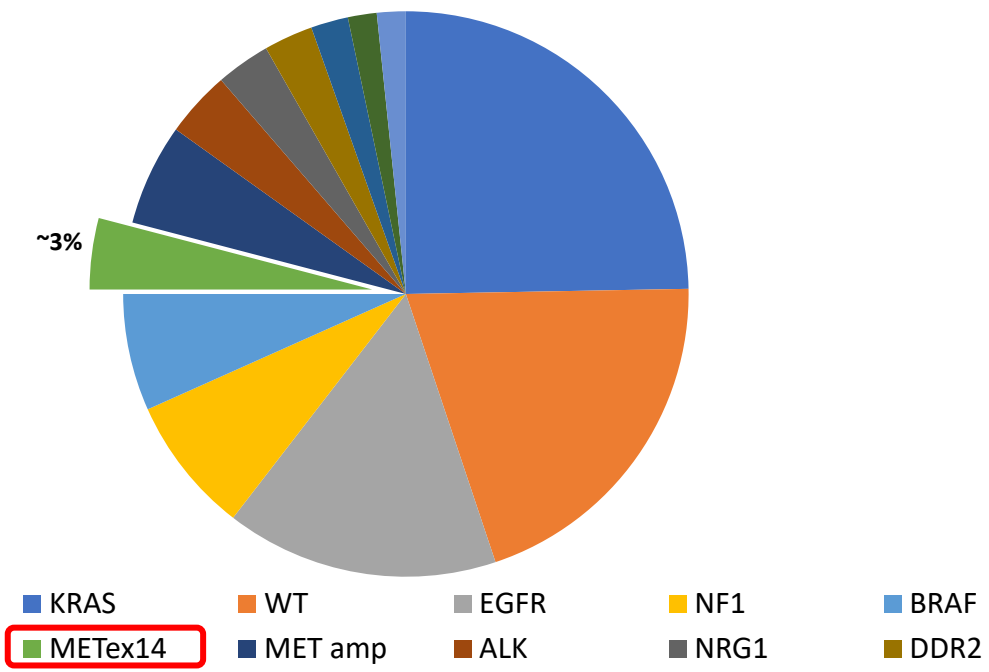
MET mutations in NSCLC

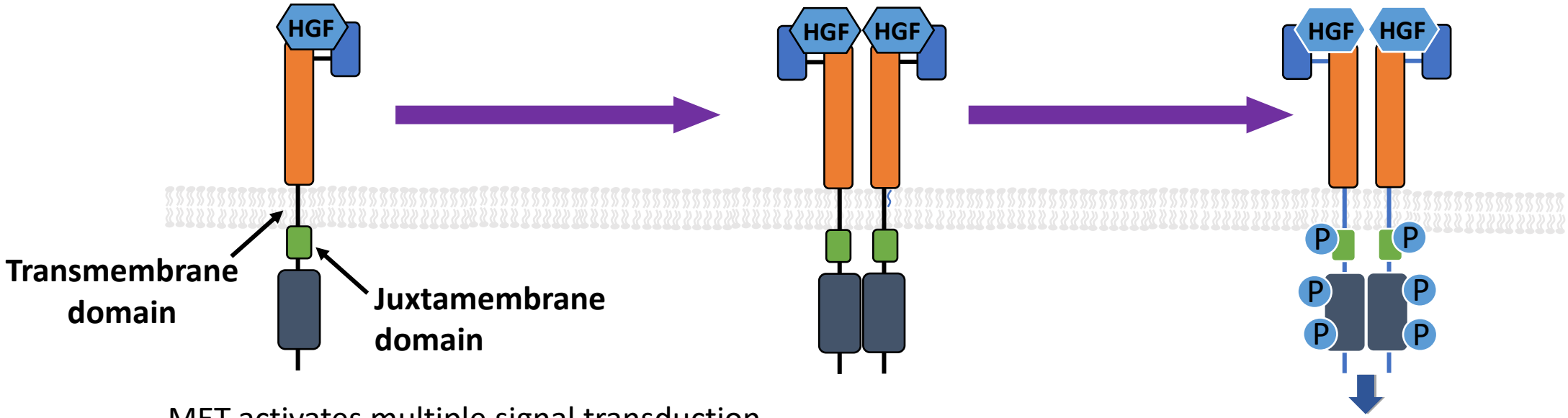
- *MET* mutation is reported to be mutually exclusive of other established molecular drivers, including *EGFR* mutations or *ALK* translocation[1–3]
- *MET* mutations in the splice site leading to exon 14 skipping result in MET juxta membrane gain-of-function alterations[4–6]
  - Originally discovered in SCLC, and later in NSCLC adenocarcinoma[4,5]
- *MET*ex14 mutations occur in 3% of NSCLC adenocarcinomas and 5–22% of other NSCLC subsets[1,3,7–10]
- *MET*ex14 mutations are linked to early-stage diagnosis and older age[10,11]

Common oncogenic mutations in NSCLC[4–9,12–14]



1. Tong JH, et al. Clin Cancer Res. 2016;22:3048-56. 2. Awad MM, et al. Lung Cancer. 2019;133:96-102. 3. Cancer Genome Atlas Research Network. Nature. 2014;511:543-50. 4. Ma PC, et al. Cancer Res. 2003;63:6272-81. 5. Ma PC, et al. Cancer Res. 2005;65:1479-88. 6. Frampton GM, et al. Cancer Discov. 2015;5:850-9. 7. Ou SHI, et al. Poster presented at ASCO 2016; abstract 9021. 8. Heist RS, et al. Oncologist. 2016;21:481-6. 9. Liu X, et al. J Clin Oncol. 2016;34:794-802. 10. Zheng D, et al. Oncotarget. 2016;7:41691-702. 11. Awad MM, et al. J Clin Oncol. 2016;34:721-30. 12. Cappuzzo F, et al. J Clin Oncol. 2009;27:1667-74. 13. Kawakami H, et al. Cancers (Basel). 2014;6:1540-52. 14. Rosell R, Karachaliou N. Lancet. 2016;387:1354-56.

Wild-Type MET Signaling



MET activates multiple signal transduction pathways

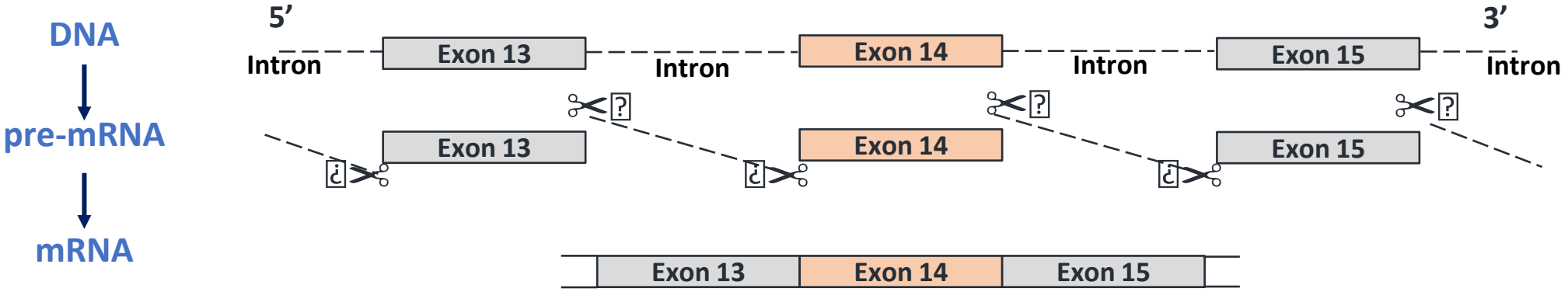
1. RAS-mitogen-activated protein kinase (MAPK) cascade,
2. the PI3K-AKT pathway
3. the Signal Transducer and Activator of Transcription (STAT)
4. NF- κB pathway

- Survival
- Decreased apoptosis
- Regulation of cytoskeletal functions
- Growth
- Differentiation
- Stemness

Salgia. Cancer Treat Rev. 2020;87:102022.

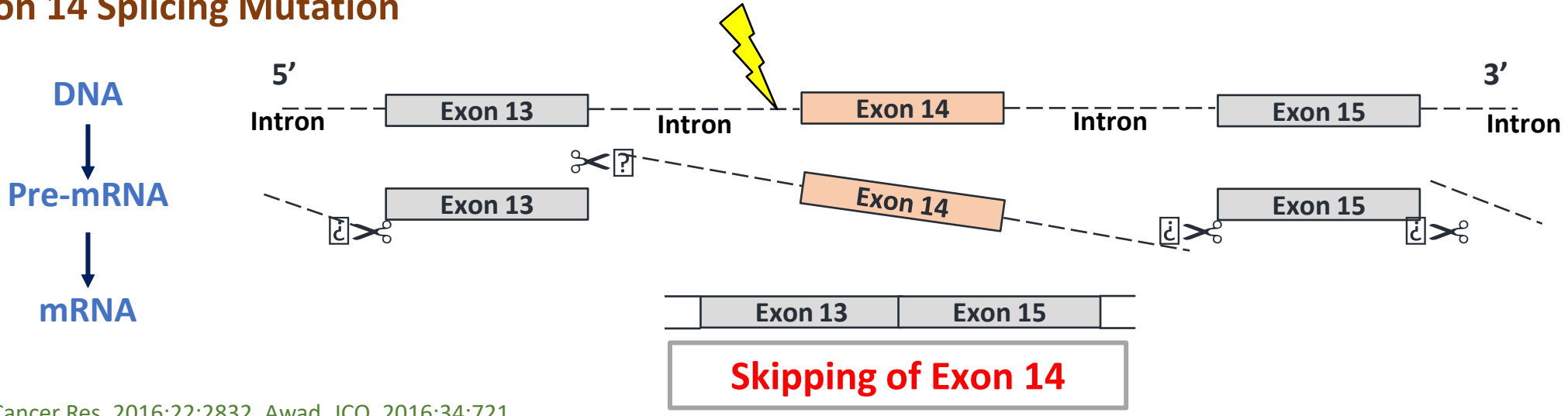
MET Exon 14–Splicing Mutations

Normal Splicing



Long arm of human chromosome 7 (7q31)

Exon 14 Splicing Mutation



Drilon. Clin Cancer Res. 2016;22:2832. Awad. JCO. 2016;34:721.

