Treatment Options Beyond MET Targeted Therapy

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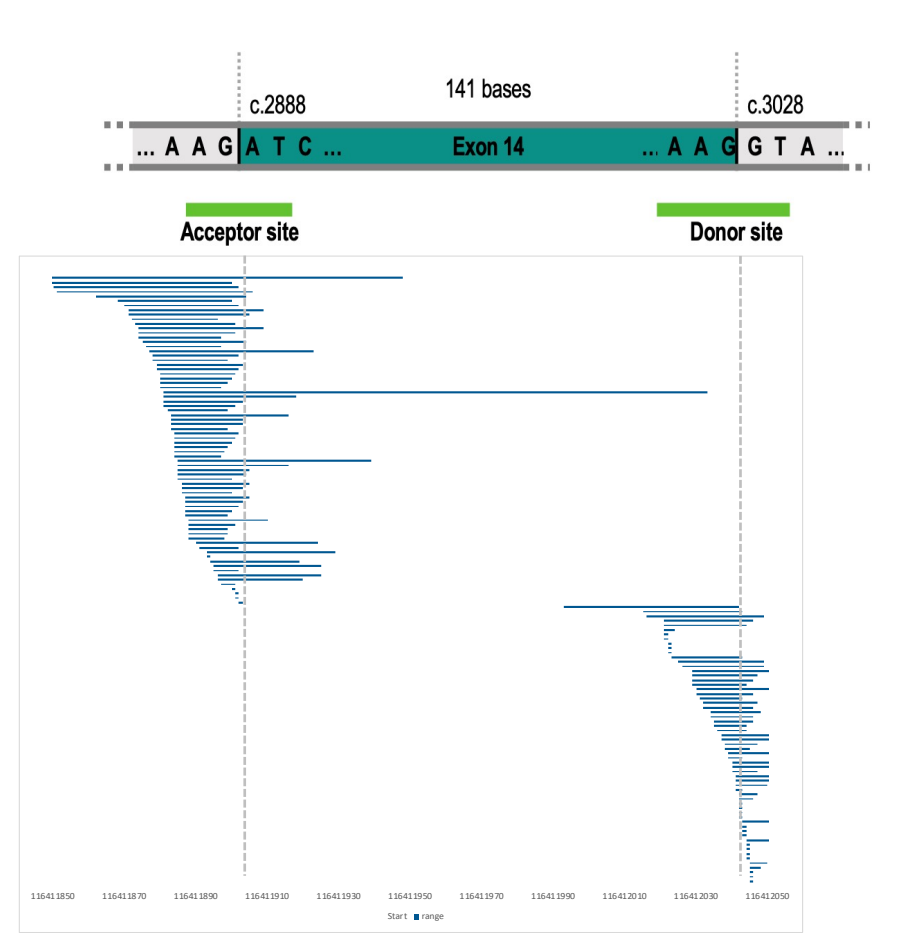
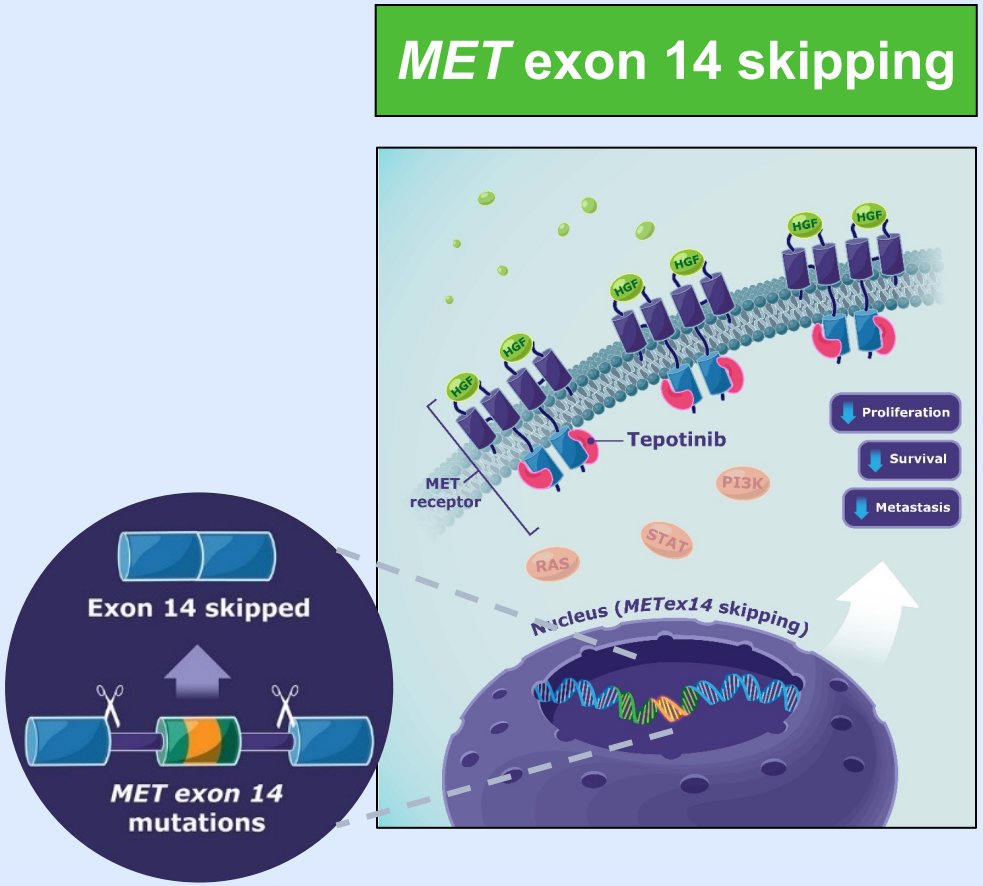
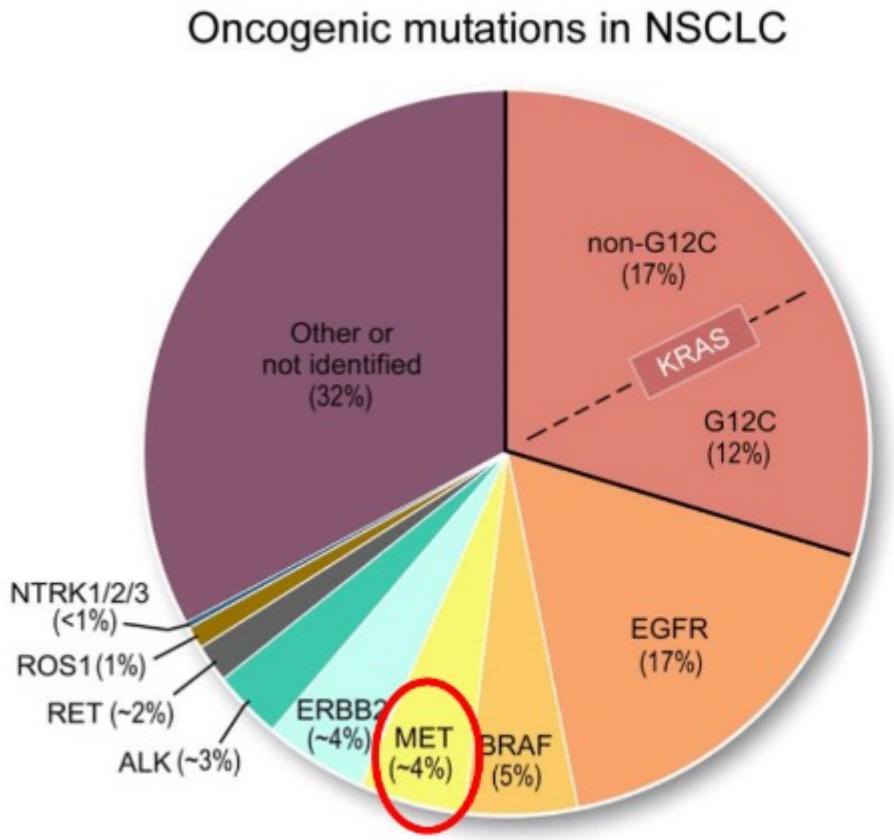
METex14 as an oncogene driver in lung cancer





FDA approved MET therapies



May 6, 2020: FDA grants accelerated approval to capmatinib for metastatic NSCLC with METex14

February 3, 2021: FDA grants accelerated approval to tepotinib for metastatic NSCLC with METex14

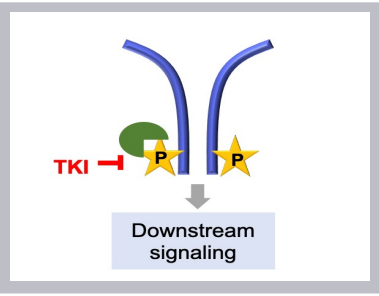
Type I MET inhibitors in MET exon 14 skipping

	Crizotinib n = 69	Capmatinib n = 28	n = 69	Tepotinib n = 69	n = 83	Savolitinib n = 28	n = 42
	Overall	1L	Previously treated	1L	Previously treated	1L	Previously treated
Median Age	72	71	71	74	73	69	
RR	32%	68%	41%	45%	45%	46%	41%
Median DOR (95% CI)	9.1 mo	12.6 mo (5.6, n.e.)	9.7 mo (5.6, 13.0)	10.8 mo (6.9, ne)	11.1 mo (9.5, 18.5)	6.8 mo (3.8, ne)	n.e. (6.9, n.e.)
Median PFS (95% CI)	7.3 mo	12.4 mo (8.2, n.e.)	5.4 mo (4.2, 7.0)	8.5 mo (6.8, 11.3)	10.9 mo (8.2, 12.7)	5.6 mo (2.8, 9.7)	13.8 (4.1, ne)

