Venkateshwar Hospital coming soon with stand alone cancer centre

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Case discussion

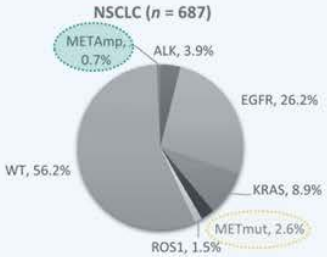
MET ex14 mut

MET amp

Molecular

~ 3% NSCLC

15% co-occurring *MET* amp



<1% NSCLC

~ 10% resist. mechanism in *EGFR*

~ 15% resist. mechanism in *ALK*

Pathology

- **Histology:**
  - Adenocarcinoma, sarcomatoid, squamous, adenosquamous, …
- **High PD-L1; low-TMB**

- **Histology:**
  - Adenocarcinoma, squamous, others…
- **High PD-L1; low-TMB**

Clinical

- Median age ~ **70 yrs**
- **Smokers**; also in never smokers
- **Female**
- **Poor survival**

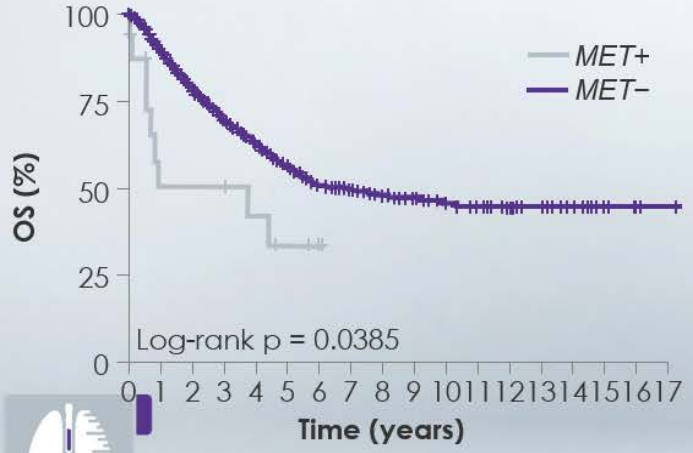
- Median age ~ **60 yrs**
- **Smokers**
- **Male**
- **Poor survival**

Tong et al, Clin Cancer Res 2016; Award et al, J Clin Oncol 2016 Lee et al, J Thorac Oncol 2017, Schorock et al, J Thorac Oncol 2016; Carcereny et al, WCLC 2019; Clavé et al, ESMO 2019

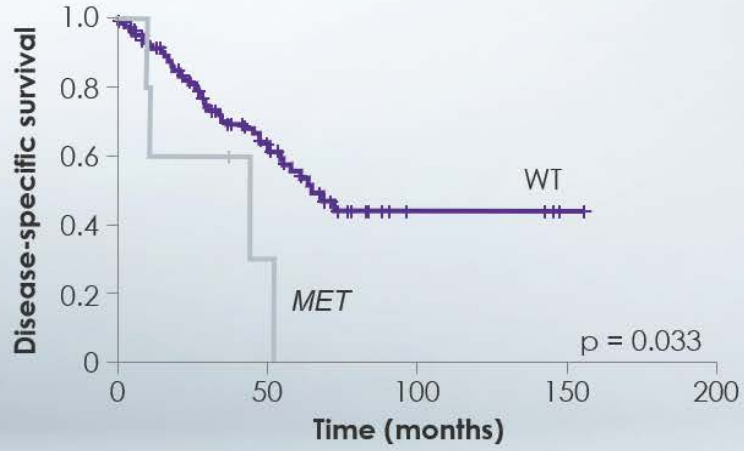
*MET*ex14 is associated with worse survival

*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.

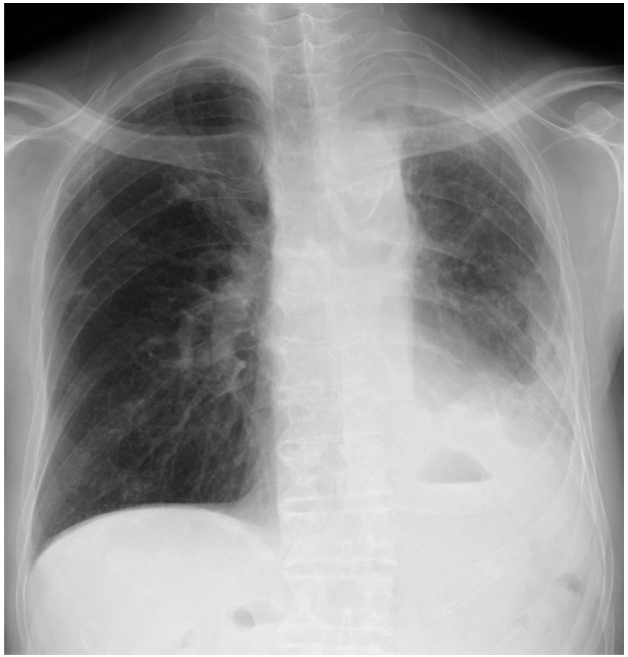
Neurotrophic tyrosine receptor kinase (NTRK) gene fusions are oncogenic drivers in a wide variety of adult and paediatric solid tumours.- The frequency of NTRK gene fusions in non-small cell lung cancer is estimated to be 0.1-1.0%.