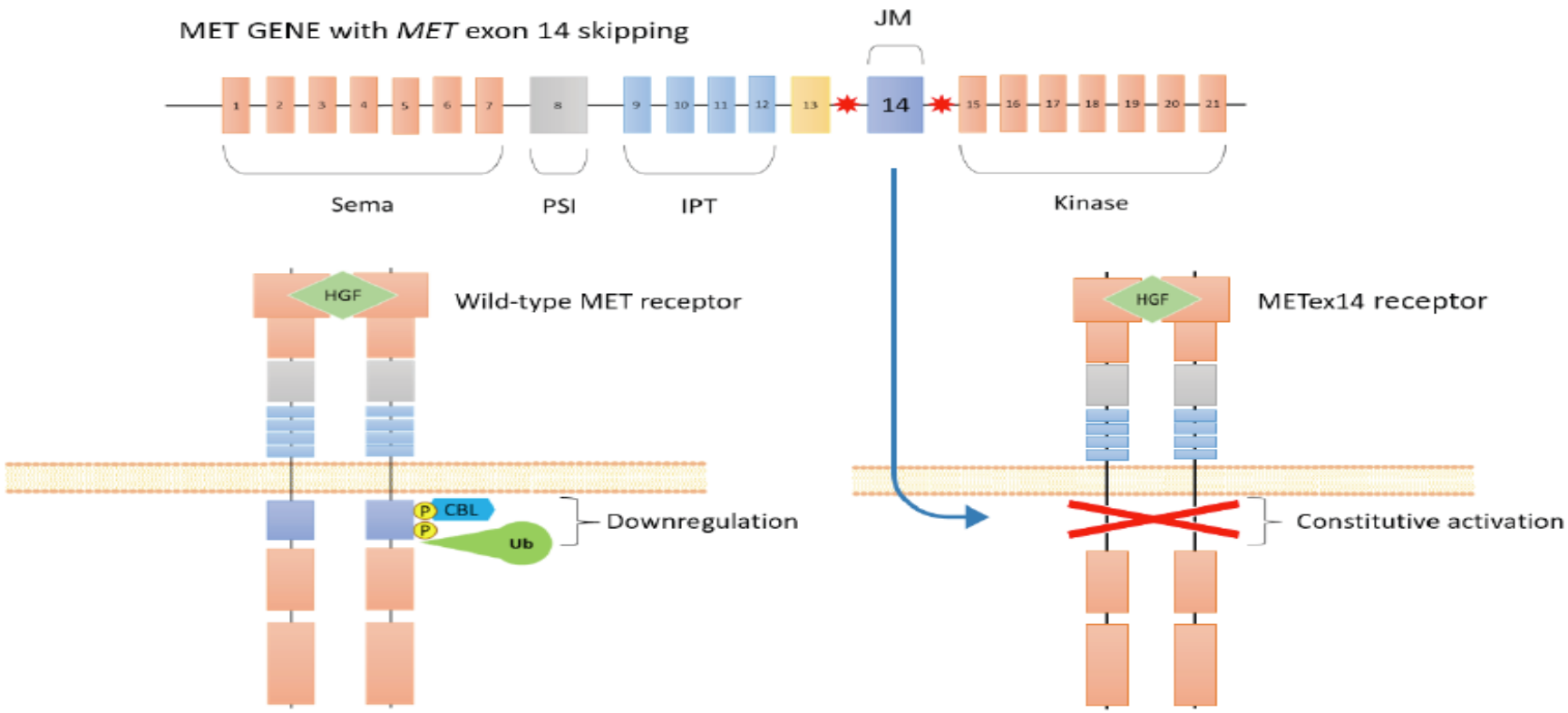


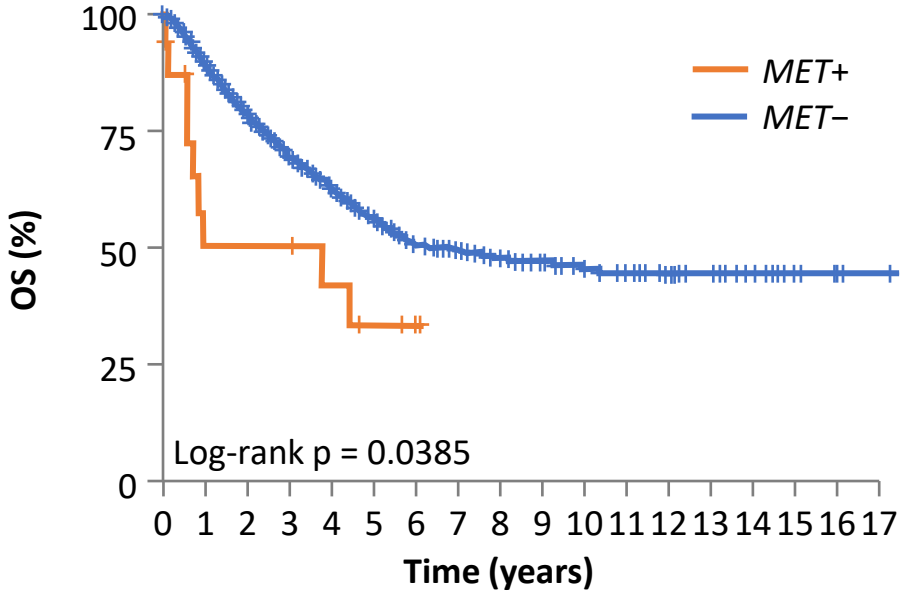
Figure 1 MET wild type and MET with exon 14 skipping mutations leading to loss of the juxtamembrane domain and constitutive activation. IPT, immunoglobulin-plexin-transcription; HGF, hepatocyte growth factor; PSI, plexin-semaphorin-integrin; JM, juxtamembrane.

Multiple different specific mutations result in the same exon 14 splice effect;
~ 20% to 30% of exon 14 mutations have coincident *MET* amplification

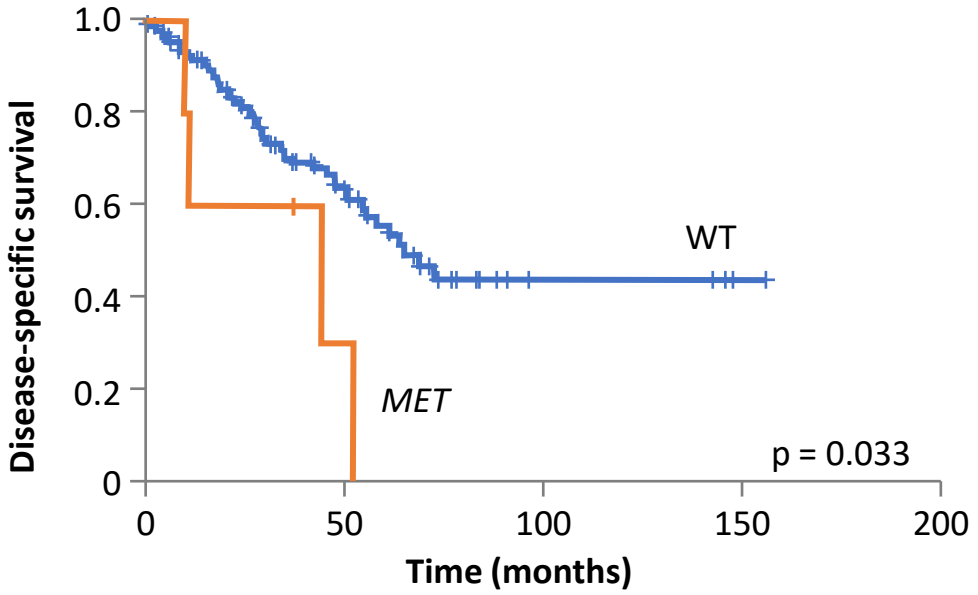
*MET*ex14 Is Associated With Worse Survival

*MET*ex14 was found to be an independent prognostic factor that predicted worse survival compared with patients without *MET* mutation[1,2]

Kaplan–Meier survival curve for OS in NSCLC according to *MET* mutation[1]



Kaplan–Meier survival curve for OS in lung adenocarcinoma according to *MET* mutation[2]

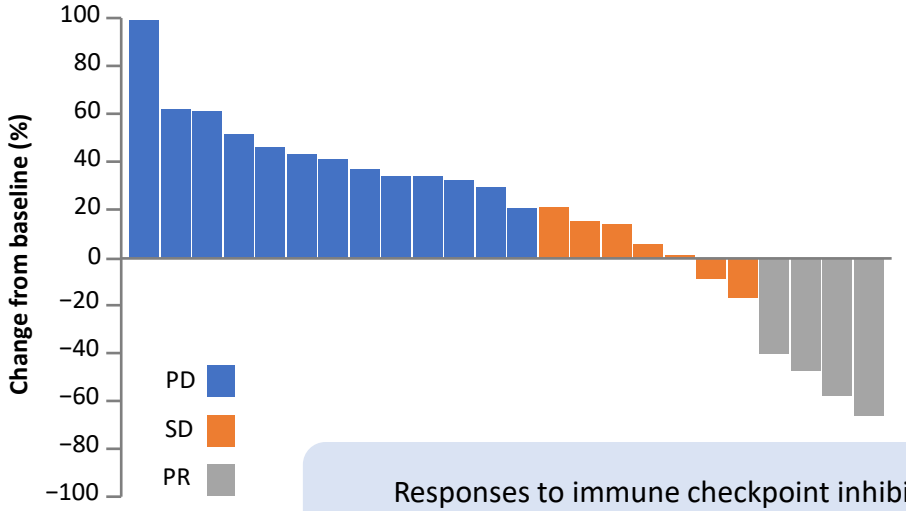


1. Tong JH, et al. Clin Cancer Res. 2016;22:3048-56.
2. Yeung SF, et al. J Thorac Oncol. 2015;10:1292-300.

*MET*ex14: Poor Response To Immunotherapy

- In a retrospective study of 147 patients with *MET*ex14 NSCLC, 24 patients who received immunotherapy were evaluable for response[1]
  - ORR 17% (95% CI 6–36)
  - Median PFS 1.9 months (95% CI 1.7–2.7)
  - Median OS 18.2 months (95% CI 12.9–NR)
- Individual case reports suggest that pembrolizumab might not be effective for NSCLC with high PD-L1 expression and *MET*ex14[2,3]

Immunotherapy	Pembro	Nivo	Nivo	Pembro	Nivo	Nivo	Nivo	Nivo	Nivo	Nivo	Durva	Pembro	Durva	Nivo	Pembro	Nivo	Pembo	Pembro	Atezo	Ipi + N	Ipi + N	Pembro	Pembro	Pembro
Histology	Sarc	Adeno	Adeno	Adeno	Adeno	Adeno	Adeno	Adeno	Adeno	Squam	Adeno	Adeno	Adeno	Adeno	Adeno	Adeno	Adeno	Adeno	Adeno	Adeno	Sarc	Adeno	Adeno	Adeno
PD-L1	90	80	80	NA	NA	0	0	0	NA	NA	90	60	NA	100	1	0	80	50	100	NA	NA	90	90	0
TMB	7.5	4.8	4.8	12.1	8.2	5.3	0.9	7.5	3.8	5.7	12.1	6.8	3.8	2.8	9.1	0.9	0.8	7.4	6.1	NA	4.9	9.9	8.4	7.3

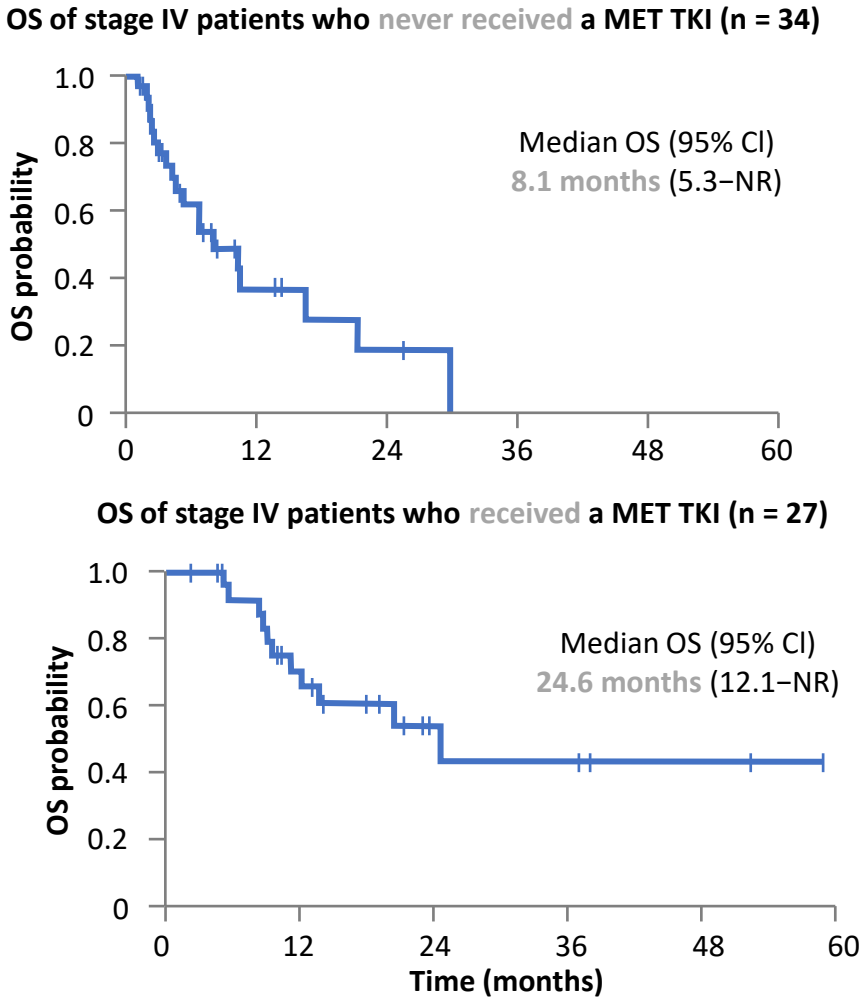


Responses to immune checkpoint inhibition were low regardless of PD-L1 expression status and TMB[1]

1. Sabari JK, et al. Ann Oncol. 2018;29:2085-91.
2. Baba K, et al. Thorac Cancer. 2019;10:369-72.
3. Reis H, et al. Clin Lung Cancer. 2018;19:e441-63.