Drilon et al Nat Med 2019; Wolf et al NEJM 2020; Paik et al WCLC 2020; Lu et al ASCO 2020

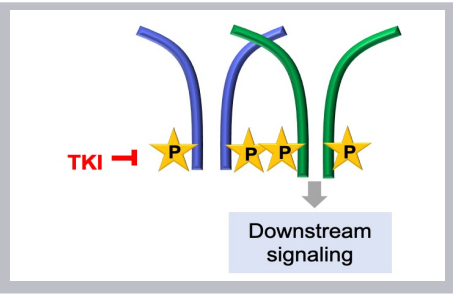
Resistance mechanisms to MET TKI

For most TKI, there are at least three classes of resistance mechanisms



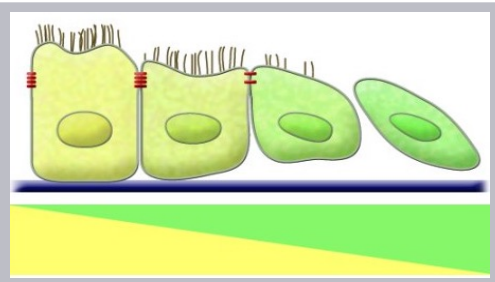
Pathway re-activation

- secondary mutation within the oncogene



Bypass pathway activation

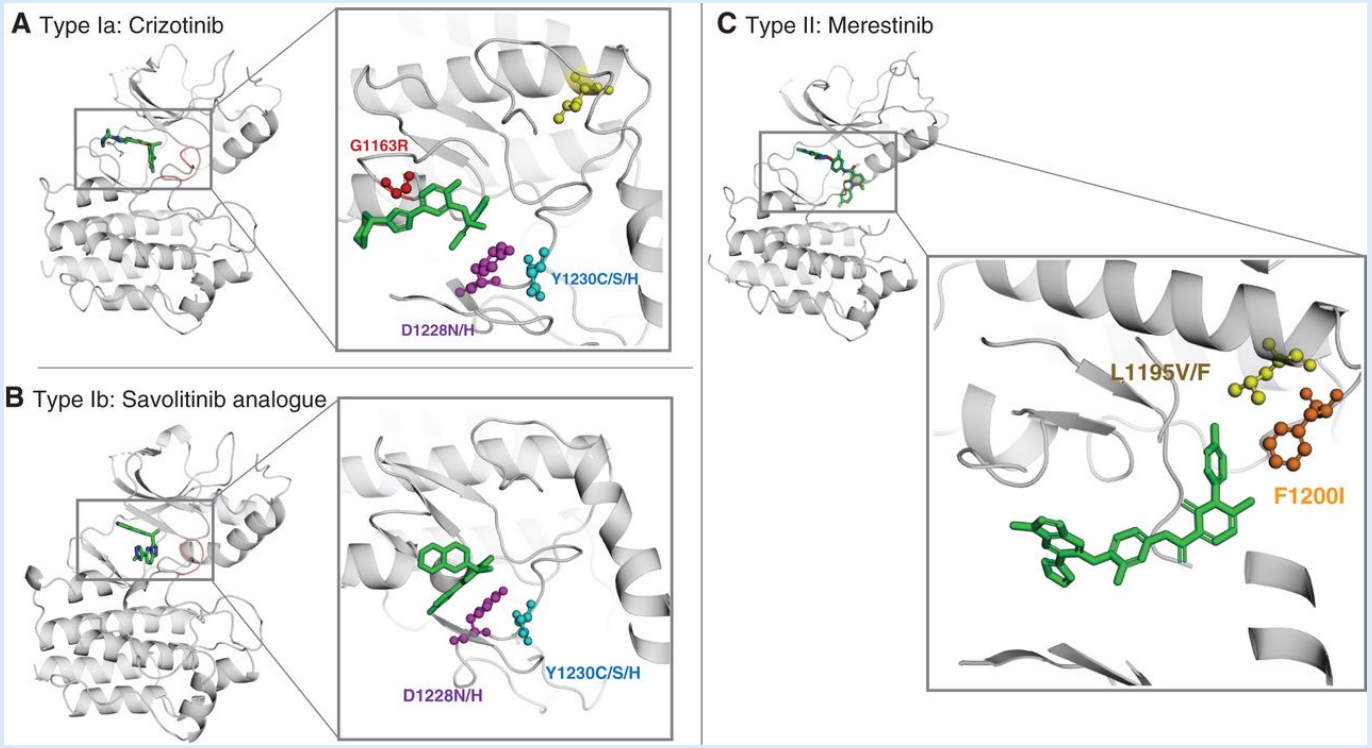
- acquired new resistant driver



Non-genetic

- For example, small cell transformation

MET re-activation due to new MET mutations



After type I (capmatinib/tepotinib)
- D1228, Y1230
- can respond to type II TKI

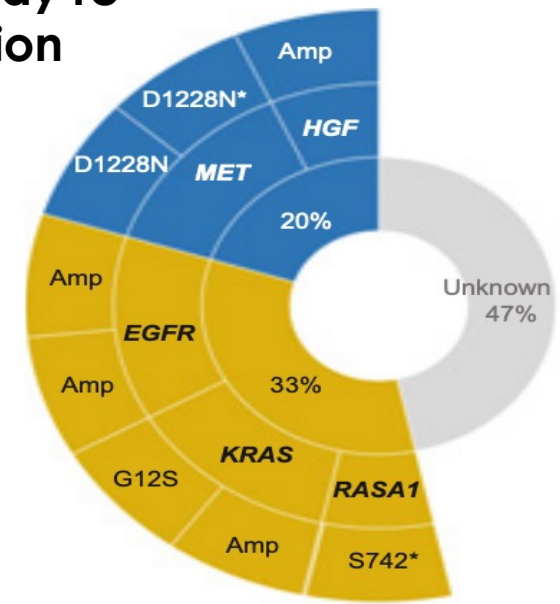
After type II (cabozantinib/merestinib)
- L1195, F1200
- Can respond to type I TKI

Recondo et al Cancer Discovery 2020

Bypass pathway activation

EGFR mutation or amplification
KRAS mutation or amplification
PIK3CA mutation
Rare fusions, ALK, RET