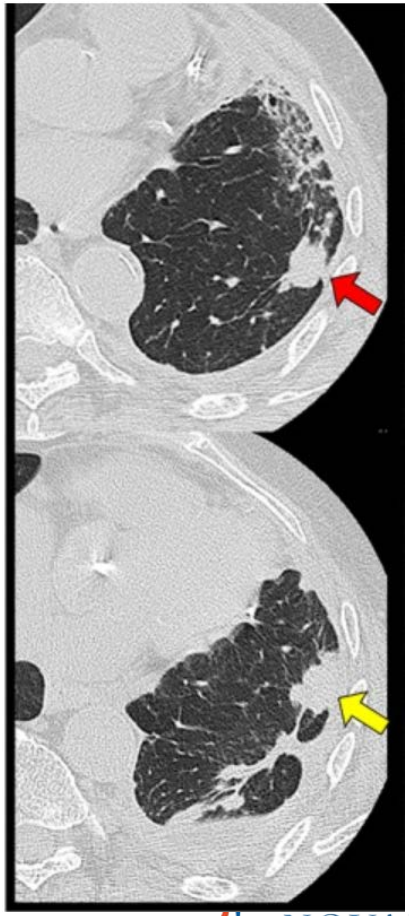
Case presentation

- 60-year-old Asian female
- No smoking history
- Presented with a persistent cough
- Left lung mass was found on chest X-ray
- Biopsy was consistent with NSCLC, adenocarcinoma
- Brain MRI revealed multiple lesions
- Abdominal CT shows an adrenal gland metastasis (left) and an asymptomatic bone lesion in the pelvis (Os Sacrum; 1 cm)

- MRI, magnetic resonance imaging.

Chest X-ray showing a dull left costophrenic angle and decrease in left lung volume.





CT scan of the chest showing nodular lesions in the left lower lobe (red arrow, 15 × 15 mm; yellow arrow, 20 × 15 mm)

According to your hospital procedure, would this patient be tested for oncogenic drivers?

A. Yes

B. No, treatment with chemotherapy would be started

C. No, treatment with immune checkpoint inhibitors would be started

D. No, treatment with chemotherapy and immune checkpoint inhibitors would be started

According to your hospital procedure, when would this patient be tested for oncogenic drivers?

A. Upfront

B. At progression

C. The patient will not be tested for oncogenic drivers

Indirect path

Advantages	Disadvantages
Fast result for *EGFR*/*ALK*	Tissue consumption
Cost saving for the significant portion of patients with *EGFR*/*ALK* mutations	Patient may likely proceed with chemo/immunotherapy first while waiting for comprehensive genomic profiling. Targeted therapy is likely to be reserved as 2nd-line therapy

- Image courtesy of Tony Mok.
- Chemo, chemotherapy; Dx, diagnosis.

Direct path

Advantages	Disadvantages
Assures sufficient tissue for comprehensive genomic profiling	Costly
Assures availability of molecular information (including the uncommon mutation) for 1st-line treatment	Delays treatment for patients with *EGFR*/*ALK* mutations

- Image courtesy of Tony Mok.

If your hospital procedure recommends this patient to be tested, which biomarkers would they be tested for?

A. None, they would be started on chemotherapy/immunotherapy

B. Only the most common oncogenic drivers, such as ***EGFR* and *ALK*, *and PD-L1***

C. Broad molecular testing using a multiplex assay would be used to test for all/most known oncogenic drivers

D. Initial testing for ***EGFR, ALK, and PD-L1***, followed by broad molecular testing if these results are negative

- ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor;
- PD-L1, programed death-ligand 1.

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Case presentation

Diagnosis:
Broad molecular testing of a tissue biopsy revealed that the patient had ***MET*ex14 NSCLC.**

PDL1 Expression >50%

- Based on your current practice, would you have correctly diagnosed this patient?

A. Yes

B. No

- *MET*ex14, *MET* exon 14 skipping mutation.

Question : If you had started on Chemotherapy before the arrival of NGS reports , what would you do now ?

1. Change to single agent IO
2. IO plus chemo
3. MET inhibitor
4. Continue same

Question : If MET inhibitor, Which one would you prefer ?