MET inhibition prolongs survival in *MET*-mutated stage IV NSCLC

- In a retrospective study (N = 148), patients with *MET*-mutated metastatic NSCLC treated with a MET inhibitor had prolonged survival compared with those treated with other therapies
- OS in *MET*-mutated stage IV NSCLC patients was
  - 8.1 months for patients who never received a MET TKI
    - 10.5 months for patients with *MET* mutation only
    - 5.2 months for patients with *MET* mutation and concurrent amplification
- 24.6 months for patients who received a MET TKI (crizotinib, glesatinib, capmatinib)



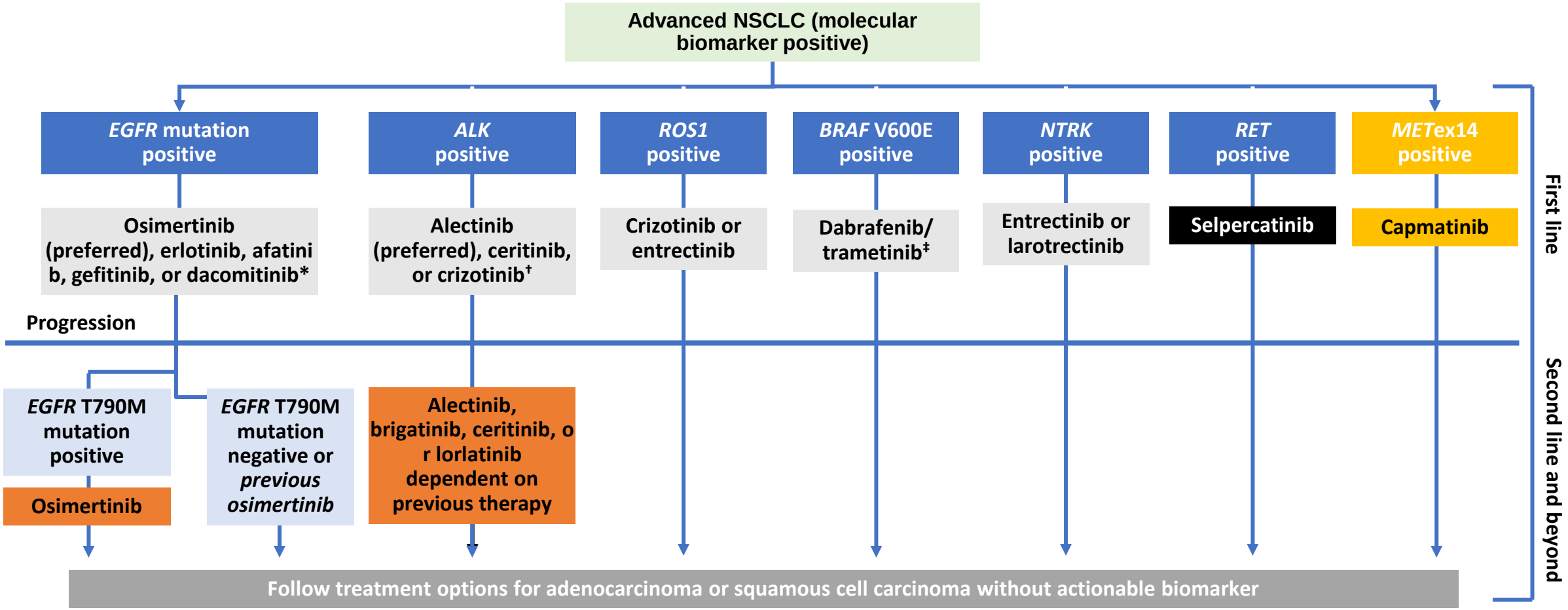
Awad MM, et al. Lung Cancer. 2019;133:96-102.

MET TKIs: Types

- Type I: ATP competitors that bind to the ATP-binding pocket of the active form (DFG-in)
    - Type Ia: more interaction with G1163
        - Crizotinib
    - Type Ib: more interaction with Y1230 (more specific)
        - Capmatinib, tepotinib, and savolitinib
- Type II: ATP competitors that bind to the inactive state (DFG-out)
    - Cabozantinib, merestinib, and glesatinib
- Type III: allosteric inhibition
    - Tivantinib

Rehman. EMJ. 2018;4:100. Reungwetwattana. Lung Cancer. 2017;103:27.
Huang. Curr Treat Options Oncol. 2020;21:33. Kufareva. J Med Chem. 2008;51:7921.

Current Treatment Paradigm for Molecular Biomarker–Positive Advanced NSCLC



*Afatinib, dacomitinib, erlotinib, gefitinib, osimertinib approved for *EGFR* exon19del, exon 21 L858R; afatinib for *EGFR* G719X, S768I, L861Q.
†Brigatinib under priority review by the FDA for first-line *ALK* positive NSCLC. ‡Or as second-line after CT.

Afatinib PI. Alectinib PI. Capmatinib PI. Ceritinib PI. Crizotinib PI. Dabrafenib PI. Dacomitinib PI. Entrectinib PI. Erlotinib PI. Gefitinib PI. Larotrectinib PI. Osimertinib PI. Selpercatinib PI. Trametinib PI.

*MET*ex14 Testing Recommendations

- IHC: Not recommended
- FISH: Not recommended
- PCR
  - DNA: design dependent
  - RNA: technical considerations
- NGS
  - DNA: design dependent, potentially detects many mutations
  - RNA: most sensitive

Guo. J Thorac Oncol. 2019;14:1666. Awad. J Clin Oncol. 2016;34:721. Pruis. Lung Cancer. 2020;140:46.
Descarpentries. J Thorac Oncol. 2018;13:1873. Davies. J Thorac Oncol. 2019;14:737.

MET Inhibitors

- **Crizotinib**: Viable off-label option for patients with *MET* exon 14–altered NSCLC but has limited CNS penetration[1]
  - Dose: 250 mg PO BID with or without food
- **Tepotinib**: On March 25, 2020, the Japanese Ministry of Health, Labour and Welfare approved tepotinib for treatment of patients with unresectable, advanced, or recurrent NSCLC with *MET* exon 14 skipping alterations[2]
  - Dose: 500 mg PO QD after food
- **Capmatinib**: On May 6, 2020, the FDA approved capmatinib for treatment of adults with metastatic NSCLC with a mutation leading to *MET* exon 14 skipping detected by FDA-approved assay[3]
  - Dose: 400 mg PO BID with or without food

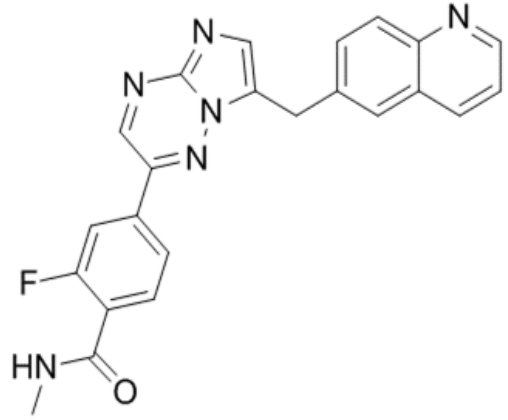
1. Drilon. Nat Med. 2020;26:47. 2. Markham. Drugs. 2020;[Epub]. 3. Capmatinib PI.

Capmatinib: A Selective MET Inhibitor

- Capmatinib is an oral, ATP-competitive, highly potent, selective, and reversible inhibitor of MET kinase[1]
  - > 10,000-fold selectivity for MET receptor kinase when assessed against a panel of 55 other human kinases[1,2]
  - Crosses the blood–brain barrier showing preliminary brain activity[3,4]
  - Potent blockade of MET activation in cell-based functional and biochemical assays, as well as in in vivo models
- Compared with other agents, capmatinib is the most potent inhibitor against *MET*ex14[5]

	Capmatinib	Savolitinib	Tepotinib	Cabozantinib	Crizotinib
IC_{50} (nM)	**0.6**	2.1	3.0	7.8	22.5

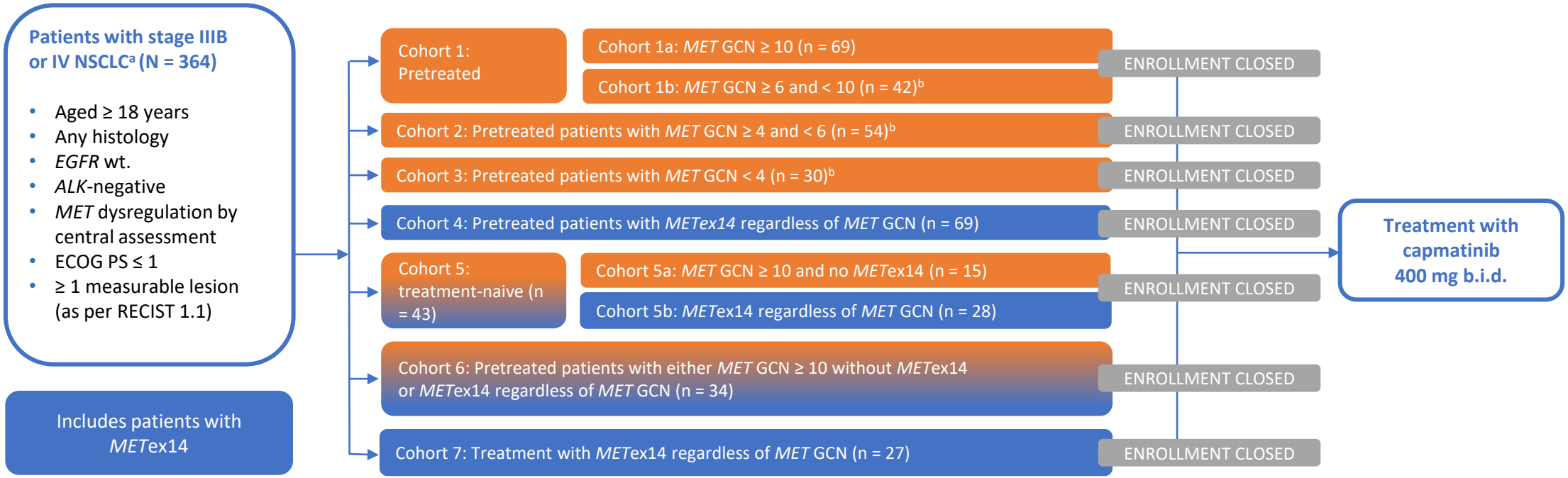
Capmatinib (INC280)[6]



1. Liu X, et al. Clin Cancer Res. 2011;17:7127-38. 2. Lara MS, et al. Clin Lung Cancer. 2017;18:281-5. 3. Wu YL, et al. Presented at WCLC 2017; abstract P1.01-97. 4. Wu Y-L, et al. J Clin Oncol. 2018;36:3101-9. 5. Fujino T, et al. Presented at WCLC 2018; abstract P1.13-41.
6. Salgia R. Mol Cancer Ther. 2017;16:555-65.

GEOMETRY mono-1: Study Design

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



[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.

GEOMETRY mono-1: Study Objectives and Endpoints

Objectives	Endpoints
Primary objective	
• Demonstrate antitumor activity of capmatinib	• ORR[a] assessed by BIRC, by cohort or Cohort
Key secondary objective	
• Evaluate the DoR to capmatinib	• DoR[a] assessed by BIRC, by cohort or Cohort
Other secondary objectives	
• Evaluate antitumor efficacy endpoints for capmatinib	• ORR and DoR[b] assessed by investigator, by cohort or Cohort • TTR, DCR, and PFS[c] assessed by investigator and BIRC, by cohort or Cohort
• Evaluate OS	• OS by cohort or Cohort
• Evaluate the safety profile of capmatinib	• AEs, vital signs, ECGs, and laboratory abnormalities
• Characterize the PK of capmatinib and metabolite CMN288	• Plasma concentration–time profiles and PK parameters

[a] BIRC-assessed using RECIST 1.1 criteria.
[b] Investigator-assessed using RECIST 1.1 criteria.
[c] BIRC- and investigator-assessed using RECIST 1.1 criteria.

INC280 (capmatinib). Clinical Trial Protocol CINC280A2201. Version 6, 28 Feb 2019. Internal data on file.
Wolf J, et al. N Engl J Med. 2020;383:944-57.

GEOMETRY mono-1: Cohort 4 and Cohort 5b – Baseline Patient Characteristics

Characteristic		METex14	
		Pretreated Cohort 4 (N = 69)	Treatment-naive Cohort 5b (N = 28)
Age	Median (range), years	71 (49–90)	71 (57–86)
	≥ 65 years, n (%)	55 (79.7)	25 (89.3)
Female, n (%)		40 (58.0)	18 (64.3)
ECOG PS, n (%)	0	16 (23.2)	7 (25.0)
	≥ 1	53 (76.8)[a]	21 (75.0)
Smoking history, n (%)	Never smoker	40 (58.0)	18 (64.3)
	Ex-smoker	27 (39.1)	9 (32.1)
	Current smoker	2 (2.9)	1 (3.6)
Histology, n (%)	Adenocarcinoma	53 (76.8)	25 (89.3)
	Squamous cell carcinoma	6 (8.7)	2 (7.1)
	Large cell carcinoma	1 (1.4)	0
	Other	9 (13.0)	1 (3.6)
Brain metastases at baseline[b], n (%)		11 (15.9)	3 (10.7)
Concurrent MET amplification, n (%)	GCN < 4	18 (26.1)	4 (14.3)
	GCN ≥ 4 and < 6	15 (21.7)	10 (35.7)
	GCN ≥ 6 and < 10	17 (24.6)	3 (10.7)
	GCN ≥ 10	11 (15.9)	4 (14.3)
	Missing	8 (11.6)	7 (25.0)

Data cut-off date: 6 January 2020.

[a] One patient in cohort 4, who had undergone randomization in error (protocol deviation), had an ECOG performance-status score of 2.

[b] For *MET*ex14 patients, 12 were identified from their medical history and 2 identified at baseline CT scan.

Wolf J, et al. N Engl J Med. 2020;383:944-57.