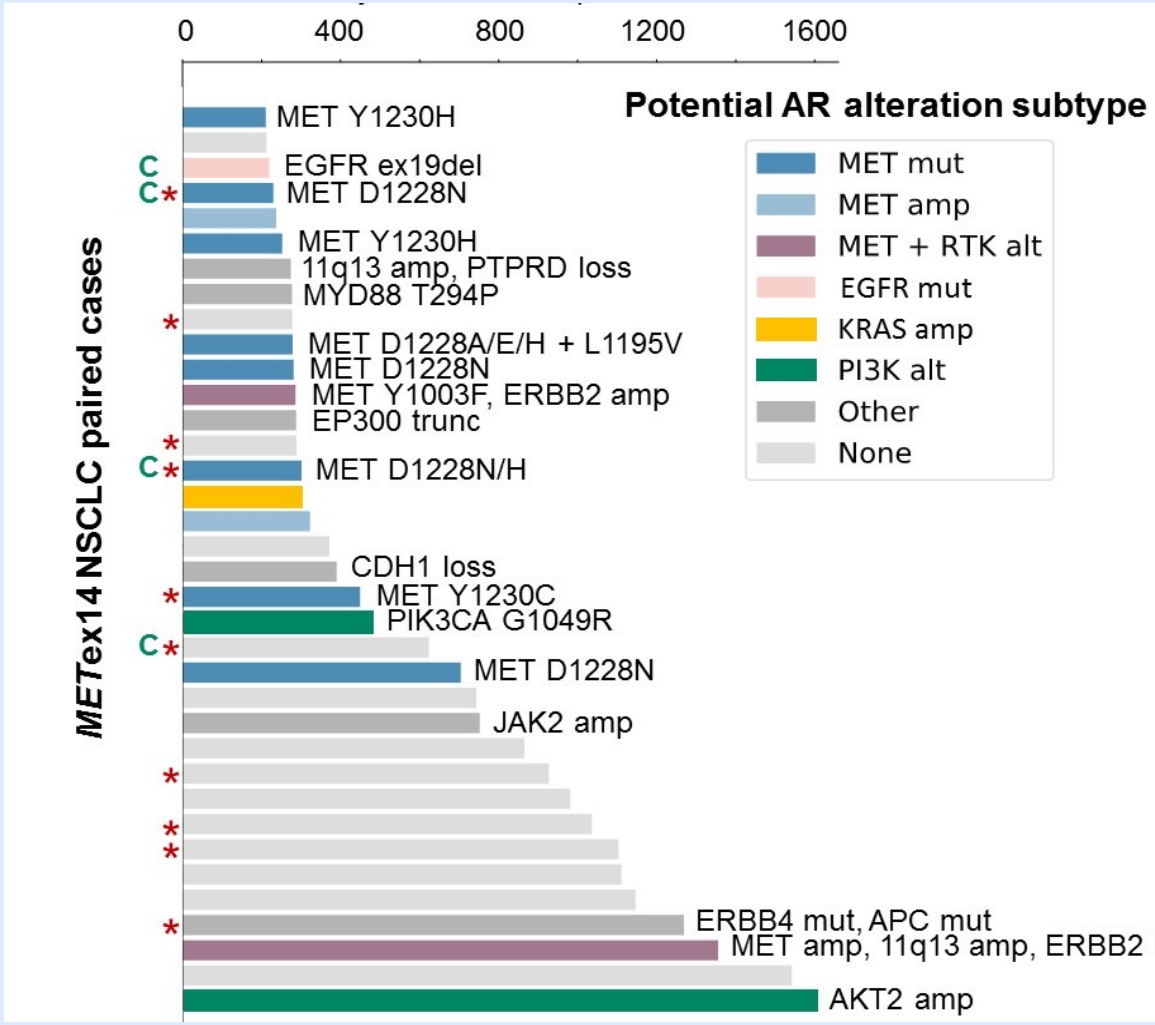
MET pathway re-activation



Bypass pathway activation

N=15

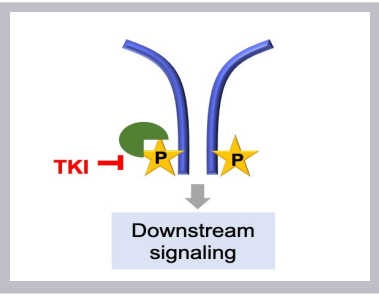
Guo et al 2020 CCR



Awad et al 2020 ASCO

Resistance mechanisms to MET TKI

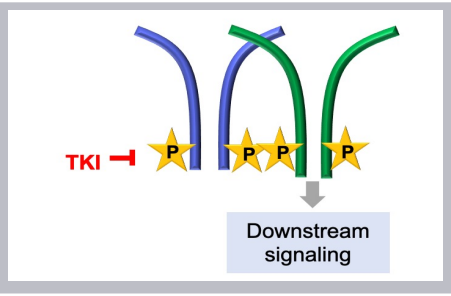
15-20% MET new mutations



Pathway re-activation

- secondary mutation within the oncogene

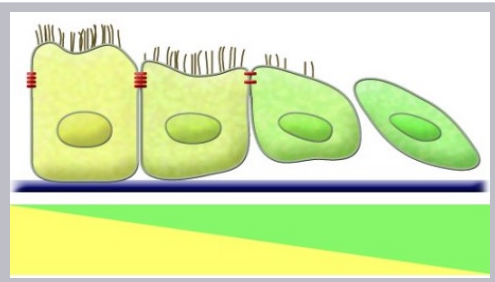
30-40% EGFR/RAS/PI3K



Bypass pathway activation

- acquired new resistant driver

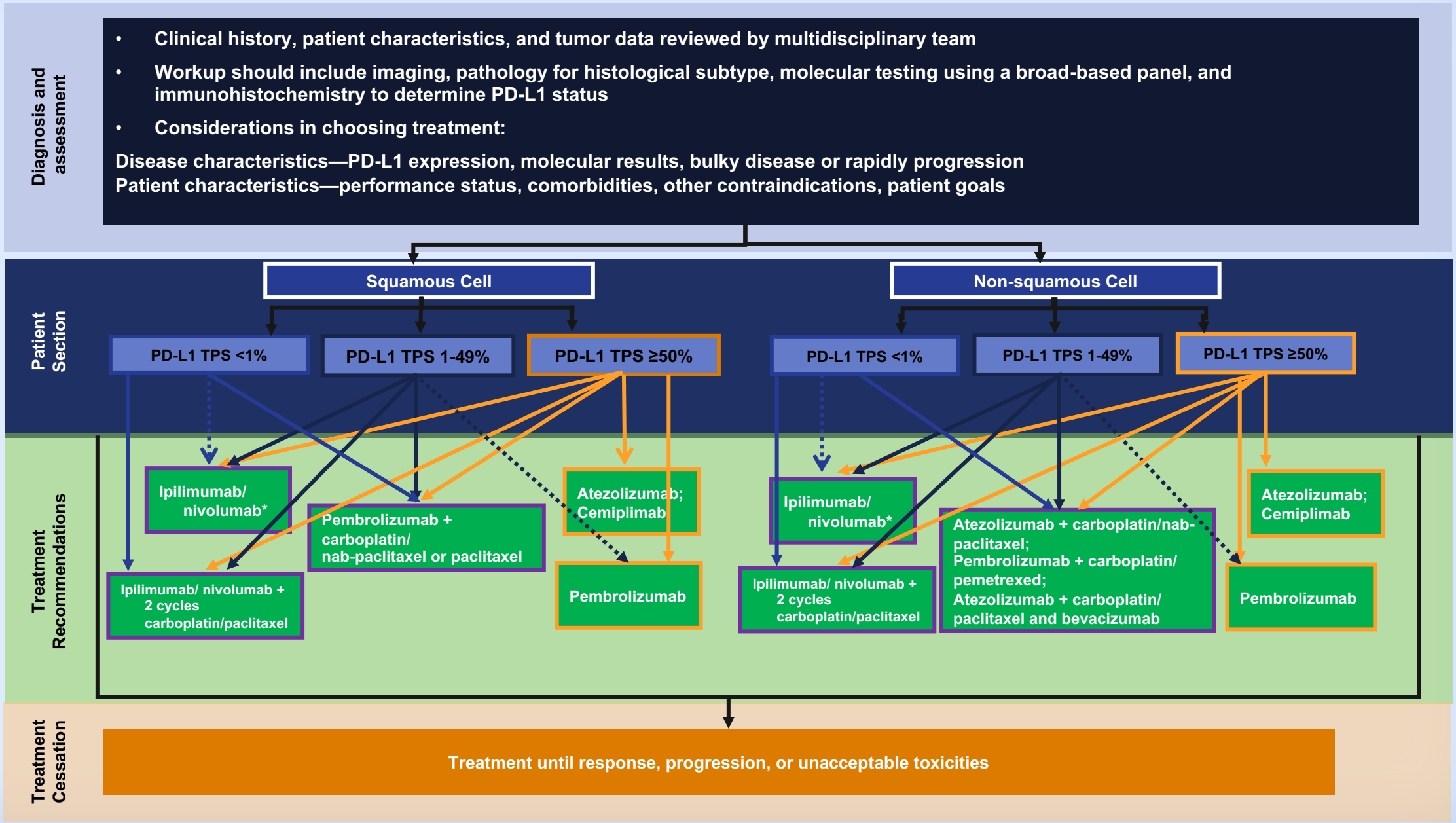
40-50% non-driver



Non-genetic

- For example, small cell transformation

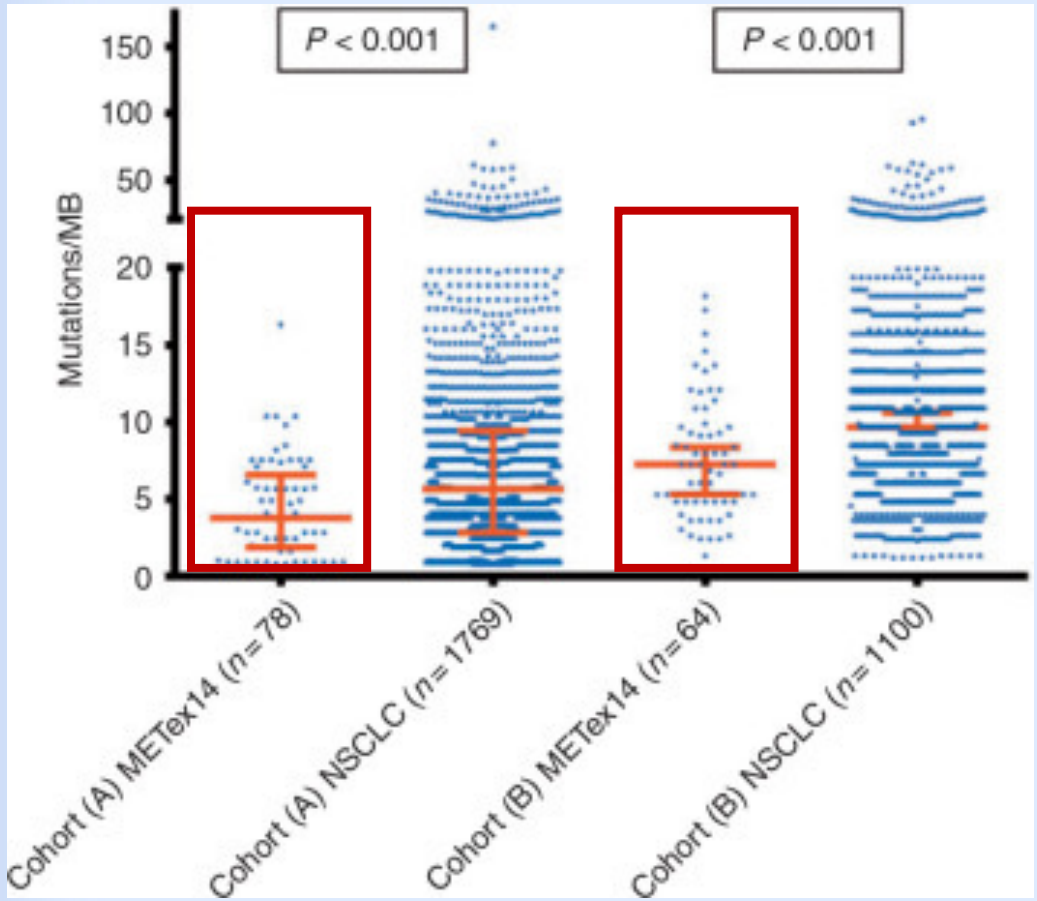
Potential post MET TK inhibitor therapy for *MET ex14* NSCLC