1. Capmatinib
2. Tepotininb
3. Savolitinib
4. Crizotinib

Classification of MET Tyrosine Kinase Inhibitors

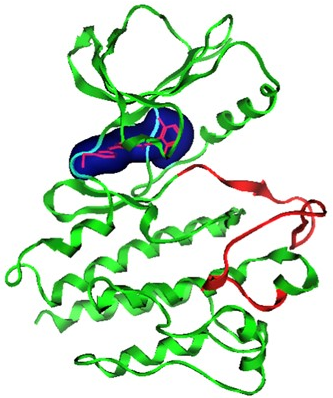
Type I a/b TKIs

Crizotinib
Savolitinib
Tepotinib

Capmatinib

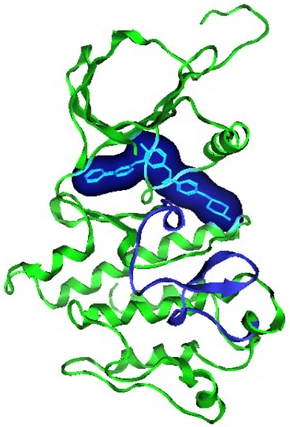
FDA approved
5/6/20

Ty 1b are more specific



Bind ATP-binding pocket in the active conformation

Type II TKIs

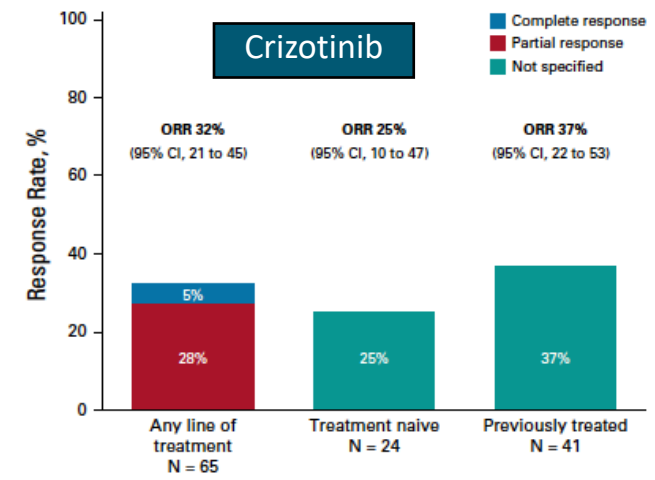


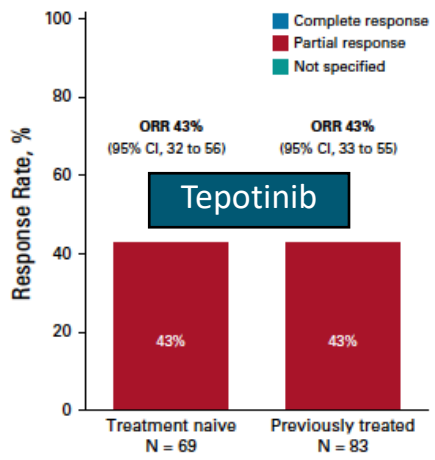
Cabozantinib
Merestinib
Glesatinib

Bind ATP-binding pocket in the inactive conformation

Ty 3: Allosteric inhibition - Tivantinib

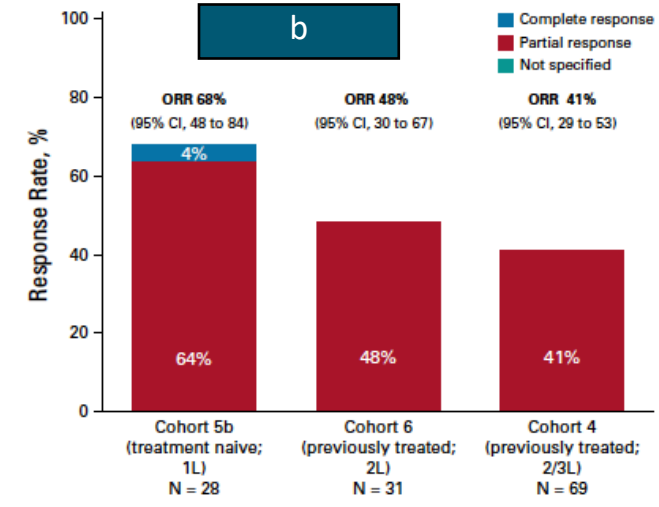
Awad IASLC TTL 2020





I vs II line?

C



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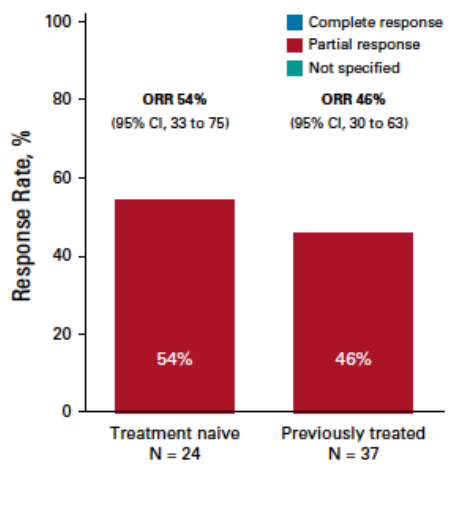


Key efficacy outcomes by BIRC : ASCO 2021 update

- In the preliminary analysis of treatment-naive patients in Cohort 7, the overall response rate (ORR) was 65.6% (21 partial responses) which was in line with the previously reported ORR of 67.9% for Cohort 5b (Table 2)[1]
- In pretreated patients, ORR was 51.6% in second-line treatment (2L) and 40.6% in second- or third-line treatment (2/3L)

	Treatment-naive			Pre-treated		
	Cohort 5b N=28	**Cohort 7 N=32**	**All patients N=60**	**Cohort 4 (2/3L) N=69**	**Cohort 6 (2L) N=31**	**All patients N=100**
Best overall response, n (%)						
Complete response	1 (3.6)	0	1 (1.7)	0	0	0
Partial response	18 (64.3)	21 (65.6)	39 (65.0)	28 (40.6)	16 (51.6)	44 (44.0)
Stable disease	7 (25.0)	11 (34.4)	18 (30.0)	25 (36.2)	11 (35.5)	36 (36.0)
Non-complete response/ non-progressive disease	1 (3.6)	0	1 (1.7)	1 (1.4)	1 (3.2)	2 (2.0)
Progressive disease	1 (3.6)	0	1 (1.7)	6 (8.7)	0	6 (6.0)
Not evaluable[a]	0	0	0	9 (13.0)	3 (9.7)	12 (12.0)
ORR,[b] % (95% CI)	67.9 (47.6-84.1)	65.6 (46.8-81.4)	66.7 (53.3-78.3)	40.6 (28.9-53.1)	51.6 (33.1-69.8)	44.0 (34.1-54.3)