GEOMETRY mono-1: Cohort 4 and Cohort 5b – Prior Therapies

Prior therapies		METex14	
		Pretreated Cohort 4 (N = 69)	Treatment-naive Cohort 5b (N = 28)
Prior lines of therapy, n (%)	1 2 3	51 (73.9) 16 (23.2) 2 (2.9)	NA
Prior therapies (any line), n (%)	Chemotherapy Platinum-based chemotherapy First line Second line Single-agent chemotherapy	65 (94.2) 61 (88.4) 57 (82.6) 5 (7.2) 9 (13.0)	NA
	Immunotherapy First line Second/third line	19 (27.5) 9 (13.0) 10 (14.5)	NA
	Targeted therapy (bevacizumab)	3 (4.3)	NA

GEOMETRY mono-1: Best Overall Response in Cohort 4

Clinically meaningful responses were observed in pretreated patients with *MET*ex14 advanced NSCLC

		METex14	
		Pretreated Cohort 4 (N = 69)	
		BIRC	Investigator
Best OR, n (%)	CR	0	1 (1.4)
	PR	28 (40.6)	29 (42.0)
	SD	25 (36.2)	21 (30.4)
	Non-CR/non-PR	1 (1.4)	2 (2.9)
	PD	6 (8.7)	7 (10.1)
	NE[a]	9 (13.0)	9 (13.0)
ORR, % (95% CI)		40.6 (28.9–53.1)	43.5 (31.6–56.0)
DCR, % (95% CI)		78.3 (66.7–87.3)	76.8 (65.1–86.1)

Data cut-off date: 6 January 2020.

[a] Not qualifying for confirmed CR or PR and without SD after > 6 weeks or progression within the first 12 weeks.

Wolf J, et al. N Engl J Med. 2020;383:944-57.

GEOMETRY mono-1: Best Overall Response in Cohort 5b

Clinically meaningful responses were observed in treatment-naive patients with *MET*ex14 advanced NSCLC

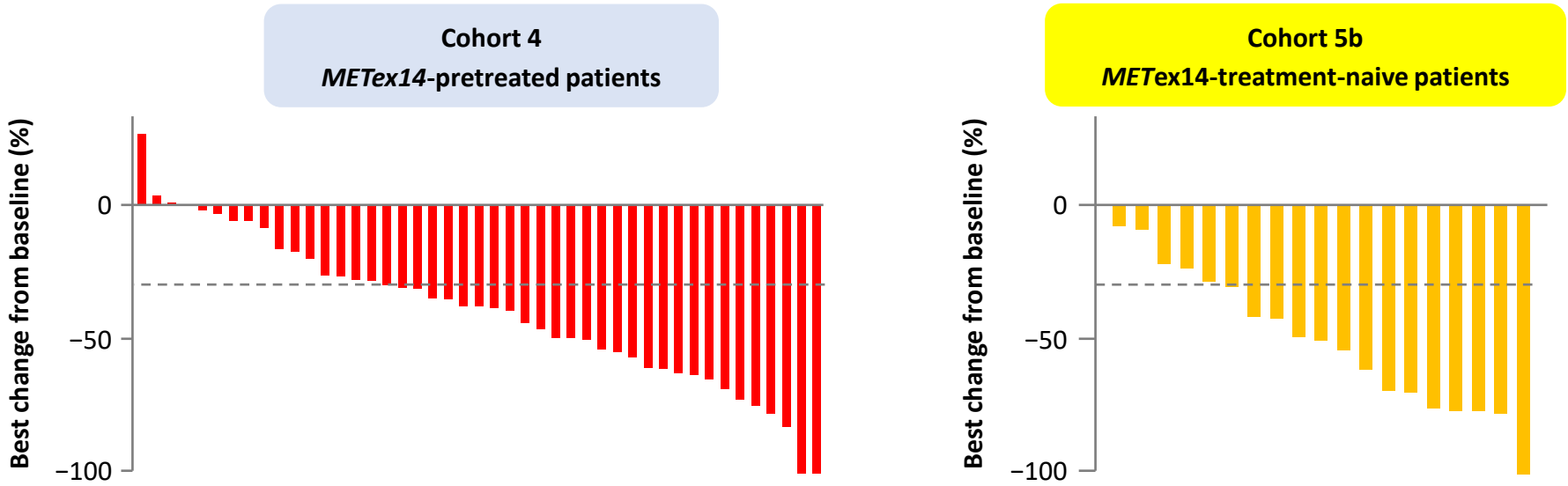
		METex14	
		Treatment-naive Cohort 5b (N = 28)	
		BIRC	Investigator
Best OR, n (%)	CR	1 (3.6)	0
	PR	18 (64.3)	17 (60.7)
	SD	7 (25.0)	10 (35.7)
	Non-CR/non-PR	1 (3.6)	0
	PD	1 (3.6)	1 (3.6)
ORR, % (95% CI)		67.9 (47.6–84.1)	60.7 (40.6–78.5)
DCR, % (95% CI)		96.4 (81.7–99.9)	96.4 (81.7–99.9)

Data cut-off date: 6 January 2020.

Wolf J, et al. N Engl J Med. 2020;383:944-57.

GEOMETRY mono-1: Cohort 4 and Cohort 5b – tumor shrinkage per BIRC

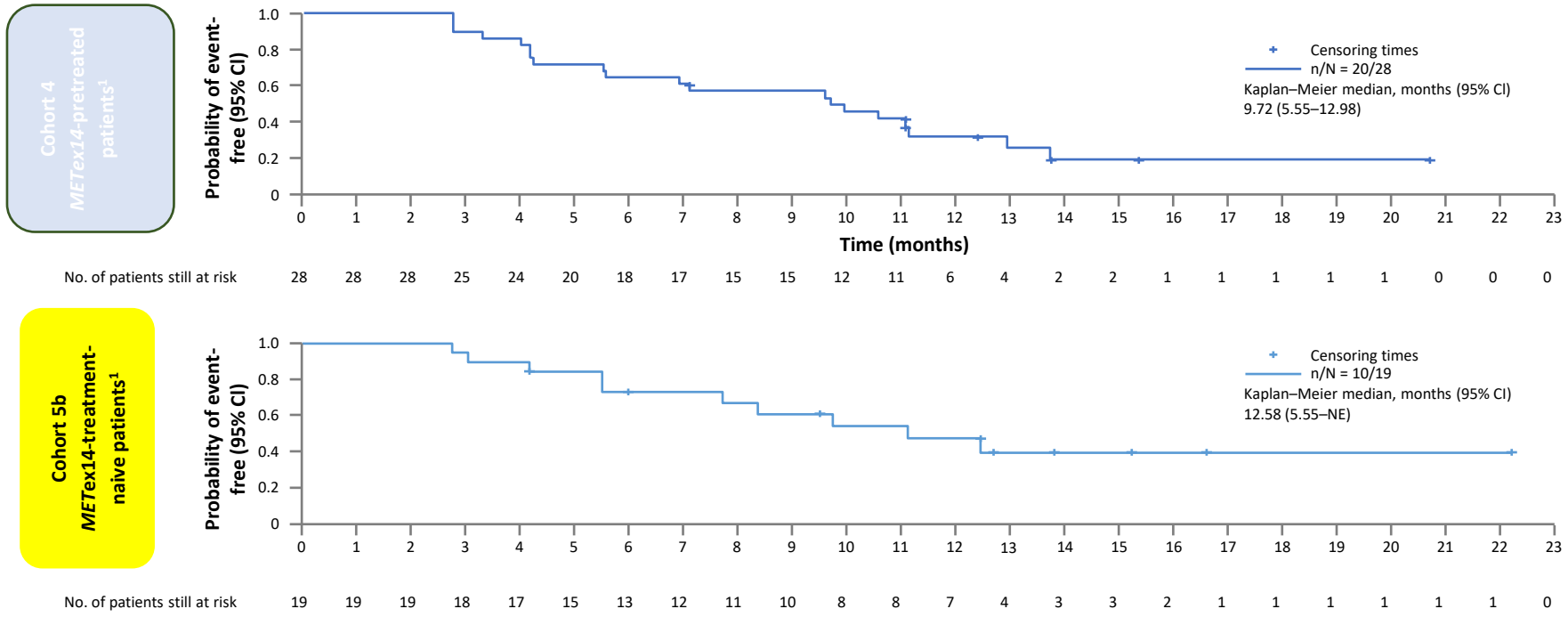
Deep responses were observed in the majority of patients across both Cohort 4 and Cohort 5b



Wolf J, et al. N Engl J Med. 2020;383:944-57.

GEOMETRY mono-1: Cohort 4 and Cohort 5b – Duration of Response per BIRC

Median DoR was 9.7 months in Cohort 4 and 12.6 months in Cohort 5b[1,2]

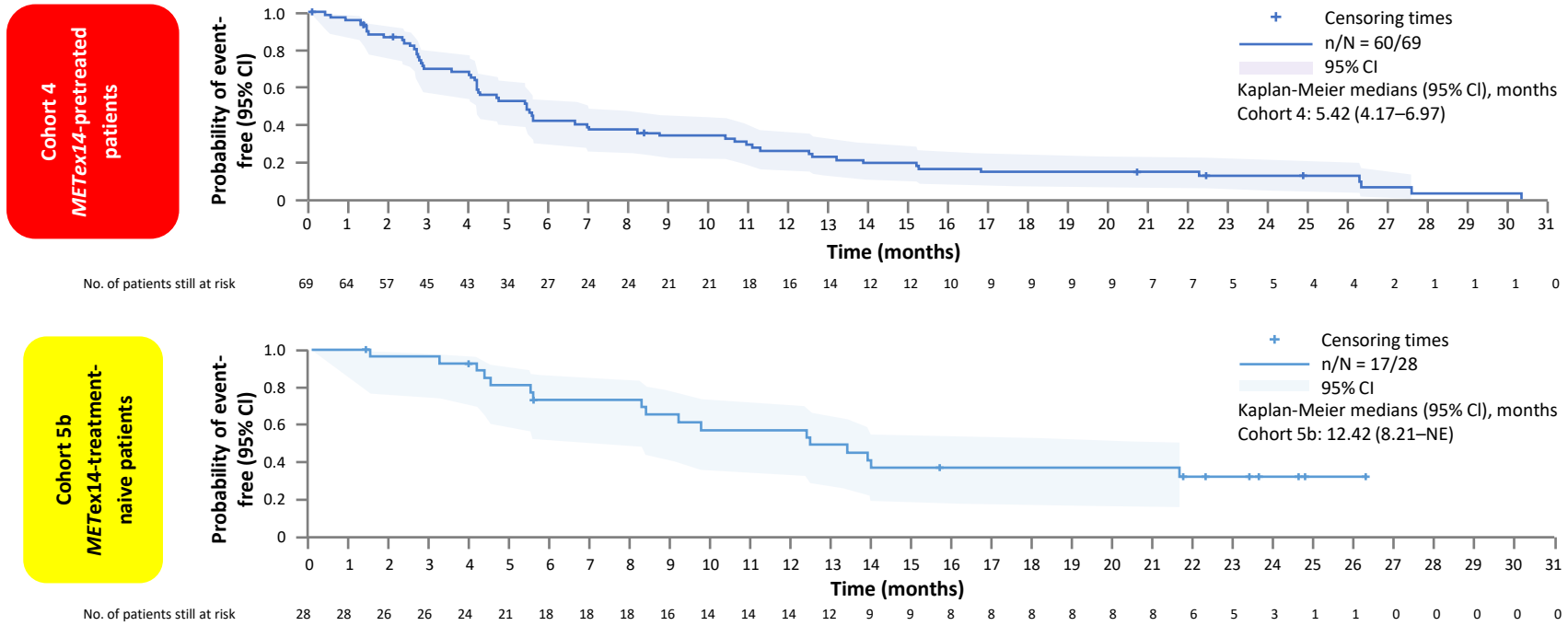


Median DoR per investigator was 8.31 months (95% CI 5.45–12.06) in Cohort 4 and 13.83 months (95% CI 4.27–25.33) in Cohort 5b.

1. Wolf J, et al. Oral presentation at ASCO 2019. J Clin Oncol. 2019;37(Suppl 15): abstract 9004.
2. Wolf J, et al. N Engl J Med. 2020;383:944-57.