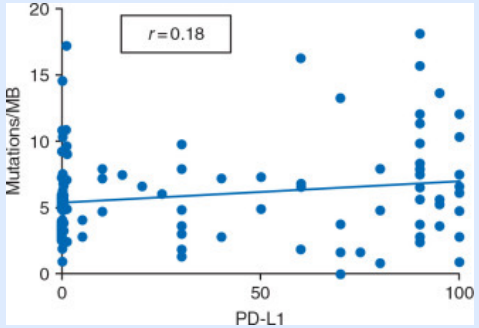


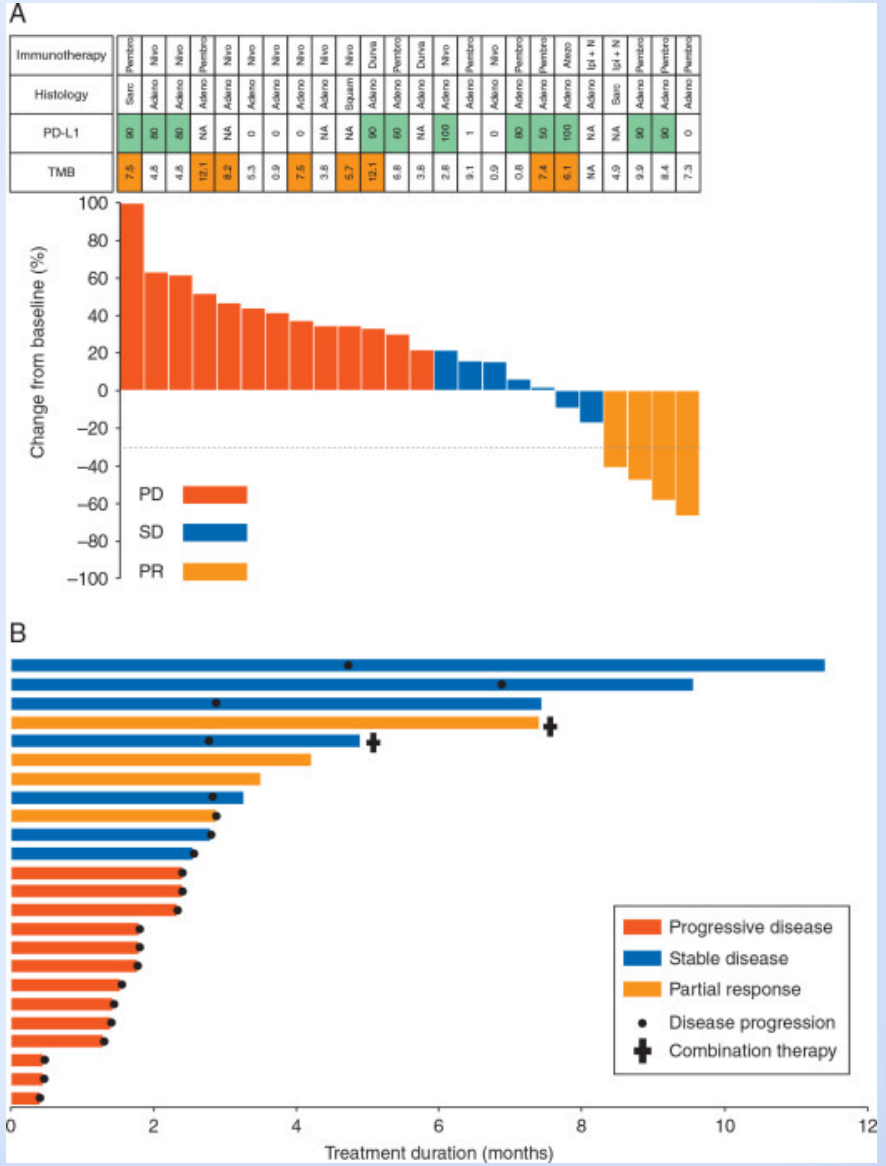
* Not FDA approved for PD-L1 <1%

Adapted from Brahmer JR, et al. *J Immunother Cancer*. 2018;6:75 and Hanna NH, et al. *J Clin Oncol*. 2020;38:168-1632.