[a] Unknown as per RECIST 1.1, ie, not qualified for confirmed complete response or partial response and without stable disease after more than 6 weeks or progression within the first 12 weeks.
[b]ORR: Patients who achieved complete or partial response. [c]DCR: Patients who achieved complete response, partial response, stable disease or non-complete response/non-progressive disease. 2/3L, second-/third-line treatment; BIRC, Blinded Independent Review Committee;; *MET*ex14, *MET* exon 14 skipping mutation.
Wolf J, et al. N Engl J Med. 2020;383:944-957

ASCO 2021 updated efficacy

- Median progression-free survival (PFS) for Cohorts 5b, 4, and 6 has been reported previously.[1] Although not mature at the data cutoff date, the median PFS for treatment-naive patients in Cohort 7 was 10.8 months

	Treatment-naive			Pre-treated		
	Cohort 5b N=28	**Cohort 7 N=32**	**All patients N=60**	**Cohort 4 (2/3L) N=69**	**Cohort 6 (2L) N=31**	**All patients N=100**
DCR,[c] % (95% CI)	96.4 (81.7-99.9)	100.0 (89.1-100.0)	98.3 (91.1-100.0)	78.3 (66.7-87.3)	90.3 (74.2-98.0)	82.0 (73.1-89.0)
DOR events,[d] n (%)	12 (63.2)	5 (23.8)	17 (42.5)	23 (82.1)	11 (68.8)	34 (77.3)
Median DOR, months (95% CI)	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)	9.7 (5.6-13.0)
PFS events, n (%)	18 (64.3)	14 (43.8)	32 (53.3)	60 (87.0)	22 (71.0)	82 (82.0)
Median PFS, months (95% CI)	12.4 (8.2-23.4)	10.8 (6.9-NE)	12.3 (8.2-21.6)	5.4 (4.2-7.00)	6.9 (4.2-13.3)	5.5 (4.2-8.1)

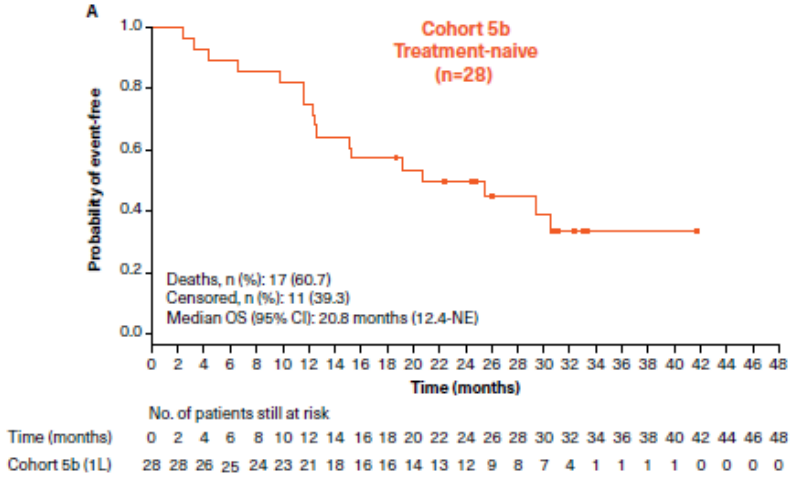
[d]For DOR calculations, the total number of responders (patients with confirmed complete or partial responses) as assessed by BIRC was used for percentage calculation: 19 responders in Cohort 5b, 21 responders in Cohort 7, 28 responders in Cohort 4, and 16 responders in Cohort 6

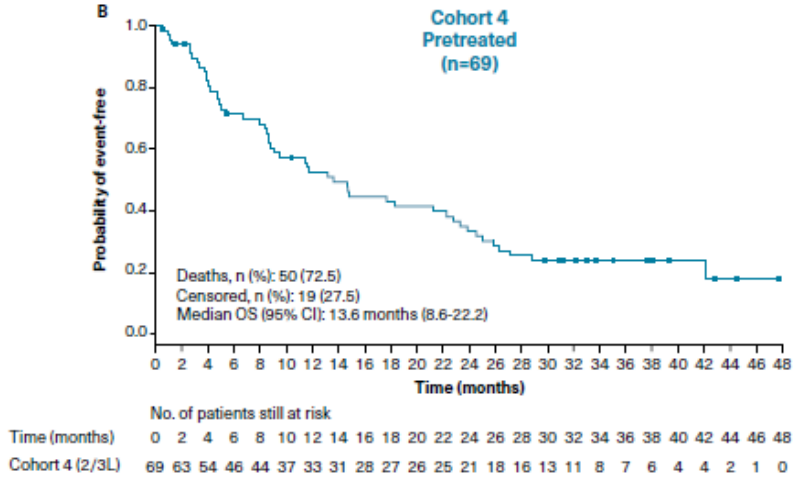
2/3L, second-/third-line treatment; BIRC, Blinded Independent Review Committee; CI, confidence interval; DCR, disease control rate; DOR, duration of response; *MET*ex14, *MET* exon 14 skipping mutation; NE, not estimated; ORR, overall response rate; PFS, progression-free survival