GEOMETRY mono-1: Cohort 4 and Cohort 5b – Progression-Free Survival per BIRC

Median PFS was 5.42 months in Cohort 4 and 12.42 months in Cohort 5b

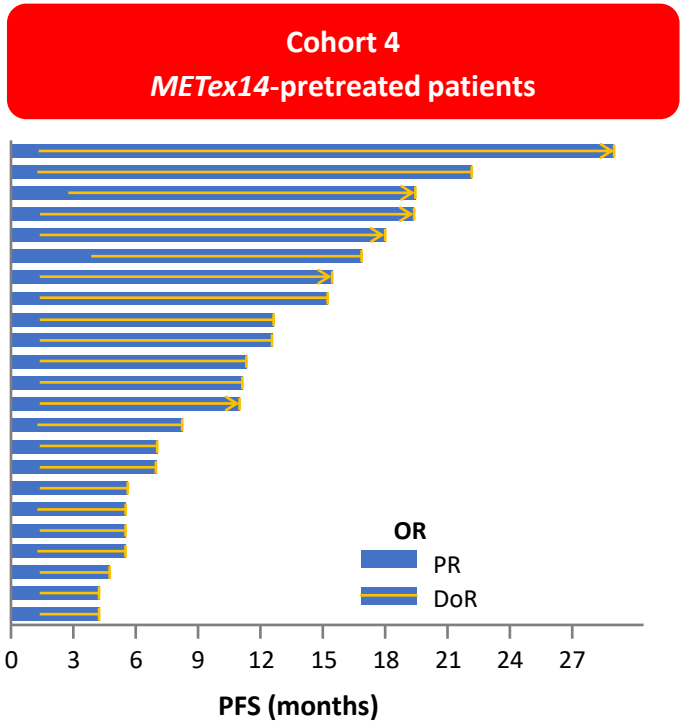


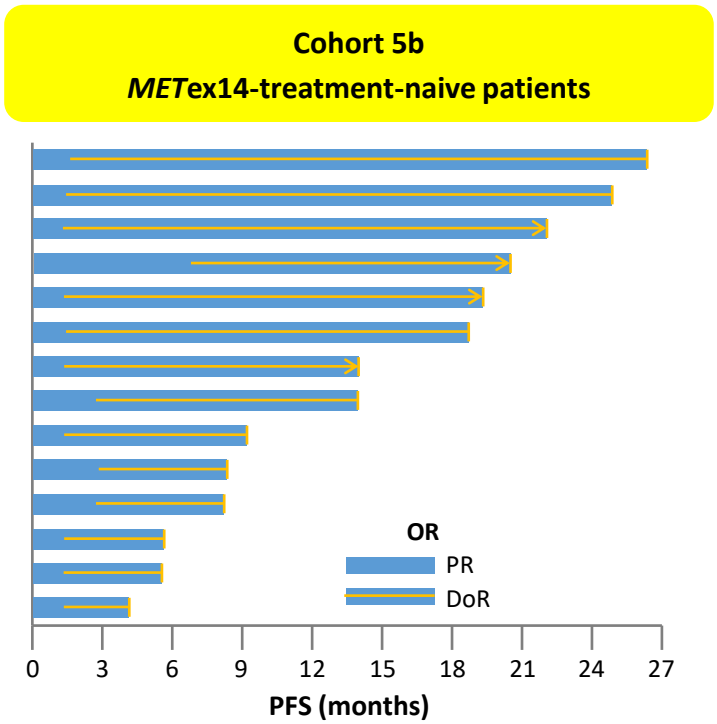
Median PFS per investigator was 4.80 months (95% CI 4.11–7.75) in Cohort 4 and 11.99 months (95% CI 5.52–16.92) in Cohort 5b.

Wolf J, et al. N Engl J Med. 2020;383:944-57.

GEOMETRY mono-1: Cohort 4 and Cohort 5b – Swimmer Plots for Responders

Rapid and durable responses across both Cohort 4 and Cohort 5b, with onset occurring at first tumor evaluation after initiating capmatinib in 82.1% of patients in Cohort 4 and 68.4% in Cohort 5b

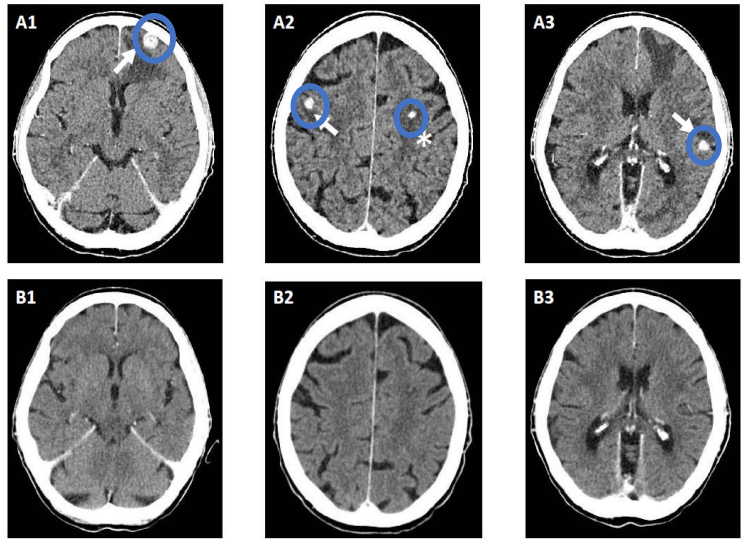




Wolf J, et al. N Engl J Med. 2020;383:944-57.

GEOMETRY mono-1 Cohort 4 and Cohort 5b – Confirmed Activity Against Brain Metastases

- 13 evaluable patients with brain metastases at baseline by BIRC (mean 3.3 lesions per patient [range 1–8])[1]
- 54% (N = 7/13) had an intracranial response[1,a]
  - 4 had complete resolution of all brain lesions
  - Of the remaining 3 patients
    - 1 had complete resolution in 3 lesions, stabilization in 4 lesions
    - 1 had complete resolution in 2 lesions, stabilization in 1 lesion
    - 1 had complete resolution in 1 lesion, stabilization in 3 lesions
- Intracranial responses were as fast as responses in extracranial lesions[1]
  - All 7 responders in the brain had an intracranial response at the first evaluation (6 weeks from the start of treatment)
- 12/13 patients had intracranial disease control[1,2]



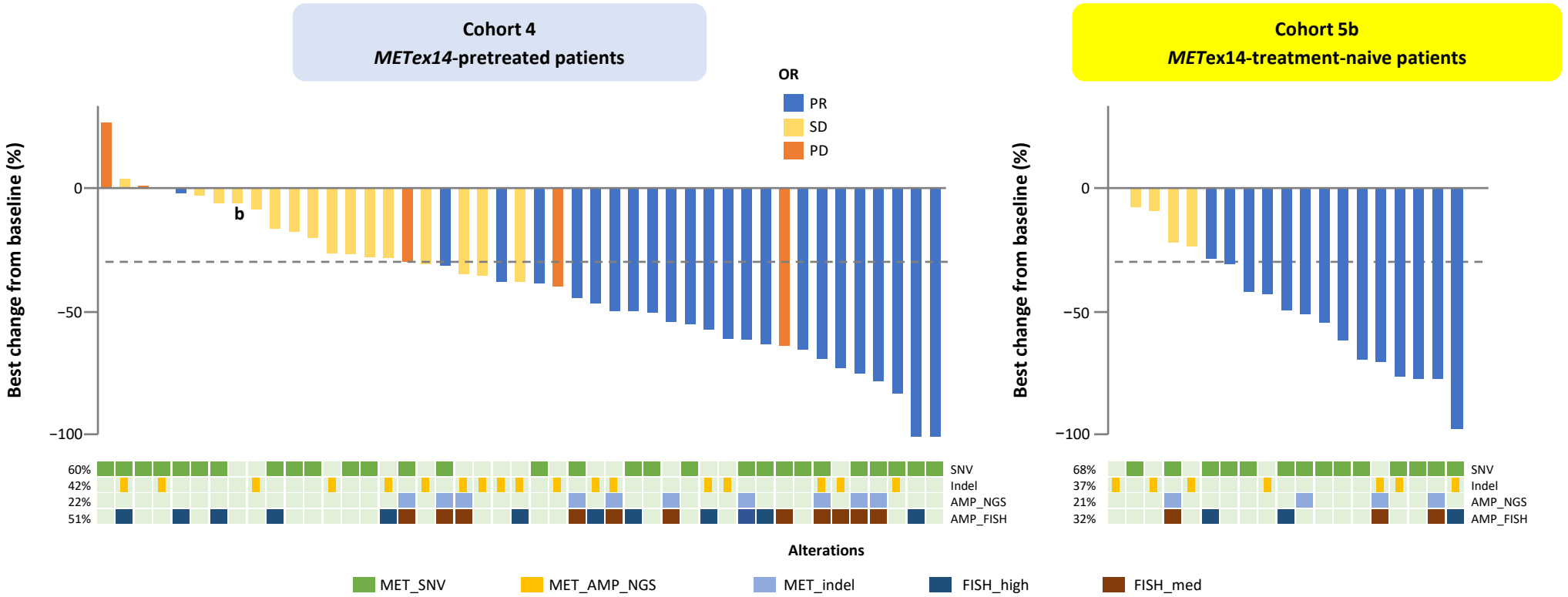
[a] All responses were confirmed at next staging.

CT images courtesy Dr Johan Vansteenkiste (University Hospitals KU Leuven, Leuven, Belgium), informed consent by the patient.

1. Garon EB, et al. Oral presentation at the AACR 2020 (virtual meeting); abstract CT082. 2. Wolf J, et al. N Engl J Med. 2020;383:944-57.

GEOMETRY mono-1: Cohort 4 and Cohort 5b – Tumor Shrinkage by *MET* alterations

Deep responses were observed independent of type of *MET* mutation (SNV, Indel), leading to *MET*ex14 or co-occurrence of *MET* amplification[a]



[a] 64 tissue samples; Cohort 4 = 45 (including 1 patient with a noncanonical *METex14* rearrangement and no canonical variants), Cohort 5b = 19.

[b] Patient had noncanonical *METex14* due to internal rearrangement and no known SNV or Indel variant.

AMP_FISH, *MET* FISH copy number; AMP_NGS, amplification detected by FM NGS panel ≥ 6 GCN.

Wolf J, et al. N Engl J Med. 2020;383:944-57.

Capmatinib in MET exon 14-mutated, advanced NSCLC: Updated results from the GEOMETRY mono-1 study

Study design

Key eligibility criteria:

- Stage IIIB/IV
- *MET*ex14 irrespective of *MET* GCN by central RT-PCR
- *EGFR* WT (for L858R and delE19) and *ALK* fusion-negative
- PS 0-1
- ≥ 1 measurable lesions (RECIST 1.1)
- Neurologically stable or asymptomatic brain metastases allowed

Capmatinib 400 mg BID

Pretreated : 1 or 2 prior treatment lines

Cohort 4: *MET*ex14 (any GCN) N = 69

Treatment-naive

Cohort 5b: *MET*ex14 (any GCN) N = 28

Pretreated : 1 prior treatment line

Expansion cohort 6: *MET*ex14 (any GCN) N = 31[a]

Treatment-naive

Expansion Cohort 7: *MET*ex14 (any GCN) N = 32

Primary endpoint

- ORR by BIRC

Key secondary endpoint

- DOR by BIRC

Secondary endpoints

- ORR and DOR (investigator)
- TTR, DCR, PFS (BIRC/investigator)
- OS
- Safety
- Pharmacokinetics

BID, twice daily; BIRC, blinded independent review committee; DCO, data cutoff; DCR, disease control rate; DOR, duration of response; GCN, gene copy number; *MET*ex14, *MET* exon 14 skipping; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; RT-PCR, reverse transcription polymerase chain reaction; TTR, time to response; WT, wild-type.

1. Wolf J, et al. *N Engl J Med*. 2020;38:944-957; 2. Wolf J, et al. *ASCO* 2021. Poster 9020.

Results: 66.7% Response Rate and 98.3% Disease Control in First-Line

- Very high overall response and disease control rates in treatment-naive patients from cohort 5b[1] was confirmed in the expansion cohort 7.[2]
- Consistent responses between BIRC and investigator assessments in treatment-naive patients with *MET*ex14 in cohort 5b[1]

	Cohort 5b; N = 28		**Cohort 7; N = 32**
Assessment	BIRC[1,2]	Investigator[1]	BIRC[2]
Best overall response, n (%)			
CR	1 (3.6)	0	0
PR	18 (64.3)	17 (60.7)	21 (65.6)
SD	8 (28.6)	10 (35.7)	11 (34.4)
PD	1 (3.6)	1 (3.6)	0
ORR[a], % (95% CI)	67.9 (47.6-84.1)	60.7 (40.6-78.5)	65.6 (46.8-81.4)
DCR[b], % (95% CI)	96.4 (81.7-99.9)	96.4 (81.7-99.9)	100.0 (89.1-100.0)

BIRC, blinded independent review committee; CI, confidence interval; CR, complete response; DCR, disease control rate; *MET*ex14, *MET* exon 14 skipping; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

1. Wolf J, et al. *N Engl J Med*. 2020;38:944-957; 2. Wolf J, et al. *ASCO* 2021. Poster 9020.

Results: 51.6% and 40.6% Response Rate for patients in second- and second/third-line, respectively

- High overall response rate and disease control rate in the second-/third-line setting in cohort 4, and in the second-line setting in the expansion cohort 6[1,2]
- 44% ORR in all 100 patients

	Cohort 4 (2/3L) N = 69		Cohort 6 (2L); Group 2, N = 31[a]
Assessment	BIRC[1,2]	Investigator[1]	BIRC[2]
Best overall response, n (%)			
CR	0	1 (1.4)	0
PR	28 (40.6)	28 (40.6)	16 (51.6)
SD	25 (36.2)	22 (31.9)	11 (35.5)
Non-CR/non-PD	1 (1.4)	2 (2.9)	1 (3.2)
PD	6 (8.7)	7 (10.1)	0
Not evaluable[b]	9 (13.0)	9 (13.0)	3 (9.7)
ORR[c], % (95% CI)	40.6 (28.9-53.1)	42.0 (30.2-54.5)	51.6 (33.1-69.8)
DCR[d], % (95% CI)	78.3 (66.7-87.3)	76.8 (65.1-86.1)	90.3 (74.2-98.0)

Cut-off date for analyses: April 15, 2019[1] and September 18, 2020[2]. All responses confirmed per RECIST 1.1.
[a] Cohort 6 also enrolled patients with *MET* amplification GCN ≥ 10 in group 1, n = 3.
[b] Not qualifying for confirmed CR or PR and without SD after > 6 weeks or progression within the first 12 weeks.
[c] ORR = CR + PR.
[d] DCR = CR + PR + SD + (non-CR/non-PD).