Use MET TKI in clinical practice

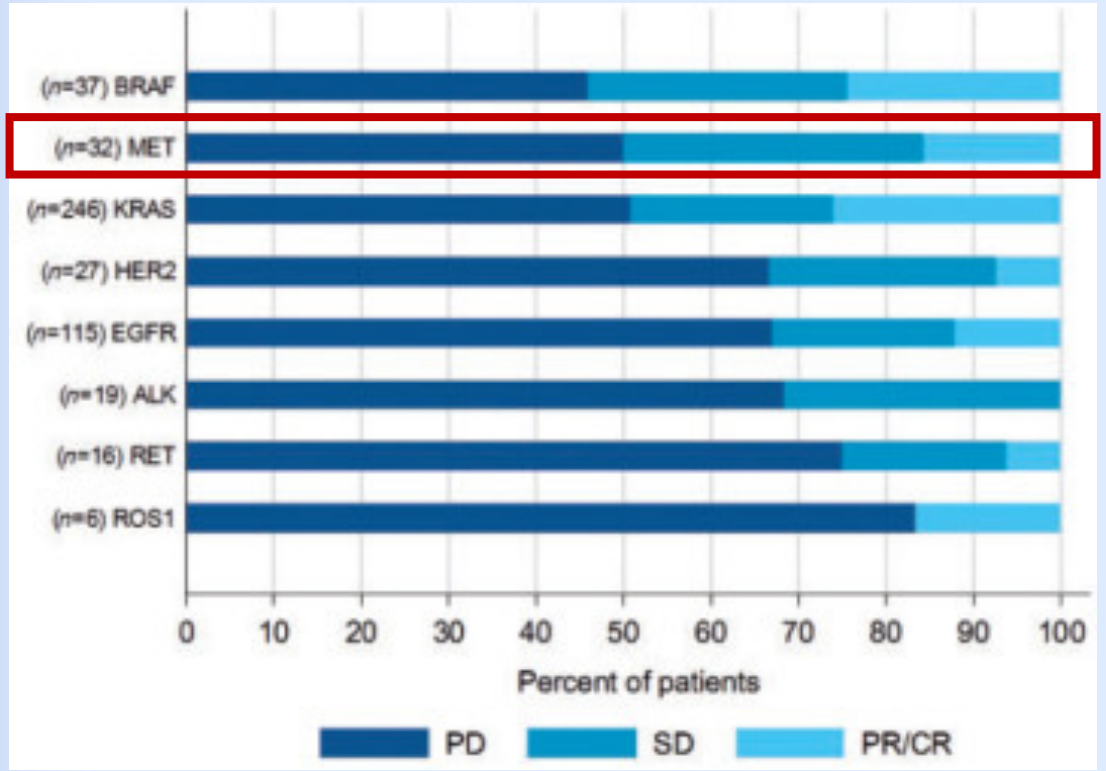


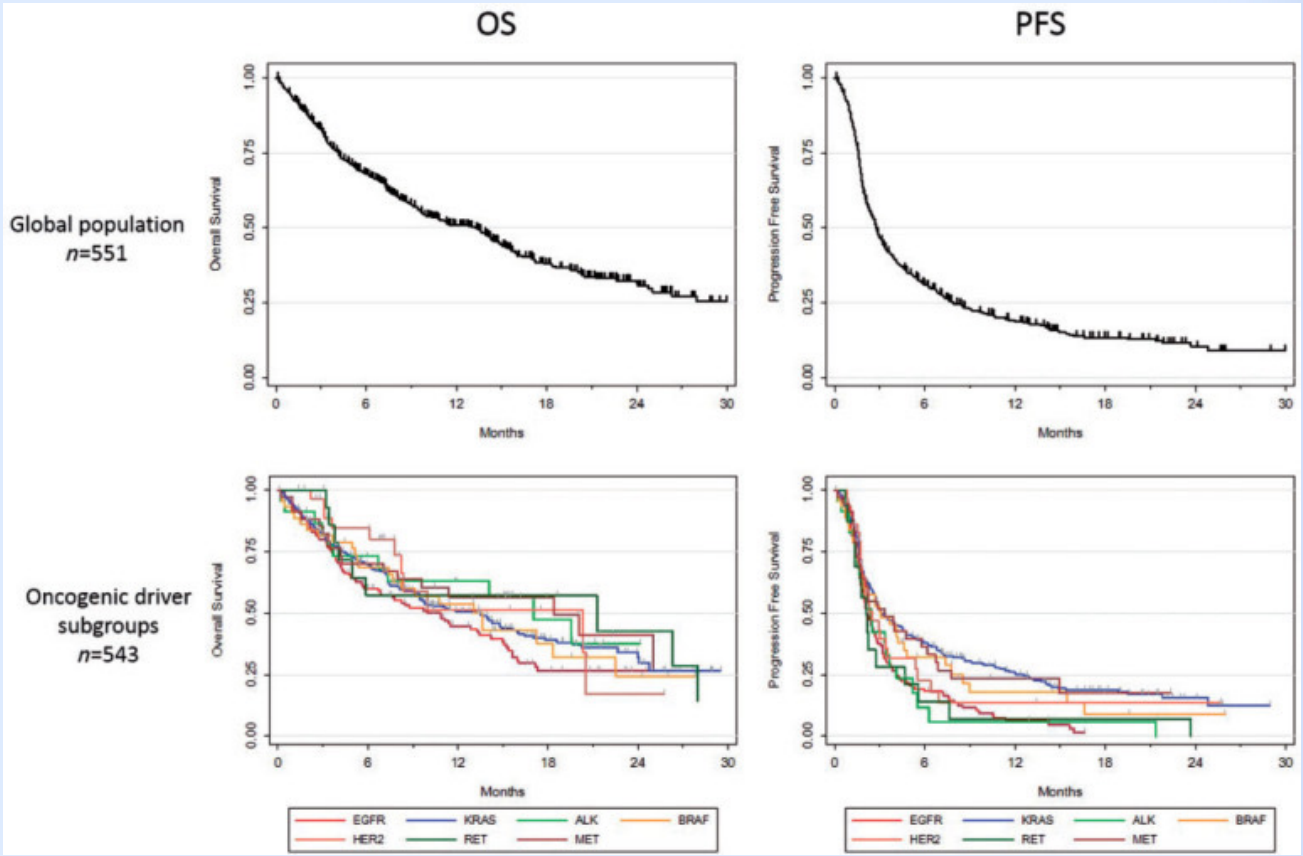




Sabari JK et al Ann Oncol 2018

MET TKI in clinical practice—response to ICI



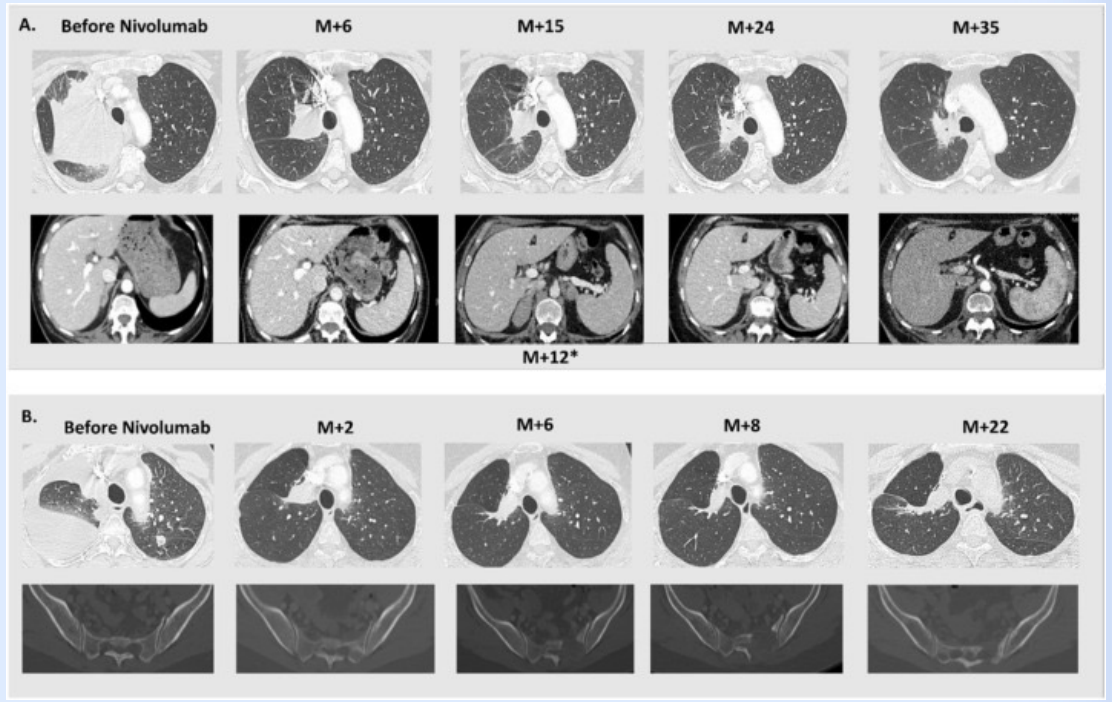


Mazieres J et al Ann Oncol 2019

MET TKI in clinical practice—response to ICI

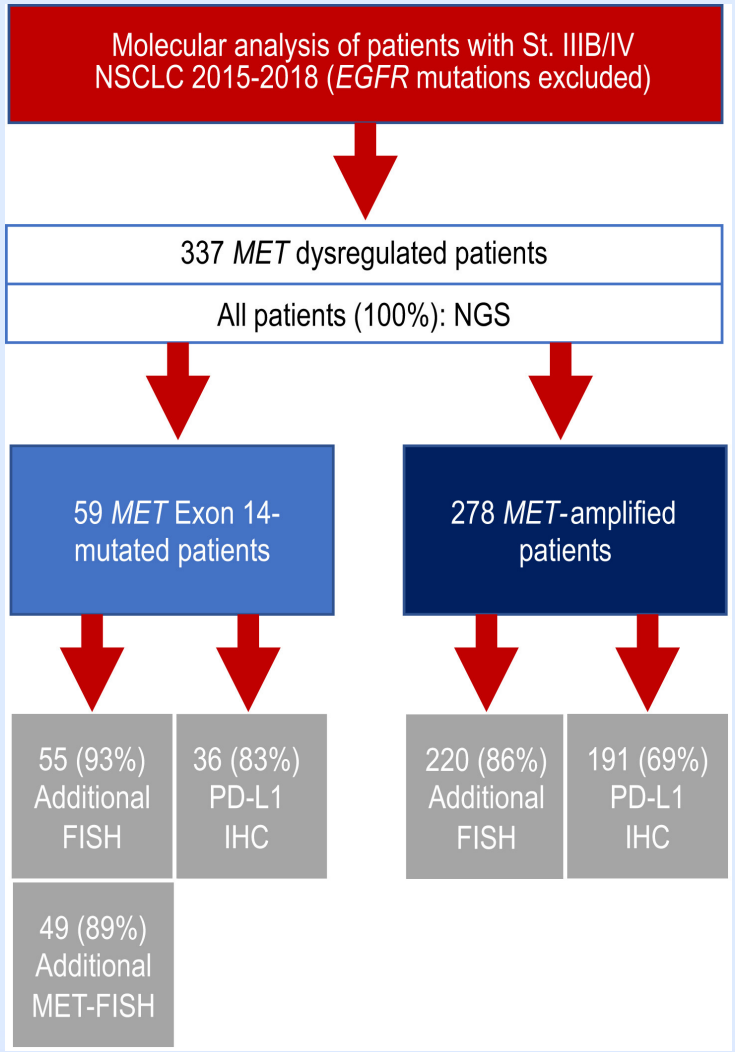
46% benefit to ICI

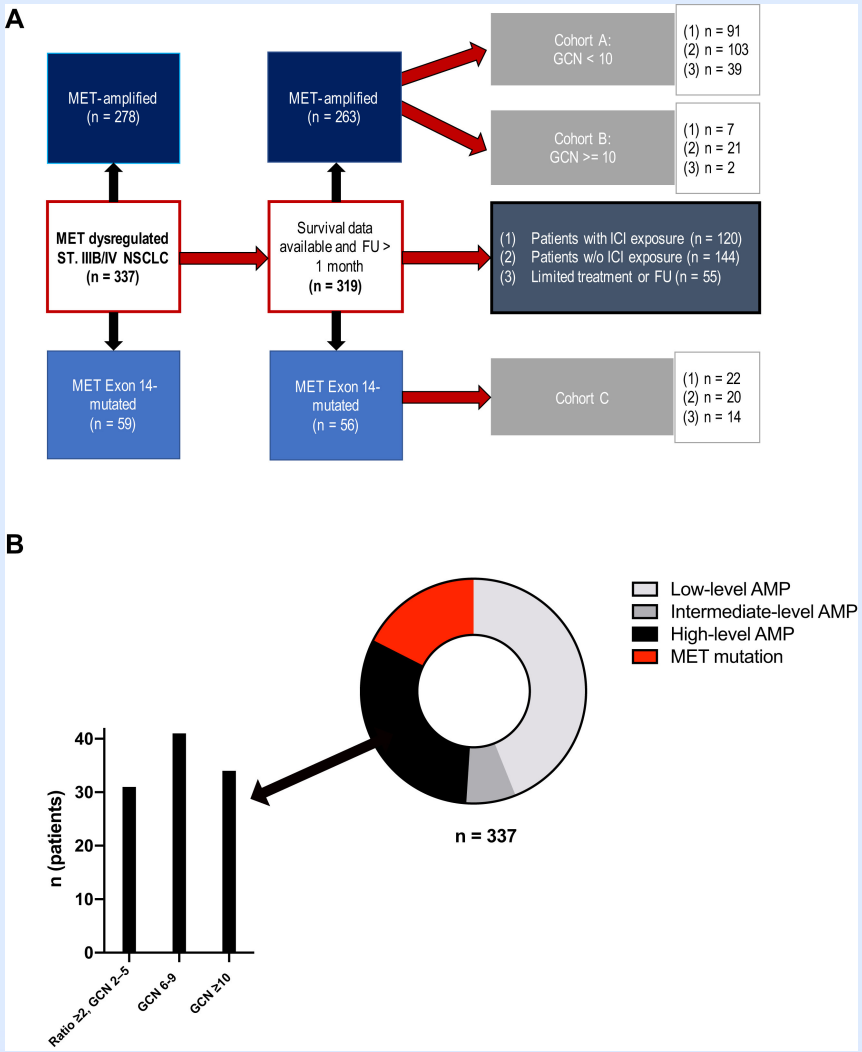
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Treatment	Pembrolizumab	Pembrolizumab	Nivolumab	Atezolizumab	Pembrolizumab	Nivolumab	Pembrolizumab
Sex	M	F	M	F	F	M	M
Age at the treatment	64	77	67	78	64	63	72
Line of treatment	1	1	2	2	2	2	1
Smoking	Never	Former	Former	Never	Former	Former	Never
PS	0	2	0	2	2	2	3
Histology	Ad	Ad	Ad	Ad	Sq	Sq	Ad
PD-L1 expression	>50%	>50%	1-49%	Unknown	>50%	Unknown	>50%
Best Response	PR	PR	NE	PR	PD	PD	PD
PFS in Months	Over 34.3	24.8	Over 23.0	Over 14.1	1.0	0.5	0.3
Variants of mutation	c.3028+2T>C (Donor site)	c.3028+2T>C (Donor site)	c.3028+1G>C (Donor site)	c.2896_2964 del (Other)	c.3027A>G (Other)	c.2888-17_2888-6del (Acceptor site)	c.2888-37_2888-18del (Acceptor site)