Wolf J, et al. N Engl J Med. 2020;383:944-957

Median overall survival

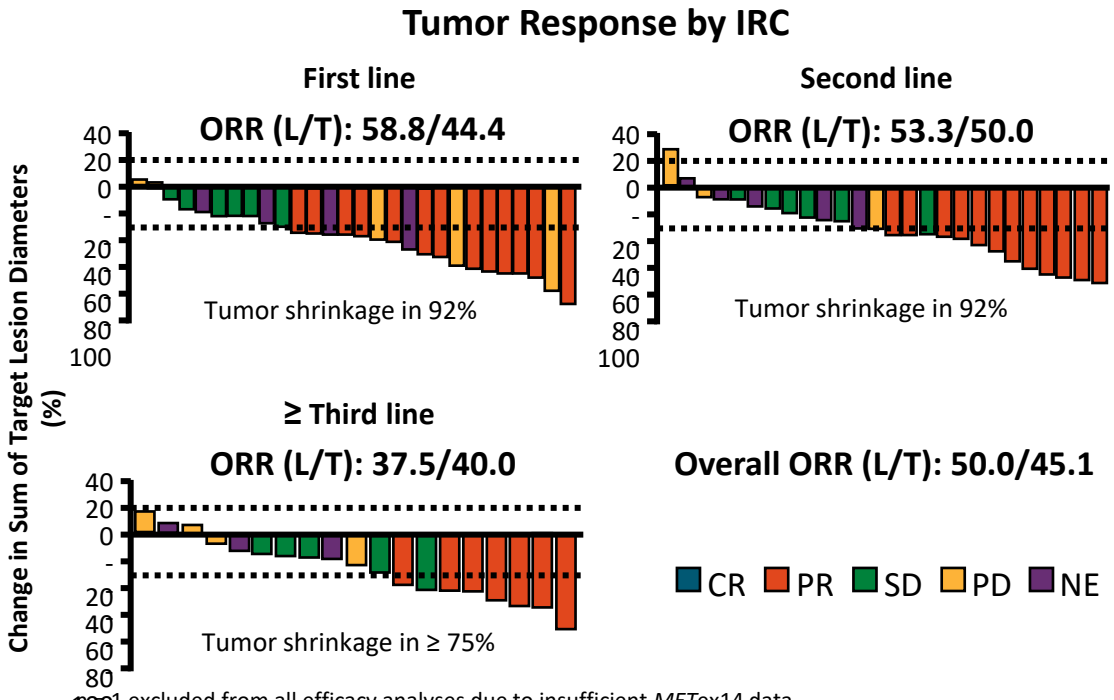
- Median overall survival (OS) for treatment-naive patients from Cohort 5b was 20.8 months (95% confidence interval [CI], 12.4-NE) and 13.6 months (95% CI, 8.6-22.2) for pretreated patients in Cohort 4. Median OS for Cohorts 6 and 7 is not yet mature





1L/2L/3L, first-/second-/third-line treatment; CI, confidence interval; *MET*ex14, *MET* exon 14 skipping mutation; NE, not estimated; NSCLC, non-small cell lung cancer; OS, overall survival

Phase II VISION: Efficacy With Tepotinib in METex14 Mutation–Positive NSCLC



1 excluded from all efficacy analyses due to insufficient *MET*ex14 data.
Patients excluded due to unavailable measurements: first line 5/8; second line 4/5; ≥ third line 4/3.

Paik. ASCO 2019. Abstr 9005.

- Durability of response
  - Overall DoR (n = 86): 14.3 mos
    - By L biopsy (n = 48): 12.4 mos
    - By T biopsy (n = 51): 15.7 mos
  - PFS:
    - By L biopsy (n = 57): 9.5 mos
    - By T biopsy (n = 58): 10.8 mos
- Both patients with and without CNS mets achieved benefit from treatment

Intracranial efficacy in GEOMETRY mono-1 and systemic efficacy in VISION in patients with *MET*ex14 NSCLC and brain metastases

Capmatinib: GEOMETRY mono-1[1,2]
Intracranial efficacy in patients with BM at baseline

- 13 evaluable patients with BM at baseline by BIRC (mean 3.3 lesions per patient [range 1–8])
- 54% (N = 7/13) had an intracranial response[a]
  - 4 patients 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 disease control was achieved in 12/13 patients

[a]All responses were confirmed at next staging.

Tepotinib: VISION[3,4]
Systemic efficacy in patients with BM at baseline

- At baseline, 23 patients (15%) had brain metastases (lesions identified according to RECIST v1.1).

Best objective response in patients with brain metastases

Objective response (IRC)	Patients with brain metastases* (n=23)
Best objective response	
Complete response	0
Partial response	11 (47.8)
Stable disease	6 (26.1)
Progressive disease	4 (17.4)
Not evaluable	2 (8.7)
Objective response rate, % (95% CI)	**47.8** (26.8, 69.4)
Disease control rate, % (95% CI)	**73.9** (51.6, 89.8)

1. Garon EB, et al. Presentation at AACR 2020; abstract CT082.
2. Wolf J, et al. N Engl J Med. 2020;383:944-57.
3. Paik PK, et al. N Engl J Med. 2020;383:931-43.
4. Viteri S, et al. Ann Oncol. 2020;31(suppl_4):S754-S840;abstract 1286P.

What are the barriers to current testing processes for newly diagnosed advanced NSCLC patients in your practice?