BIRC, blinded independent review committee; CI, confidence interval; CR, complete response; DCR, disease control rate; GCN, gene copy number; L, line of therapy; *MET*ex14, *MET* exon 14 skipping; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

1. Wolf J, et al. *N Engl J Med*. 2020;38:944-957; 2. Wolf J, et al. *ASCO* 2021. Poster 9020.

Results: The majority of patients experienced a tumor response at first evaluation after initiating capmatinib, with durable responses.

- Rapid and durable responses were observed irrespective of line of therapy.[1]
  - In patients with a response to capmatinib, the majority of responses occurred within **2 months of starting treatment**.[1]
- Median DOR to capmatinib
  - 12.6 months in first-line
  - 8.4 months in second-line
  - 9.7 months in second/third-line[1]
- Median PFS
  - 12.3 months in first-line
  - 6.9 months in second-line
  - 5.4 months in second/third-line[1]

Outcome	Cohort 5b (1L), N = 28	Cohort 7 (1L), N = 32	All patients 1L N = 60	Cohort 4 (2/3L), N = 69	Cohort 6 (2L), N = 31
DOR, months, median (95% CI)[a]	12.6 (5.6-NE)	NE (5.5-NE)	12.6 (8.4-NE)	9.7 (5.6-13.0)	8.4 (4.2-NE)
PFS, months, median (95% CI)[a]	12.4 (8.2-23.4)	10.8 (6.9-NE)	12.3 (8.2-21.6)	5.4 (4.2-7.0)	6.9 (4.2-13.3)
TTR ≤ 7 weeks, n/N (%)[b]	13/19 (68.4)	14/21 (66.7)	27/40 (67.5)	23/28 (82.1)	10/16 (62.5)

Data cut-off September 18, 2020.

[a] BIRC assessment.

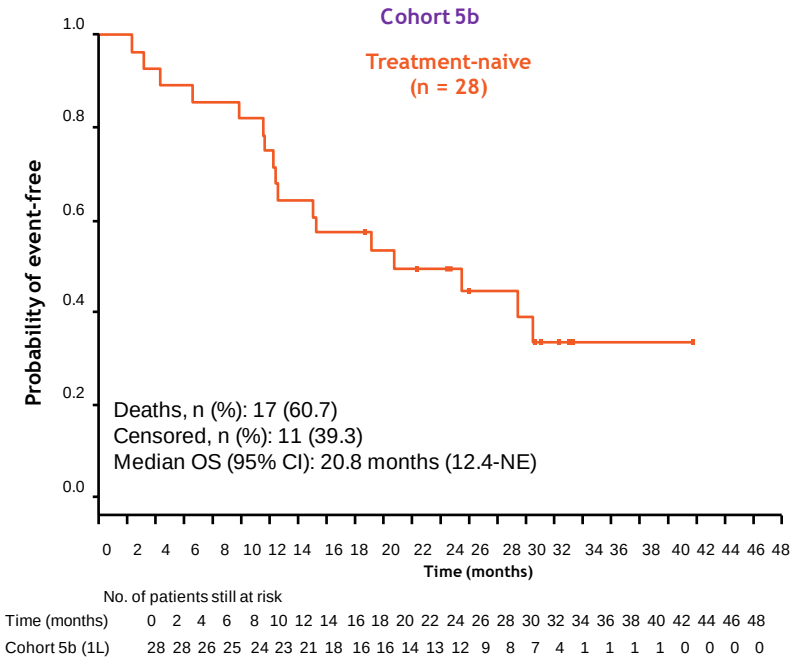
[b] The denominator N refers to the number of patients who had a response.

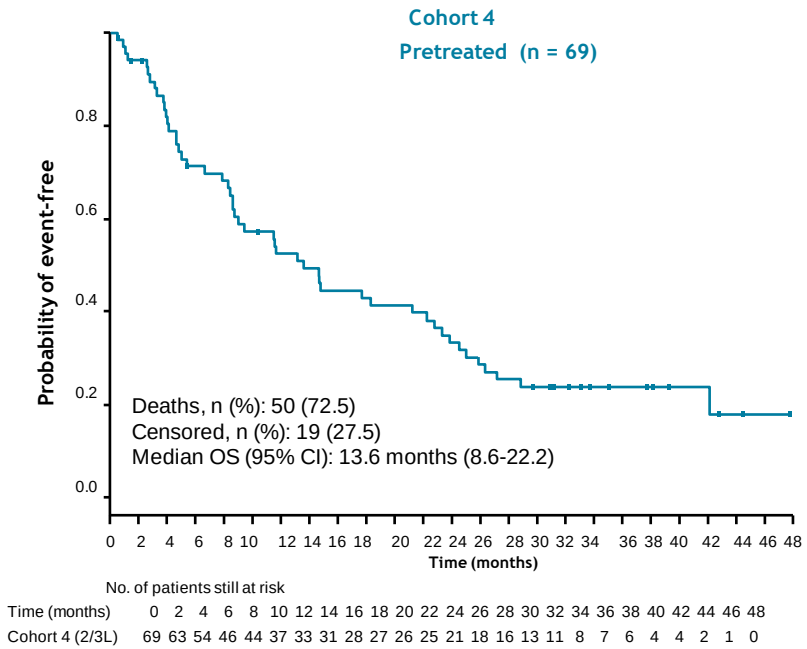
BIRC, blinded independent review committee; CI, confidence interval; DOR, duration of response; L, line of therapy; *MET*ex14, *MET* exon 14 skipping; NE, not estimable; NSCLC, non-small cell lung cancer; PFS, progression-free survival; TTR, time to response.

1. Wolf J, et al. ASCO 2021. Poster 9020.

Results: A clinically meaningful median Overall Survival of 20.8 months in first-line (cohort 5b) and 13.6 months in second/third-line (cohort 4) was observed.

- Mature OS data reported for cohorts 5b and 4
- Data still immature for expansion cohorts 6 and 7[1]





CI, confidence interval; L, line of therapy; *MET*ex14, *MET* exon 14 skipping; NE, not estimable; NSCLC, non-small cell lung cancer; OS, overall survival.

1. Wolf J, et al. *ASCO* 2021. Poster 9020.

GEOMETRY mono-1: Safety

TRAEs With Capmatinib Occurring in ≥ 10% of Patients,* n (%)	All Patients (N = 334)	
	Any Grade	Grade 3/4
Any	282 (84.4)	119 (35.6)
Peripheral edema	139 (41.6)	25 (7.5)
Nausea*	111 (33.2)	6 (1.8)
Creatinine increased†	65 (19.5)	0
Vomiting*	63 (18.9)	6 (1.8)
Fatigue	46 (13.8)	10 (3.0)
Appetite decreased†	42 (12.6)	3 (0.9)
Diarrhea	38 (11.4)	1 (0.3)

*Capmatinib given under fasting conditions; food restrictions lifted for subsequent Cohorts 6-7. †Known to inhibit creatinine transporters.

Safety Outcome, n (%)	All Patients (N = 334)
Median exposure, wks	14.9
Grade 4 AE	15 (4.5)
Dose adjustment due to TRAE	73 (21.9)
Discontinuation due to TRAE	37 (11.1)
Most common TRAEs leading to discontinuation in ≥ 1% of patients ▪ Peripheral edema ▪ Pneumonitis ▪ Fatigue	 6 (1.8) 5 (1.5) 5 (1.5)
Serious TRAE	43 (12.9)

- Safety analysis performed on largest dataset to date of patients with *MET*-altered NSCLC
- Capmatinib well tolerated; limited grade 3/4 AEs

Wolf. ASCO 2019. Abstr 9004.

Results: Peripheral edema, gastrointestinal symptoms, and increased blood creatinine were the most frequent adverse events.

- Out of 373 patients across all cohorts, including patients with *MET*ex14 and *MET* amplification, 367 (98.4%) experienced an AE of any grade irrespective of study-drug relationship.
- Peripheral edema (54%), nausea (45%), vomiting (28%), and increased blood creatinine (27%) reported in the GEOMETRY mono-1 trial[1]
- SAEs of any grade and irrespective of study-drug relationship were reported in 190 (50.9%) patients.

AEs regardless of causality (≥ 20% all grades)	All patients (N = 373)	
	All grades, n (%)	Grade 3/4, n (%)
Any	367 (98.4)	256 (68.6)
Peripheral edema	202 (54.2)	36 (9.7)
Nausea	168 (45.0)	9 (2.4)
Vomiting	105 (28.2)	9 (2.4)
Increased blood creatinine[a]	99 (26.5)	0
Dyspnea	87 (23.3)	25 (6.7)
Fatigue	83 (22.3)	16 (4.3)
Decreased appetite	79 (21.2)	4 (1.1)

The safety set includes patients with *MET*ex14 or *MET* amplification.
Data cut-off September 18, 2020.

AE, adverse event; *MET*ex14, *MET* exon 14 skipping; NSCLC, non-small cell lung cancer; SAE, serious adverse event.

1. Wolf J, et al. *ASCO* 2021. Poster 9020.

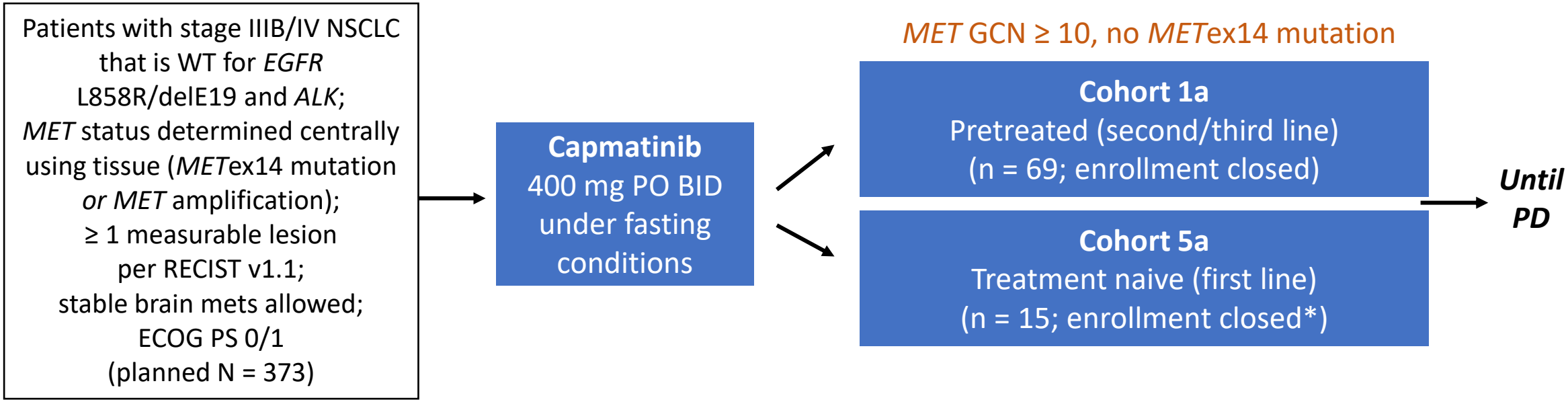
Conclusions

- The preliminary efficacy results of expansion cohort 7 (65.6% ORR) are comparable to those previously reported for cohort 5b (67.9% ORR), both in treatment-naive patients with *MET*ex14 NSCLC.
- In pretreated patients, the ORR was 51.6% in 2L (cohort 6) and 40.6% in 2/3L (cohort 4).
- Clinically meaningful median OS of 20.8 months and 13.6 months were observed in treatment-naive (cohort 5b) and pretreated patients (cohort 4), respectively, demonstrating a long-term survival benefit of capmatinib in these patient populations.
- The manageable safety profile of capmatinib remains unchanged based on the updated safety results from the GEOMETRY mono-1 study.
- The updated results further confirm *MET*ex14 as a targetable oncogenic driver in NSCLC and strengthen the evidence for capmatinib as a valuable targeted treatment option for patients with *MET*ex14 NSCLC.