Kato Y et al Int J Clin Oncol 2021; Mayenga M et al Lung Cancer 2020

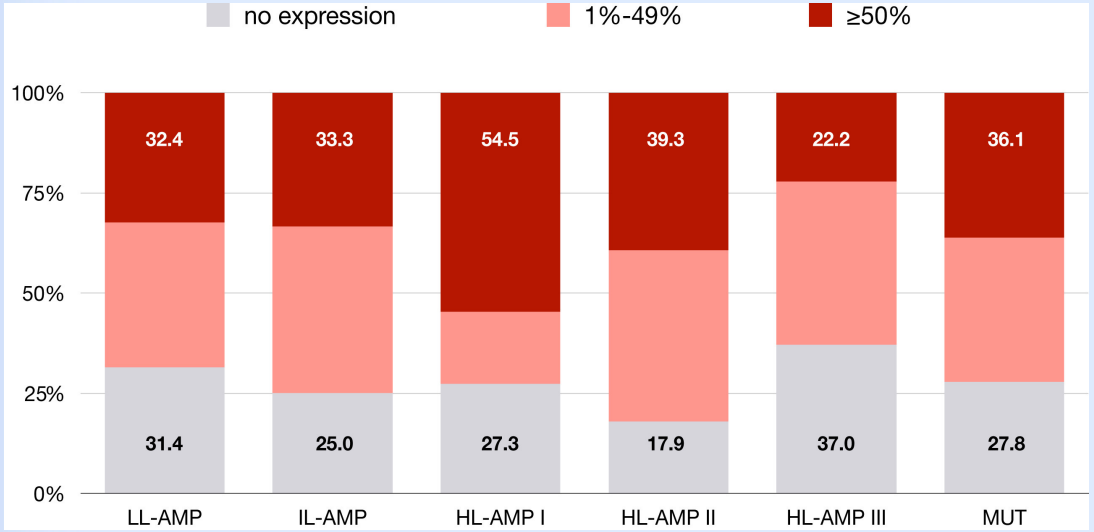
MET TKI in clinical practice—MET alterations

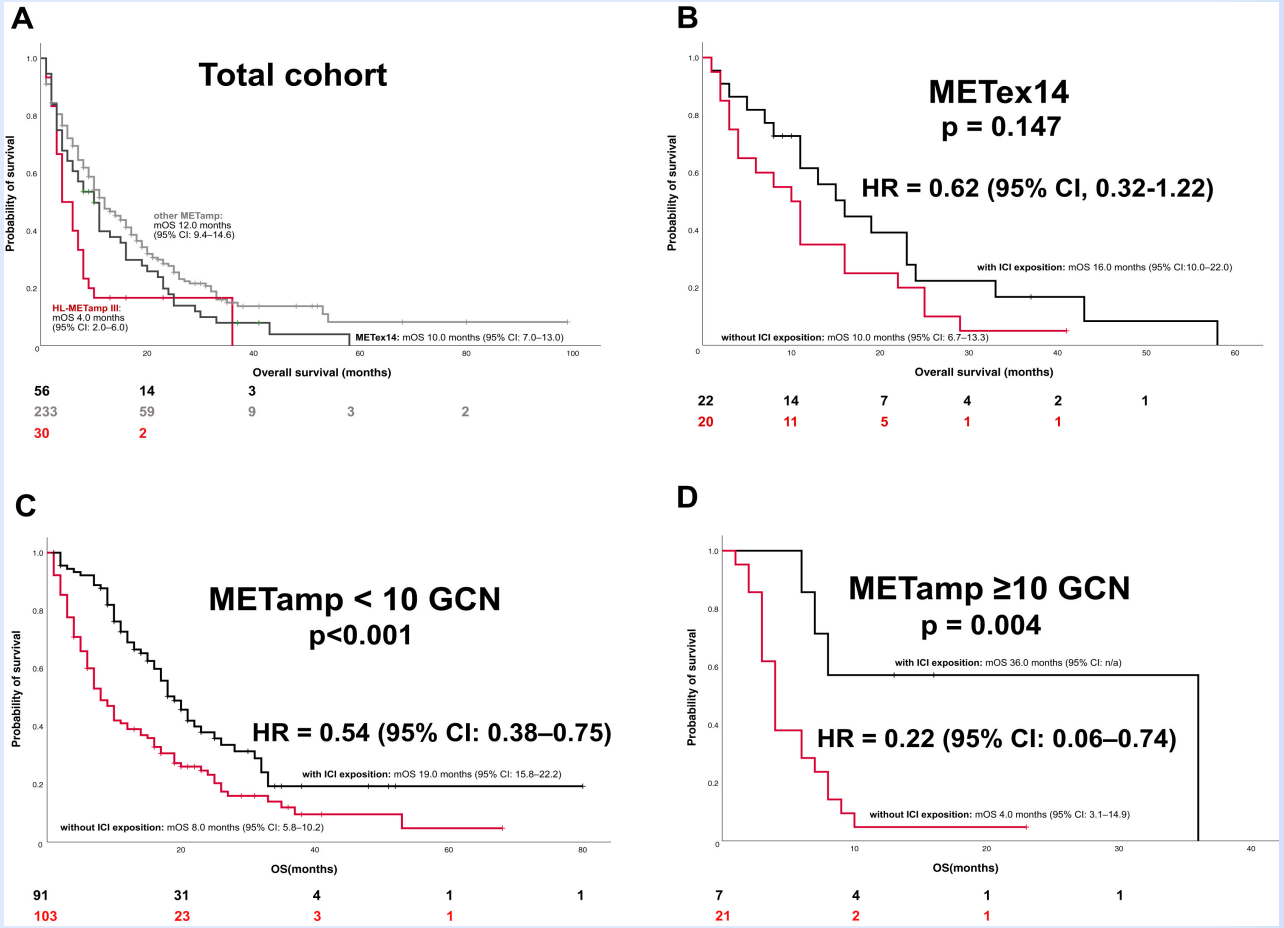




Kron A et al. J Thorac Oncol 2020; 10.1016/j.jtho.2020.11.017

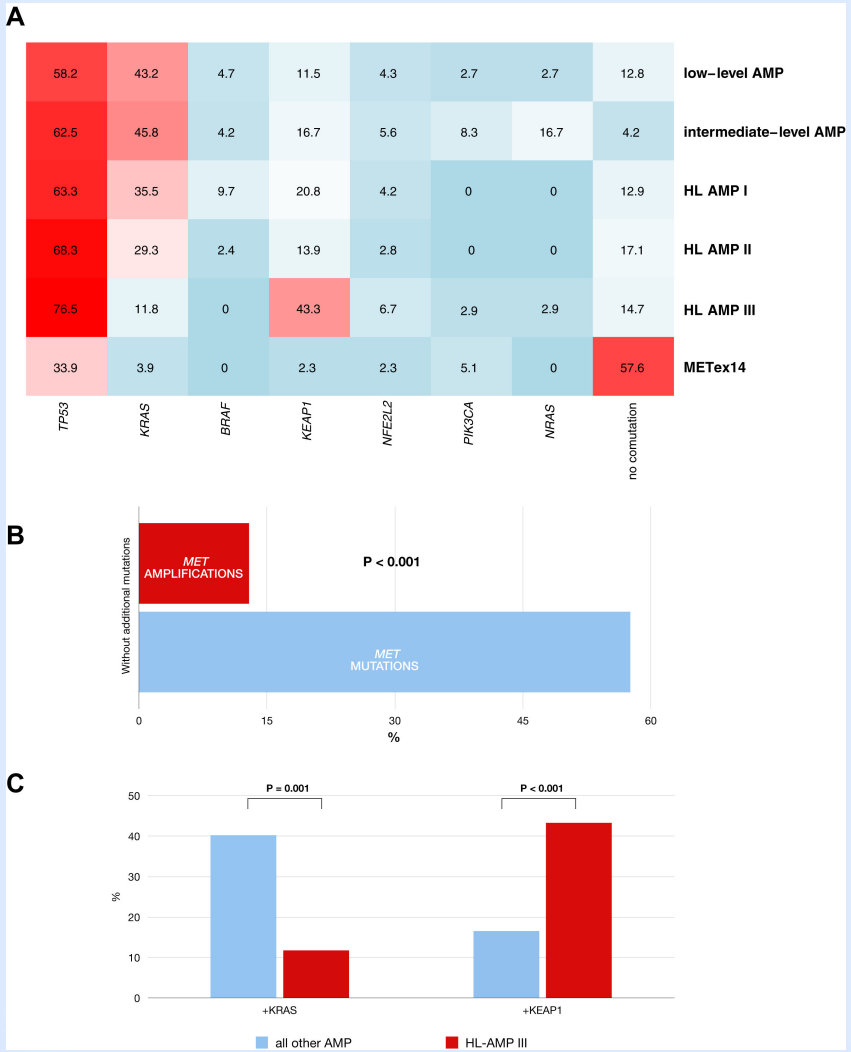
MET TKI in clinical practice—PD-L1 expression