A. Insufficient tumor tissue and/or low sample quality

B. Non-availability of appropriate testing methodology

C. Long turnaround time to perform comprehensive biomarker testing

D. Low awareness of adequate biomarker testing

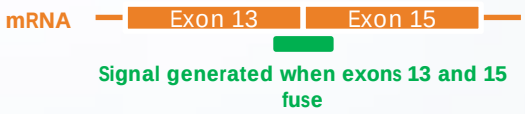
E. Inadequate technical expertise within my hospital

F. Inadequate reimbursement to cover all relevant biomarkers

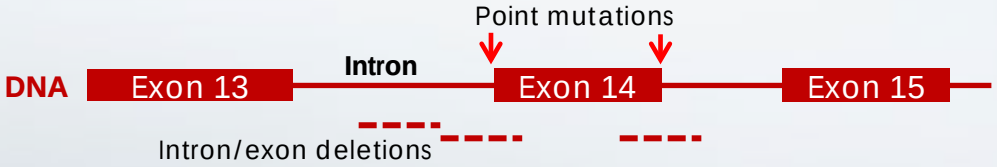
Detecting *MET*ex14: RNA- vs DNA-based methods

RNA-based	DNA-based
Direct approach to detect *MET*ex14; always the same event on an RNA level RT-PCR or RNA-sequencing	Diverse events (variable in size and position) on a DNA level that lead to exon 14 skipping DNA-sequencing should cover all regions involved in splicing (the branch site, polypyrimidine tract, splice acceptor, and donor site of *MET* exon 14)
Not all labs are routinely performing RNA analysis	Labs are routinely performing DNA analysis

RNA-based NGS platform: Analyzes the direct result of altered splicing (fusion of exons 13 and 15)



DNA-based NGS platform: Analyzes the genomic variant that alters or eliminates a splicing site



LungLab
Innovating lung cancer care, together

Pruis MA, et al. Lung Cancer. 2020;140:46-54.

- In what scenarios will you evaluate the option of Liquid biopsy for METex14 skipping mutation detection ?

Comparison of efficacy outcomes for METex14-positive patients identified by NGS-based liquid biopsy vs Clinical Trial Assay

	*MET*ex14 LDx		*MET*ex14 CTA	
	Cohort 5b Treatment-naïve (N=16)	**Cohort 4 Pre-treated (N=41)**	**Cohort 5b Treatment-naïve (N=28)**	**Cohort 4 Pre-treated (N=69)**
Best overall response by BIRC, n (%)				
CR	1 (6.3)	0 (0)	1 (3.6)	0 (0)
PR	12 (75.0)	20 (48.8)	18 (64.3)	28 (40.6)
SD	3 (18.8)	12 (29.3)	7 (25.0)	25 (36.2)
PD	0 (0)	5 (12.2)	1 (3.6)	6 (8.7)
Unknown	0 (0)	4 (9.8)	0 (0)	9 (13.0)
ORR[a], % (95% CI)	81.3 (54.4–96.0)	48.8 (32.9–64.9)	67.9 (47.6–84.1)	40.6 (28.9–53.1)
Median DOR by BIRC[b], months (95% CI)	20.3 (4.2–NE)	9.8 (4.2–19.5)	12.6 (5.6–NE)	9.7 (5.6–13.0)
Median PFS, months, (95% CI)	12.4 (4.5–NE)	5.4 (4.0–6.6)	12.4 (8.2–23.4)	5.4 (4.2–7.00)
Median OS, months (95% CI)	17.9 (9.8–NE)	13.6 (6.6–23.3)	20.8 (12.4–NE)	13.6 (8.6–22.2)

[a]ORR was defined as the proportion of patients with a best overall response of CR or PR. [b]DOR is based on the subset of patients with confirmed CR or PR (*MET*ex14 LDx: cohort 5b, n=13; cohort 4, n=20; METex14 CTA: cohort 5b, n=19; cohort 4, n=28).
BIRC, blinded independent review committee; CTA, clinical trial assay; CR, complete response; DoR, duration of response; LDx, NGS-based liquid biopsy assay; *MET*ex14, *MET* exon 14 skipping mutation; N, number per group; PD, progressive disease; PR, partial response; SD, stable disease.

MET Inhibitor Safety Overview

TRAEs With Capmatinib,* 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)

*≥ 10% of patients. †Capmatinib administered in fasting conditions at the time, a restriction that has since been removed. ‡Known to inhibit creatinine transporters.

TRAEs With Tepotinib,* n (%)	All Patients (N = 87)	
	Any Grade	Grade 3
Any	71 (81.6)	17 (19.5)
Peripheral edema	42 (48.3)	7 (8.0)
Nausea	20 (23.0)	0
Diarrhea	18 (20.7)	1 (1.1)
Creatinine increased	11 (12.6)	0
Asthenia	8 (9.2)	1 (1.1)
Amylase increased	7 (8.0)	2 (2.3)
ALT increased	6 (6.9)	2 (2.3)
AST increased	5 (5.7)	1 (1.1)
Hypoalbuminemia	5 (5.7)	0