L, line of therapy; *MET*ex14, *MET* exon 14 skipping; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival

Capmatinib in NSCLC With High-Level *MET* Amplification (GEOMETRY mono-1): Study Design

- Single-arm, multicohort phase II study
  - Current analysis of cohorts 1a, 5a with NSCLC and high-level *MET* amplification (data cutoff: Jan. 6, 2020)



Primary endpoint: ORR per BIRC

Key secondary endpoint: DoR per BIRC

Other secondary endpoints: investigator-assessed DoR, ORR; investigator-/BIRC-assessed DCR, PFS, TTR; OS; PK; safety

Wolf. ASCO 2020. Abstr 9509. NCT02414139.

Capmatinib in NSCLC With High-Level *MET* Amplification (GEOMETRY mono-1): Response

Response	Pretreated Cohort 1a (n = 69)		Treatment-Naive Cohort 5a (n = 15)	
	BIRC	Investigator	BIRC	Investigator
Best overall response, n (%)				
▪ CR	1 (1.4)	1 (1.4)	0	0
▪ PR	19 (27.5)	18 (26.1)	6 (40.0)	6 (40.0)
▪ SD	28 (40.6)	23 (33.3)	4 (26.7)	5 (33.3)
▪ Non-CR/non-PD	1 (1.4)	0	0	0
▪ PD	12 (17.4)	21 (30.4)	4 (26.7)	3 (20.0)
▪ Not evaluable*	8 (11.6)	6 (8.7)	1 (6.7)	1 (6.7)
ORR, % (95% CI)	**29.0 (18.7-41.2)[‡]**	27.5 (17.5-39.6)	**40.0 (16.3-67.7)[‡]**	40.0 (16.3-67.7)
DCR,[†] % (95% CI)	71.0 (58.8-81.3)	60.9 (48.4-72.4)	66.7 (38.4-88.2)	73.3 (44.9-92.2)
Median DoR, mos (95% CI)	**8.31 (4.17-15.44)[§‖]**	6.80 (4.21-20.73)[¶]	**7.54 (2.56-14.26)[§#]**	9.66 (4.01-17.08)[#]

*All other cases (ie, those not qualifying for confirmed CR/PR and also without SD > 6 wks or PD within first 12 wks).
[†]DCR = CR + PR + SD + non-CR/non-PD. [‡]Primary endpoint. [§]Key secondary endpoint. [‖]n = 20. [¶]n = 19. [#]n = 6.

- Deep responses found in most patients in both cohorts when tumor shrinkage assessed by BIRC

Wolf. ASCO 2020. Abstr 9509.

Capmatinib in NSCLC With High-Level *MET* Amplification (GEOMETRY mono-1): Conclusions

- In patients with NSCLC and high-level *MET* amplification (GCN ≥ 10) on GEOMETRY mono-1, capmatinib associated with antitumor activity in pretreated and treatment-naive patients
  - ORR per BIRC (primary endpoint): pretreated Cohort 1a, 29.0%; treatment-naive Cohort 5a, 40.0%
  - Lower ORRs vs those with *MET* exon 14 skipping mutation (pretreated, 40.6%; treatment naive, 67.9%)
- In GEOMETRY mono-1 study population, a higher proportion of patients with high-level *MET* amplification were male, had a history of smoking compared to those with *MET*ex14 mutations
  - High-level *MET* amplification: male, 73.3% to 78.3%; never smoked, 7.2% to 13.3%; *MET* exon 14 skipping mutation: male, 35.7% to 42.0%; never smoked, 58.0% to 64.3%
- Favorable safety profile, with no new safety signals observed
- Investigators concluded that patients with NSCLC and high-level *MET* amplification may benefit from MET inhibitor–based therapy
  - All pretreated cohorts with lower-level *MET* amplification (GCN < 10) closed due to futility

Wolf. ASCO 2020. Abstr 9509. Wolf. ASCO 2019. Abstr 9004.

Update of Phase II GEOMETRY mono-1 Study of Capmatinib in *MET*-Amplified or *METex14+* NSCLC

Efficacy Outcome	Cohort 1a[1] (2/3L, *MET* Amp*) (n = 69)		Cohort 5a[1] (1L, *MET* Amp*) (n = 15)		Cohort 6[2] (2L, *METex14+*) (n = 31)	
	BIRC	**Investigator**	**BIRC**	**Investigator**	**BIRC**	**Investigator**
ORR, % (95% CI)	29 (18.7-41.2)	27.5 (17.5-39.6)	40 (16.3-67.7)	40 (16.3-67.7)	48.4 (30.2-66.9)	41.9 (24.5-60.9)
DCR, % (95% CI)	71.0 (58.8-81.3)	60.9 (48.4-72.4)	66.7 (38.4-88.2)	73.3 (44.9-92.2)	90.3 (74.2-98.0)	90.3 (74.2-98.0)
Median PFS, mos (95% CI)	4.07 (2.86-4.83)	4.14 (2.79-5.52)	4.17 (1.45-6.87)	2.76 (1.45-6.87)	8.11 (4.17-9.86)	6.9 (5.55-NE)
Median DoR, mos (95% CI)	(n = 20) 8.31 (4.17-15.44)	(n = 19) 6.80 (4.21-20.73)	(n =6) 7.54 (2.56-14.26)	(n = 6) 9.66 (4.01-17.08)	(n = 15) 6.93 (4.17-NE)	(n = 13) 8.18 (4.17-NE)

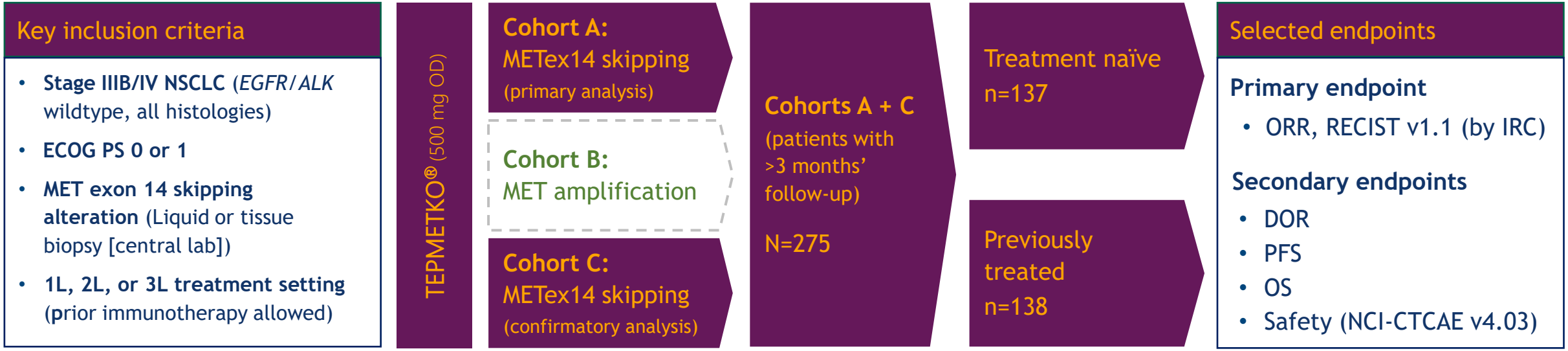
*High-level MET amp (GCN ≥ 10).

- Most common AEs in ≥ 25%: peripheral edema, nausea, vomiting, fatigue, back pain

1. Wolf. ASCO 2020. Abstr 9509. 2. Groen. ASCO 2020. Abstr 9520.

VISION is a Phase II multicenter trial of tepotinib in patients with NSCLC harboring MET alterations

- Patients received oral tepotinib 500 mg once daily until disease progression, intolerable toxicity, or withdrawal of consent[1,2]
- **Efficacy** was assessed in patients in Cohorts A and C with >3 months' follow-up (N=275)[2]
- **Safety** was analyzed in all patients in Cohorts A and C who had received at least one dose of tepotinib by the data cutoff date (February 1, 2021; n=291)[2]

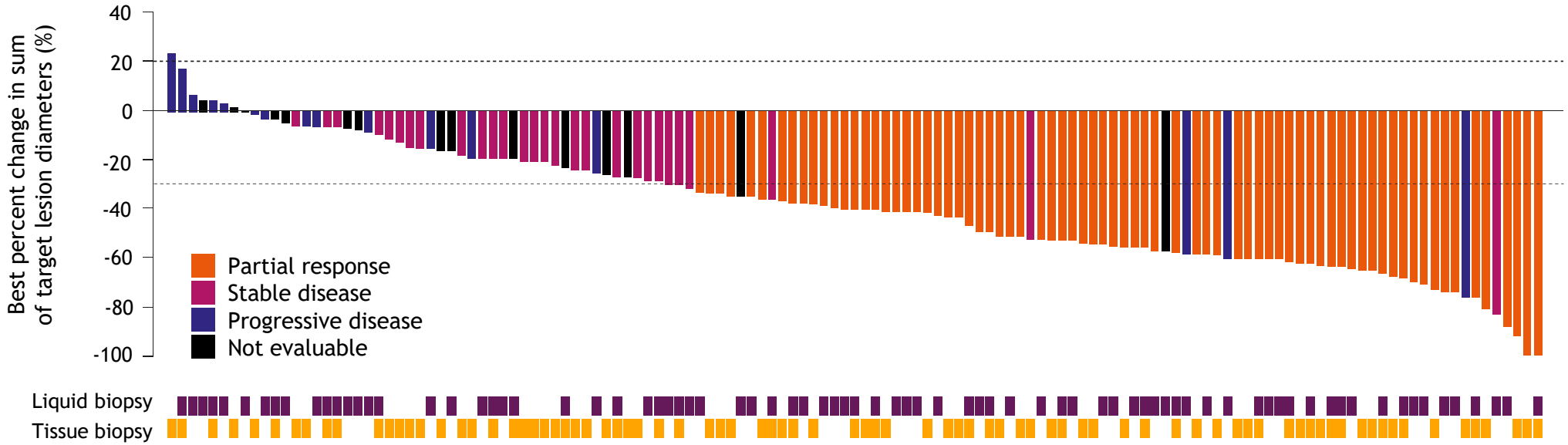


DOR, duration of response; IRC, independent review committee; MET, mesenchymal-epithelial transition factor; METex14, MET exon 14; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

1. Paik PK, et al. *N Engl J Med* 2020; 383:931-943. 2. Thomas T, et al. Presented at the DGHO Congress 2021, Oct 1-4, 2021 (V52).

Over 90% of treatment-naïve patients treated with tepotinib experienced tumor shrinkage

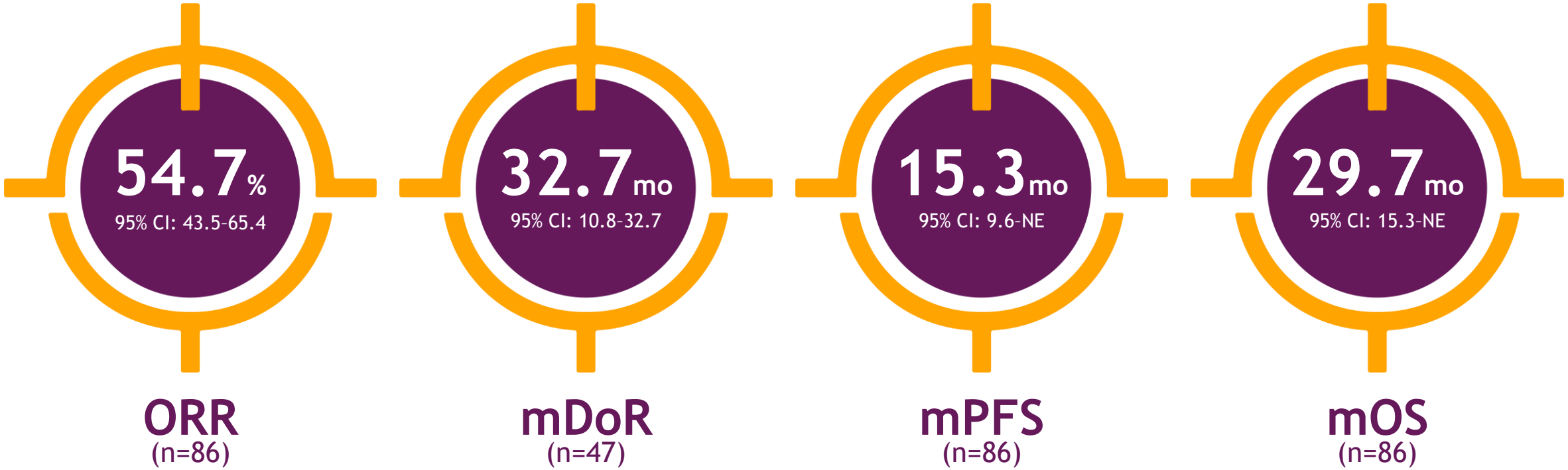
Tumor responses in treatment-naïve patients (n=137)



ORR, objective response rate.
Felip E, et al. Presented at the WCLC 2021, Sept 8–14, 2021 (Abstract 170).