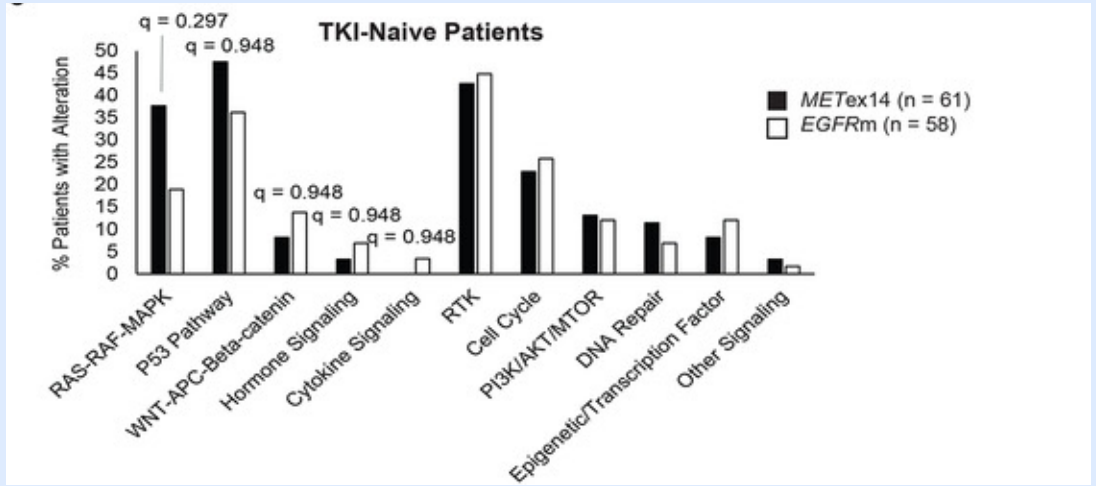




Kron A et al. J Thorac Oncol 2020; 10.1016/j.jtho.2020.11.017

MET TKI in clinical practice—co-mutations





- Targeted sequencing analysis of co-occurring genomic alterations in cell-free circulating tumor DNA samples collected from patients with *MET* exon 14–mutated advanced NSCLC (N = 289)
  - Activating *KRAS* mutations: 5.2%
    - *KRAS* G12C/D/S/V, 3.5%; G13C, 1%; Q22K, 0.3%; Q61H, 0.3%
  - Canonical activating *EGFR* mutations: 3.5%
    - *EGFR* del19, 3.1%; L858R, 0.7%; T790M, 2%
  - *ALK* rearrangement: 0.7%
  - *HER2* exon 20 insertion identified in 1 patient

Kron A et al. J Thorac Oncol 2020; 10.1016/j.jtho.2020.11.017; Rotow J et al Clin Cancer Res 2020

MET TKI in clinical practice—choices post TKI

- **FDA analysis comparing chemo-ICI and ICI alone in PD-L1 1-49%**

Primary Objective:

Compare OS and PFS between Chemo-IO and IO alone

Analysis population:

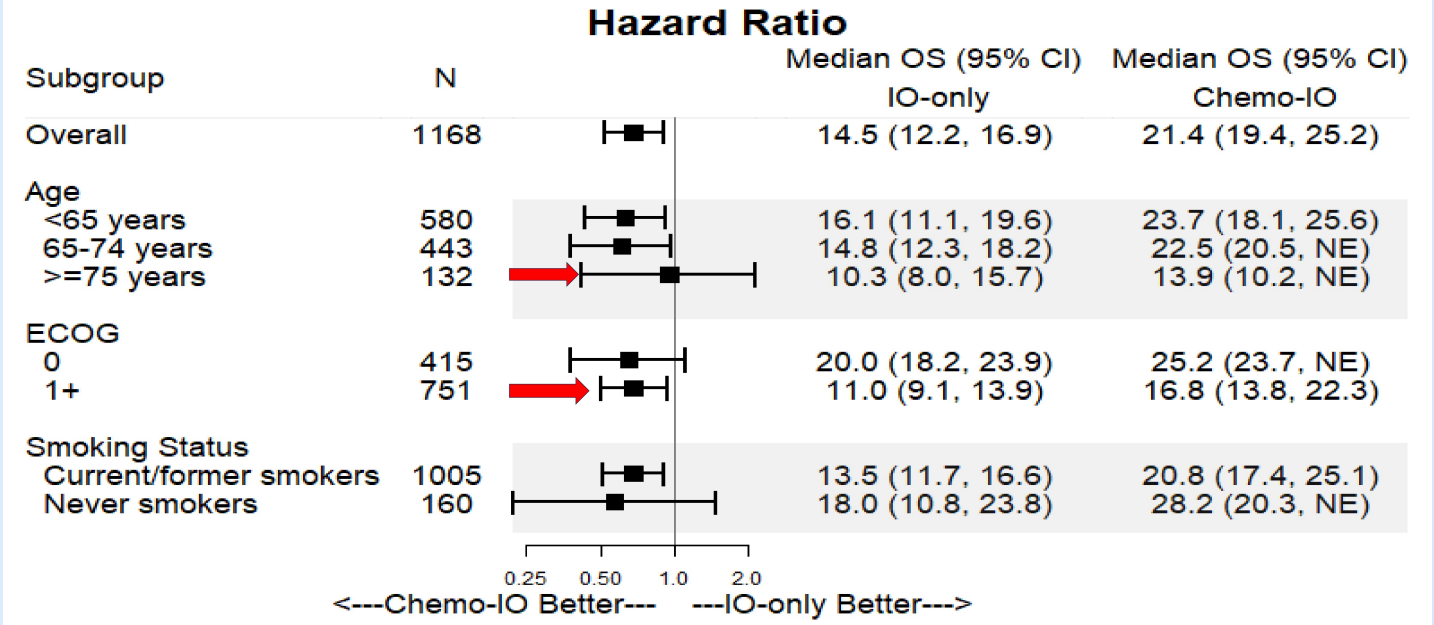
Data from studies of IO alone or IO-chemo that resulted in FDA approvals

Analysis approach:

Cox model adjusting for characteristics, stratified by study

OS in PDL1 1-49%: Subgroup analyses

FDA



Akinboro O et al. ASCO 2021

MET TKI in clinical practice—Biomarker testing

- **Patients that don't have testing will never be treated with the appropriate targeted therapy**

All patients with NSCLC				
	NSCLC overall N=14,768	White N=9,793	Black/AA N=1,288	P-value, White vs Black/AA
Ever tested	11,297 (76.5%)	**7477 (76.4%)**	**948 (73.6%)**	**0.03**
Tested prior to first line therapy		6,064 (61.9%)	784 (60.9%)	0.47
Ever NGS tested	7,185 (48.7%)	**4,904 (50.1%)**	**513 (39.8%)**	**<0.0001**
NGS tested prior to first line therapy		**3,081 (31.5%)**	**332 (25.8%)**	**<0.0001**
Patients with non-squamous NSCLC				
	Non-squamous N=10,333	White N=6,705	Black/AA N=922	P-value, White vs Black/AA
Ever tested	8,786 (85.0%)	5,699 (85.0%)	764 (82.9%)	0.09
Tested prior to first line therapy		4,881 (72.8%)	662 (71.8%)	0.52
Ever NGS tested	5,494 (53.2%)	**3,668 (54.7%)**	**404 (43.8%)**	**<0.0001**
NGS tested prior to first line therapy		**2,452 (36.6%)**	**274 (29.7%)**	**<0.0001**

AA = African American; NGS = next-generation sequencing

Bruno D et al. ASCO 2021

MET TKI in clinical practice—NILE Study

Guideline-Recommended Biomarkers, %	The Cancer Genome Atlas	cfDNA		Tissue	
		Total Cohort	Frequency of Alteration*	Total Cohort	Frequency of Alteration*
EGFR mutation	11.3	15.2	16.0	14.2	17.3
ALK fusion	1.3	2.1	2.2	3.2	4.0
ROS1 fusion	1.7	0	0	0.7	1.2
BRAF mutation (V600E)	7.0	0.7	0.7	0.7	2.1
RET fusion	0.9	1.1	1.1	0	0
ERBB2 mutation	1.7	1.1	1.1	0.4	1.6
MET exon 14 skipping variant	4.3	3.5	3.7	1.8	7.5
MET amplification	2.2	5.3	5.6	0.4	1.6
▪ *MET* focal amplification		1.8	1.9		
▪ *MET* aneuploidy		3.5	3.7		
KRAS mutation	32.2	31.6	33.2	8.5	32.9

*In patients with completed testing for biomarker of interest.