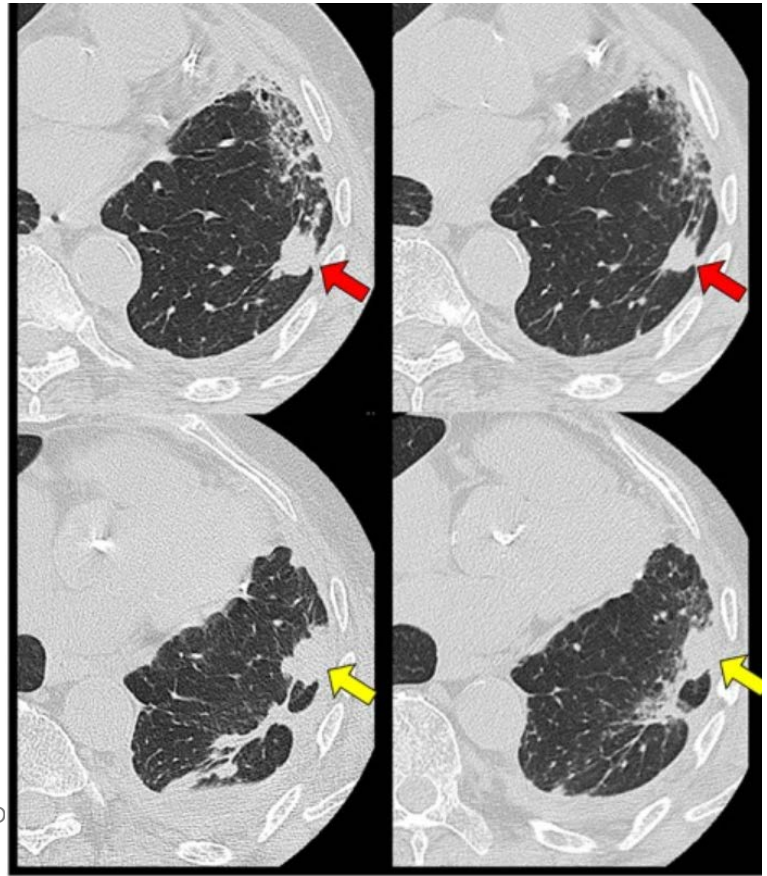
*≥ 5 of patients.

Paik. ASCO 2019. Abstr 9005. Wolf. ASCO 2019. Abstr 9004.

Case cont.

- Patient was started on Tab Capmatinib 400mg BD through access program in July 2020
- Patient suffered from grade 1 rash, grade 1 fatigue and grade 2 peripheral edema, dose reduced to 300mg BD
- Treatment continued for 6 months

Follow up scan – 3 months post Capmatinib



Disease status –stable

CT scan of the chest showing nodular lesions in the left lower lobe (red arrow, 15 × 15 mm; yellow arrow, 20 × 15 mm) pre and post Capmatinib

Target lesions (red arrow, 11 × 11 mm; yellow arrow, 14 × 12 mm) decreased from baseline

Choice of immunotherapy

- How would you have treated these patients if PDL1 was >50% ?

- Would you consider using Immuno/immunochemo agents in 1st line for BRAFm+ / cMET ex14 skipping lesion in NSCLC?

*MET*ex14 NSCLC is associated with poor response to chemotherapy, immunotherapy, and other therapies

Retrospective study of chemotherapy in patients with stage IIIB/IV NSCLC

	1L (n = 43,551)	2L (n = 4,318)
ORR, %	26.4	6.8
Median OS, months	8.5	6.6

- Response to 1L chemotherapy in advanced NSCLC is generally short, and ORR with 2L chemotherapy is lower[1]

Retrospective study of immunotherapy in patients with *MET*ex14 NSCLC[2]

	1L/2L/3L (N = 147)
ORR, %	17.0
Median PFS, months	1.9

- ORR with immunotherapy was poor
- PD-L1 expression levels or TMB did not correlate with the response to immunotherapy[2]
- TMB was lower in *MET*ex14 NSCLC vs non-selected NSCLC[2]

Study of crizotinib[b] in patients with advanced *MET*ex14 NSCLC[3]

	≥ 1L (N = 69)
ORR, %	32.0
Median PFS, months	7.3

- Crizotinib[b] provided a suboptimal benefit for patients with advanced *MET*ex14 NSCLC[3]

[a] Anti-PD-1/-PD-L1/-CTLA-4.
[b] Crizotinib is not an approved therapy for *MET*ex14 NSCLC.
1. Hotta K, et al. J Thorac Oncol. 2007;2:402-7. 2. Sabari JK, et al. Ann Oncol. 2018;29:2085-91. 3. Drilon A, et al. Nat Med. 2020;26:47-51.
1L/2L/3L, first/second/third line; ORR, objective response rate; PD-L1, programmed death-ligand 1; TMB, tumor mutational burden.

Is it important to include METex14 in the broad molecular testing panel for patients with NSCLC? (cont.)

- **Test for *EGFR, ALK, ROS1, BRAF* V600E, *NTRK*, *RET*, and *MET*ex14 in all nonsquamous NSCLC[3]**
  - Use broad NGS testing to detect most mutations using least amount of tissue
  - For squamous NSCLC, consider testing in young, never/light smokers or if biopsy specimen is of mixed histology
- **Accurate detection of METex14 requires a well-designed approach to cover the diverse genomic events varying in size and position that lead to exon 14 skipping**
- **Capmatinib has demonstrated clinically meaningful efficacy in advanced NSCLC patients harboring METΔex14 mutations.**
- **Wait for results of NGS before acting on PD-L1 results**

1. Masters. JCO. 2015;33:3488. 2. Mukhopadhyay. Am J Surg Pathol. 2011;35:15.
3. Pennell. ASCO Educ Book. 2019;39:351. 4. Lindeman. J Thorac Oncol. 2018;13:323.