Tepotinib demonstrated robust and lasting efficacy as a 1L treatment

In treatment-naïve patients with METex14 skipping NSCLC detected by tissue biopsy, Tepotinib achieved:



mDoR, median duration of response; METex14, MET exon 14; mOS, median overall survival; mPFS, median progression free survival; NE, not estimable; NSCLC, non-small cell lung cancer; ORR, overall response rate.
Felip E, et al. Presented at the WCLC 2021, Sept 8-14, 2021 (Abstract 170).

Tumors showed consistent sensitivity to Tepotinib therapy regardless of biopsy method

	Treatment-naïve (n=137)		Previously treated (n=138)	
	Tissue biopsy	Liquid biopsy	Tissue biopsy	Liquid biopsy
ORR, % (95% CI)	54.7 (43.5–65.4) n=86	54.3 (42.9–65.4) n=81	47.7 (37.0–58.6) n=88	43.6 (32.4–55.3) n=78
mDoR, months (95% CI)	32.7 (10.8–32.7) n=47	13.8 (7.2–NE) n=44	10.1 (8.3–15.7) n=42	11.1 (8.4–19.4) n=34
mPFS, months (95% CI)	15.3 (9.6–NE) n=86	8.5 (6.9–11.3) n=81	11.1 (8.2–16.8) n=88	8.3 (5.7–11.0) n=78
mOS, months (95% CI)	29.7 (15.3–NE) n=86	15.1 (9.5–22.1) n=81	22.3 (17.0–27.2) n=88	19.9 (12.8–22.3) n=78

mDoR, median duration of response; mOS, median overall survival; mPFS, median progression free survival; NE, not estimable; ORR, objective response rate.
Felip E, et al. Presented at the WCLC 2021, Sept 8–14, 2021 (Abstract 170).

Tepotinib had a manageable safety profile across the different patient subgroups

Treatment-related adverse events, n (%)*	Overall	Age subgroup, years			
	(N=291)	<65 (n=64)	≥65 to <75 (n=107)	≥75 to <85 (n=96)	≥85 (n=24)
Any grade	264 (90.7)	52 (81.3)	105 (98.1)	84 (87.5)	23 (95.8)
Grade ≥3	86 (29.6)	9 (14.1)	28 (26.2)	39 (40.6)	10 (41.7)
Leading to dose reduction	90 (30.9)	10 (15.6)	36 (33.6)	36 (37.5)	8 (33.3)
Leading to temporary interruption	114 (39.2)	14 (21.9)	39 (36.4)	46 (47.9)	15 (62.5)
Leading to permanent discontinuation	41 (14.1)	4 (6.3)	14 (13.1)	17 (17.7)	6 (25.0)

*Safety was analyzed in all patients who received at least one dose of TEPMETKO®.
Garassino M, et al. Presented at the ESMO Virtual Congress 2021, Sept 16–21, 2021 (1254P)

The simple once-daily regimen of Tepotinib improves patient compliance[1–3]

The safety profile of tepotinib has been reinforced by data from 291 patients with METex14 skipping NSCLC

FEW DISCONTINUATIONS

Only **14.1%** of adverse events led to treatment discontinuation[1]

LOW TREATMENT-RELATED PERIPHERAL EDEMA

10.7% of patients had Grade ≥3 treatment-related peripheral edema, with only 4.3% of reactions leading to discontinuation[3]

MANAGEABLE adverse reactions

When required, ARs were effectively managed with simple dose modifications[1]

MOST COMMON ALL-GRADE adverse reactions

Edema (65.6%), nausea (29.9%), and hypoalbuminemia (27.8%)[1]

AR, adverse reaction; METex14, MET exon 14; NSCLC, non-small cell lung cancer.

1. Garassino M, et al. Presented at the ESMO Virtual Congress 2021, Sept 16–21, 2021 (1254P). 2. Richter A et al. *Clin Ther*. 2003;25:2307-2335. 3. TEPMETKO (Tepotinib) Summary of Product Characteristics (Oct 14, 2021).

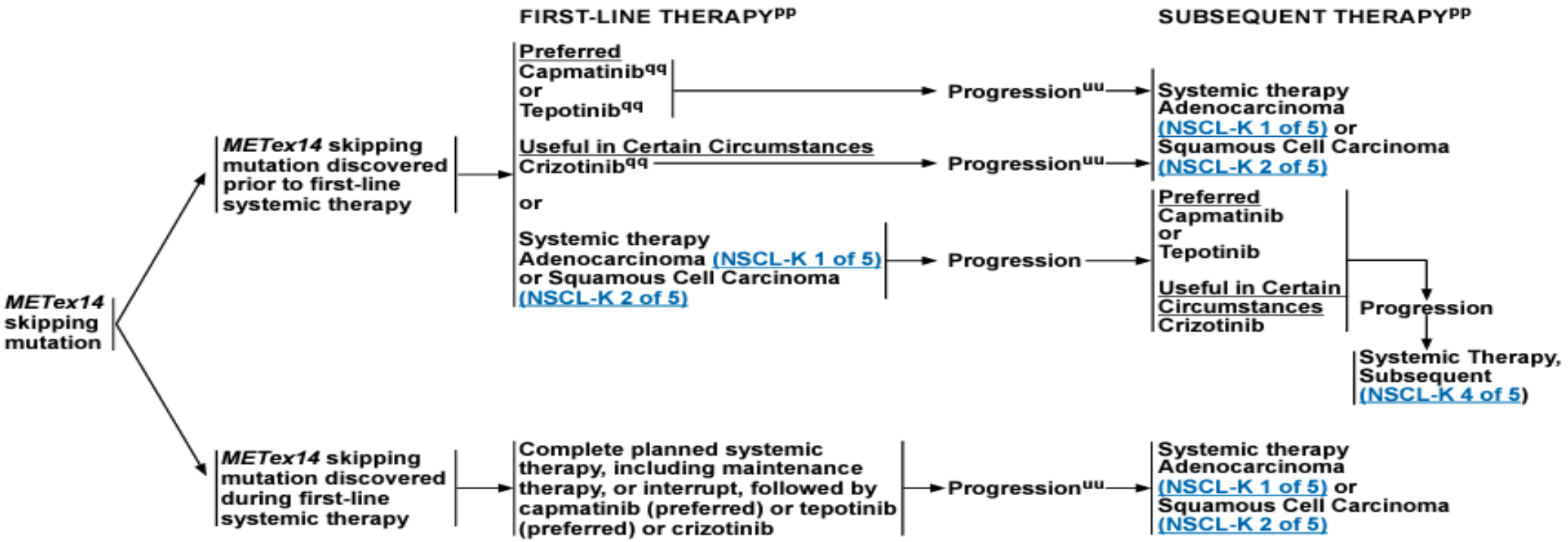
Key Trials Evaluating MET Inhibitors for *MET* Exon 14–Altered NSCLC

MET Inhibitor	Trial and Cohorts	Testing	ORR, %	Median DoR, Mos	Median PFS, Mos
Crizotinib[1,2]	PROFILE 1001 expansion cohort ▪ Treatment naive and pretreated (n = 65)	Tumor	32	9.1	7.3
Capmatinib[3,4]	Phase II GEOMETRY mono-1 ▪ Pretreated (2L/3L) (n = 69) ▪ Treatment naive (1L) (n = 28)	Tumor	 40.6 67.9	 9.7 11.1	 5.4 9.7
Tepotinib[5,6]	Phase II VISION ▪ *MET*ex14+ by liquid biopsy (n = 48) • 2L/3L (n = 31) • 1L (n = 17) ▪ *MET*ex14+ by tissue biopsy (n = 51) • 2L/3L (n = 33) • 1L (n = 18)	Tumor or ctDNA	 50.0 45.2 58.8 45.1 45.5 44.4	 12.4 12.4 -- 15.7 12.4 --	 9.5* -- -- 10.8† -- --
Savolitinib[7,8]	Phase II (NCT02897479) ▪ Treatment naive (n = 61)	Tumor	47.5	--	6.8

Data shown for capmatinib and tepotinib by IRC. *n = 57. †n = 58.

1. Drilon. Nat Med. 2020;26:47. 2. NCT00585195. 3. Wolf. ASCO 2019. Abstr 9004. 4. NCT02414139.
5. Paik. ASCO 2019. Abstr 9005. 6. NCT02864992. 7. Lu. ASCO 2020. Abstr 9519. 8. NCT02897479.

METex14 SKIPPING MUTATION[mm]



[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).
[qq] For performance status 0–4.
[uu] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

EMERGING BIOMARKERS TO IDENTIFY NOVEL THERAPIES FOR PATIENTS WITH METASTATIC NSCLC

Genetic Alteration (ie, Driver event)	Available Targeted Agents with Activity Against Driver Event in Lung Cancer
High-level *MET* amplification*	Crizotinib[1-2] Capmatinib[3] Tepotinib[4]
ERBB2 (HER2) mutations**	Ado-trastuzumab emtansine[5] Fam-trastuzumab deruxtecan-nxki[6]

* The definition of high-level *MET* amplification is evolving and may differ according to the assay used for testing. For NGS-based results, a copy number greater than 10 is consistent with high-level *MET* amplification.

** For oncogenic or likely oncogenic *HER2* mutations, refer to definitions at oncokb.org.

Ongoing trials

Multitarget tyrosine kinase inhibitors (TKIs)			
Crizotinib	NCT02465060 (NCI-MATCH)	II	No
	NCT02664935 (Matrix)	II	No
	NCT00965731	I	No
Cabozantinib	NCT00596648	IB/II	Erlotinib
	NCT03911193	II	No
	NCT01639508	II	No
	NCT02132598	II	No
	NCT03468985	II	Nivolumab +/– ipilimumab
Foretinib	NCT02034097	II	Erlotinib
Glesatinib	NCT02954991	II	Nivolumab
	NCT02544633	II	No
Merestinib	NCT02920996	II	No
Selective met tyrosine kinase inhibitors			
Tepotinib	NCT03940703 (INSIGHT 2)	II	Osimertinib
	NCT02864992 (VISION)	II	No
Savolitinib	NCT02897479	II	No
	NCT02143466 (TATTON)	I	Osimertinib
	NCT02374645	I	Gefitinib
	NCT03778229 (SAVANNAH)	II	Osimertinib
	NCT03944772 (OCHARD)	II	Osimertinib
	NCT02117167 (SARIF02_Lung)	II	No
Capmatinib	NCT03693339	II	No

Ongoing trials

Capmatinib	NCT03693339	II	No
	NCT03647488	II	Spartalizumab; docetaxel
	NCT03240393	II	No
	NCT02414139	II	No
	NCT02276027	II	No
	NCT02323126	II	Nivolumab
	NCT02335944	I/II	EGF 816
	NCT01911507	I	Erlotinib
	NCT02468661	I	Erlotinib; platinum + pemetrexed
	NCT02750215	II	No
Tivantinib	NCT01069757	I	Erlotinib
	NCT01251796	I	Erlotinib
	NCT02049060	I/II	Platinum + pemetrexed

Ongoing trials

Table 2 *(continued)*

Drug inhibitor	Clinical trial	Phase	Drug combined
SAR125844	NCT02435121	II	No
Anti-met antibodies			
Onartuzumab	NCT01887886	III	Erlotinib
	NCT01519804	II	Platinum + paclitaxel
	NCT01496742	II	Paclitaxel, pemetrexed, bevacizumab
	NCT02031744	III	Erlotinib
	NCT02044601 (BATTLE-XRT)	I/II	Erlotinib
Telisotuzumab	NCT03574753 (Lung-MAP S1400K)	II	No
JNJ-61186372	NCT02609776	I	No
Anti-HGF antibodies			
Ficlatuzumab	NCT01039948	IB/II	Gefitinib
	NCT02318368	II	Erlotinib

NSCLC, non-small cell lung cancer.

- In patients with *MET* exon 14-altered NSCLC, reported objective responses to *MET* inhibition do not seem to be influenced by the absence, presence, or levels of concurrent *MET* amplification.
- In studies evaluating *MET* amplification in the absence of *MET* exon 14 alteration, higher levels of *MET* amplification reveal increased objective responses with *MET* TKIs
- There are molecular variants of *MET*ex14 mutations, and the true biological roles of each of them are yet unknown
- MET is a validated clinical target in this setting and deserves to be therapeutically exploited

THANK YOU