- Biomarker frequency calculated across the entire cohort (n = 282)

MET TKI in clinical practice—VISION

Efficacy Outcomes	Liquid Biopsy (L+)		Tissue Biopsy (T+)	
	IRC (n = 48)	Investigator (n = 47)	IRC (n = 51)	Investigator (n = 51)
BOR by RECIST 1.1, n (%)				
CR	0 (0)	3 (6.4)	0 (0)	3 (5.9)
PR	24 (50.0)	23 (48.9)	23 (45.1)	25 (49.0)
SD	8 (16.7)	5 (10.6)	14 (27.5)	11 (21.6)
PD	7 (14.6)	10 (21.3)	8 (15.7)	6 (11.8)
Not evaluable	9 (18.8)	6 (12.8)	6 (11.8)	6 (11.8)
ORR,* n (%; 95% CI)	24 (50.0; 35.2-64.8)	26 (55.3; 40.1-69.8)	23 (45.1; 31.1-59.7)	28 (54.9; 40.3-68.9)
Median DoR, mos (95% CI)	12.4 (5.8-NE)	17.1 (7.2-NE)	15.7 (9.0-NE)	14.3 (5.7-NE)
DCR,† n (%; 95% CI)	32 (66.7; 51.6-79.6)	31 (66.0; 50.7-79.1)	37 (72.5; 58.3-84.1)	39 (76.5; 62.5-87.2)

*CR + PR. †Confirmed CR/PR or SD for ≥ 12 wks.

Efficacy analysis includes patients having ≥ 2 postbaseline assessments or who discontinued treatment for any reason.

L+, METex14-skipping mutation-positive in ctDNA; T+ METex14-skipping mutation–positive in tissue.

Paik. NEJM 2020; Paik. ASCO 2019. Abstr 9005.

MET TKI in clinical practice—post TKI trials

NIH Identifier: NCT02323126
Link: https://clinicaltrials.gov/ct2/ show/NCT02323126
Title: Study of Efficacy and Safety of Nivolumab in Combination with EGF816 and of Nivolumab in Combination With INC280 in Patients With Previously Treated Non-small Cell Lung Cancer (EGF816)

NIH Identifier: NCT04310007
Link: https://clinicaltrials.gov/ct2/ show/NCT04310007
Title: PhII Chemotherapy, Cabozantinib, to the Standard Immune Therapy Nivolumab Compared to Standard Chemotherapy for Non-small Cell Lung Cancer

NIH ID: NCT02954991
Link: https://clinicaltrials.gov/ct2/ show/NCT02954991
Title: Phase 2 Study of Glesatinib, Sitravatinib or Mocetinostat in Combination with Nivolumab in Non-Small Cell Lung Cancer

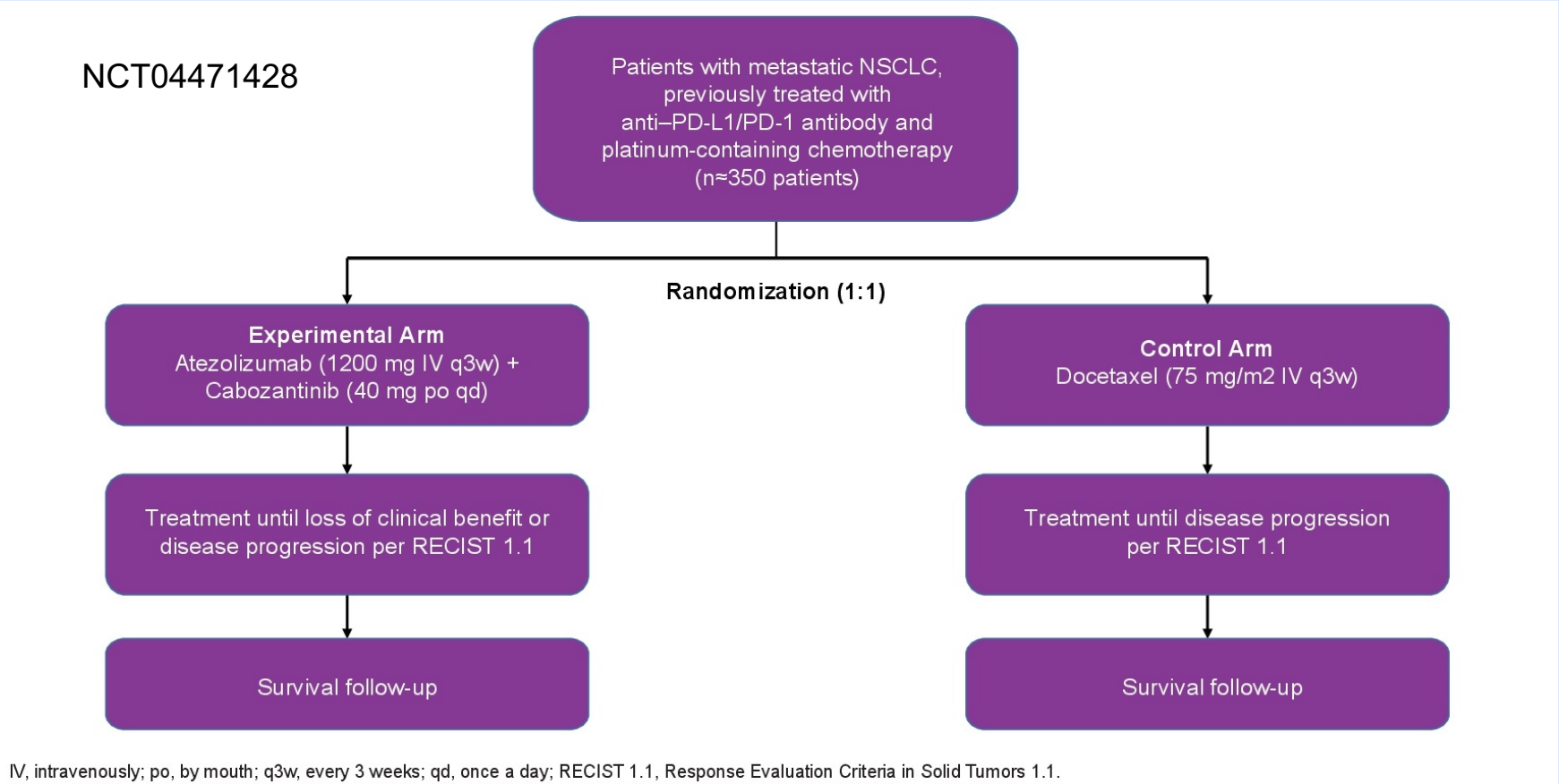
NIH ID: NCT03666143
Link: https://clinicaltrials.gov/ct2/ show/NCT03666143
Title: A Phase 1b Study to Assess Sitravatinib in Combination with Tislelizumab in Patients With Advanced Solid Tumors

NIH ID: NCT04323436
Link: https://clinicaltrials.gov/ct2/ show/NCT04323436
Title: Study of Capmatinib and Spartalizumab/Placebo in Advanced NSCLC Patients with MET Exon 14 Skipping Mutations

NIH ID: NCT04139317
Link: https://clinicaltrials.gov/ct2/ show/NCT04139317
Title: Safety and Efficacy of Capmatinib (INC280) Plus Pembrolizumab vs Pembrolizumab Alone in NSCLC With PD-L1≥ 50%

MET TKI in clinical practice—ICI trials

Contact-01 Study design



IV, intravenously; po, by mouth; q3w, every 3 weeks; qd, once a day; RECIST 1.1, Response Evaluation Criteria in Solid Tumors 1.1.

Neal JW et al. ASCO 2021 abstract TPS9134

Conflict of Interest

Dr. Xiuning Le receives consulting/advisory fees from EMD Serono (Merck KGaA), AstraZeneca, Spectrum Pharmaceutics, Novartis, Hengrui, Eli Lilly, Daiichi Sankyo, Boehringer Ingelheim, and Bristol-Myers Squibb, and Research Funding from Eli Lilly and Boehringer Ingelheim.

Dr. Mark Awad reports grants and personal fees from Genentech, grants and personal fees from Bristol-Myers Squibb, grants and personal fees from AstraZeneca, grants from Lilly, and personal fees from Merck, Maverick, Blueprint Medicine, Syndax, Ariad, Nektar, Gritstone, ArcherDX, Mirati, NextCure, Novartis, EMD Serono, Panvaxal/NovaRx.

Dr. Karen Reckamp receives consulting/advisory fees from Amgen; AstraZeneca; Bluprint; Boehringer Ingelheim; EMD Serono; Genentech; GSK; Guardant; Janssen; Lilly; Loxo; Mirati Seattle Genetics; Takeda, and research funding to the institution from AbbVie, Acea, Adaptimmune, Boehringer Ingelheim, Bristol Myers Squibb, Calithera; Daiichi Sankyo; Elevation Oncology Genentech, GlaxoSmithKline, Guardant, Janssen, Loxo Oncology, Seattle Genetics, Takeda, Xcovery, Zeno

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