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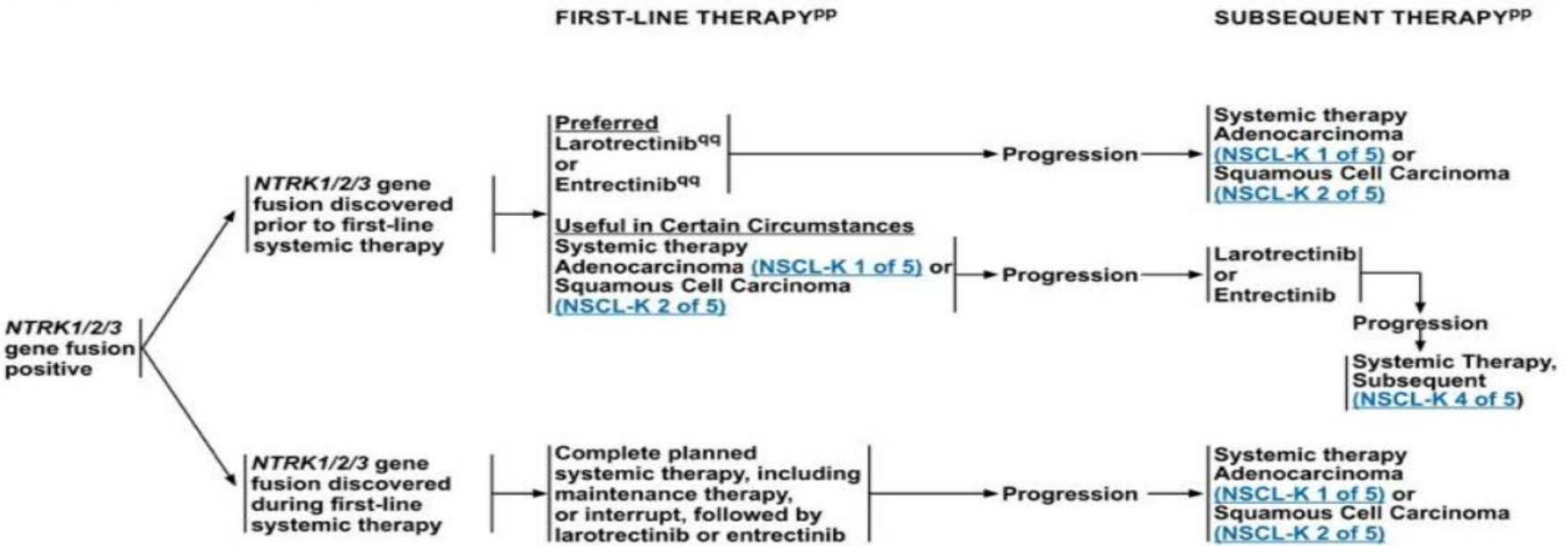
NTRK GENE FUSION POSITIVE[mm]



[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
[qq] For performance status 0–4.

Note: All recommendations are category 2A unless otherwise indicated.

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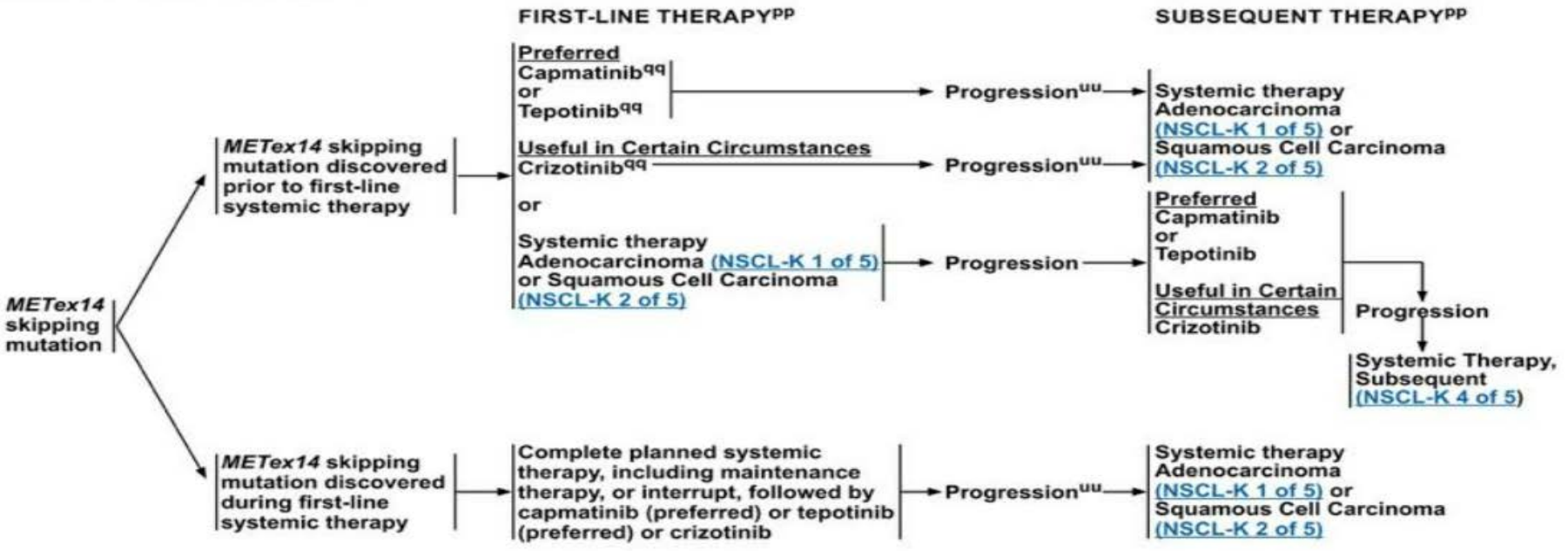
METex14 SKIPPING MUTATION[mm]



[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Molecular or Biomarker-Directed Therapy 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.

Thank you

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