Mechanism of resistance to MET TKI And therapy post resistance in NSCLC

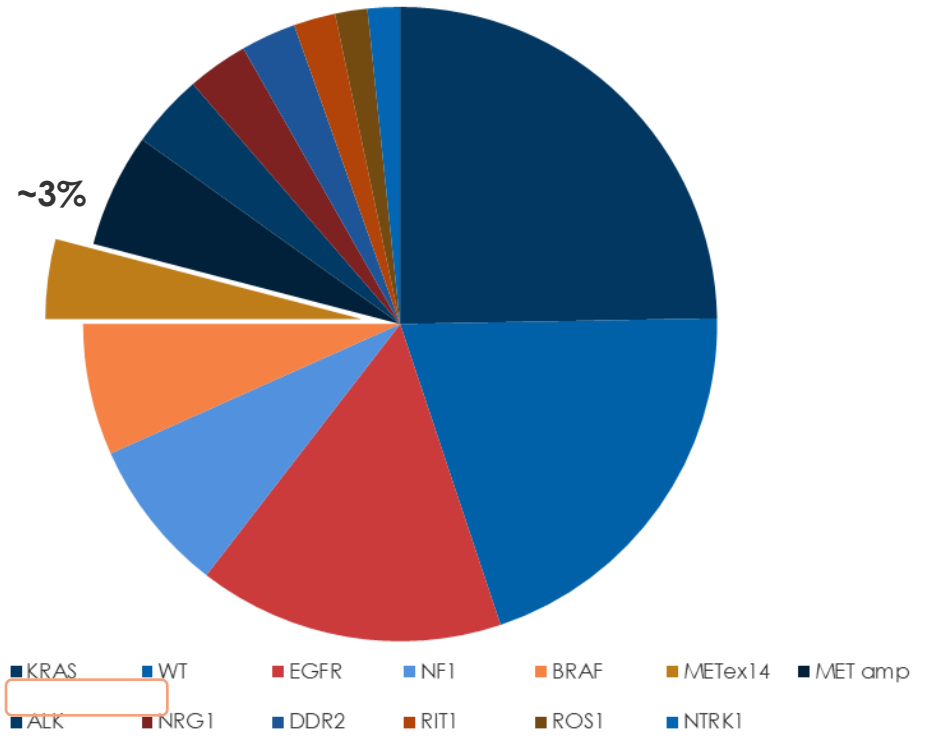
Dr Sudeep Das

Medica Oncology, Kolkata

MET mutations in NSCLC

- *MET* mutation is 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 juxtamembrane 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]

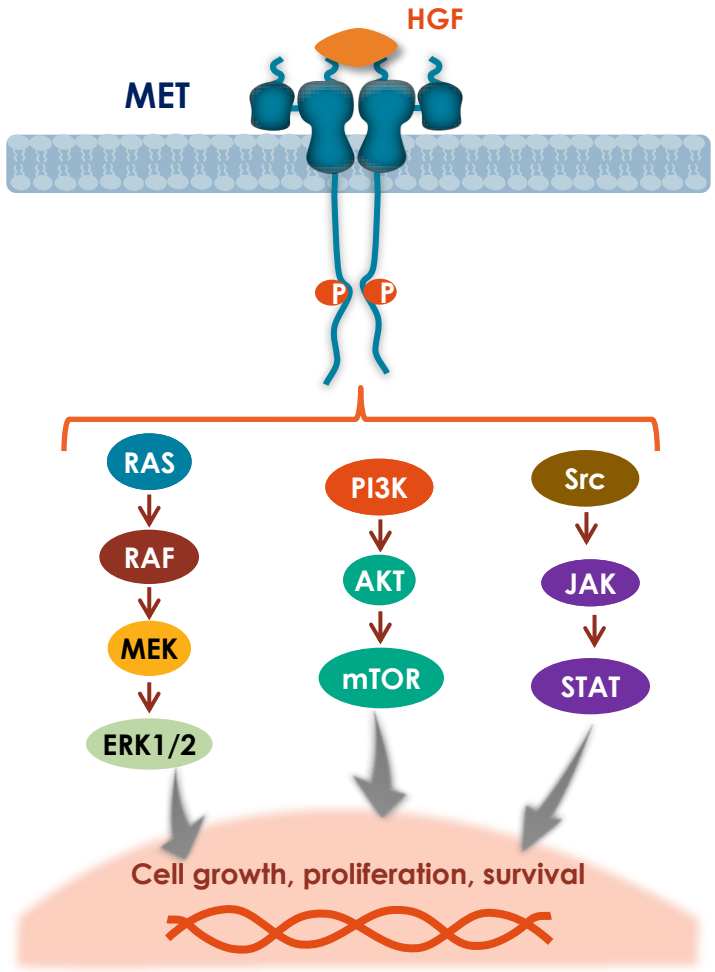
Common oncogenic mutations in NSCLC[4–9,12–14]



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.

Normal MET signaling

- The MET (c-Met, c-MET or HGF receptor) pathway is normally activated by the binding of its natural ligand, HGF
- Ligand-dependent dimerization leads to autophosphorylation and facilitates recruitment of cytoplasmic effector proteins to activate transmembrane signaling
- Normal MET activation facilitates processes for cell proliferation, survival, and metastases

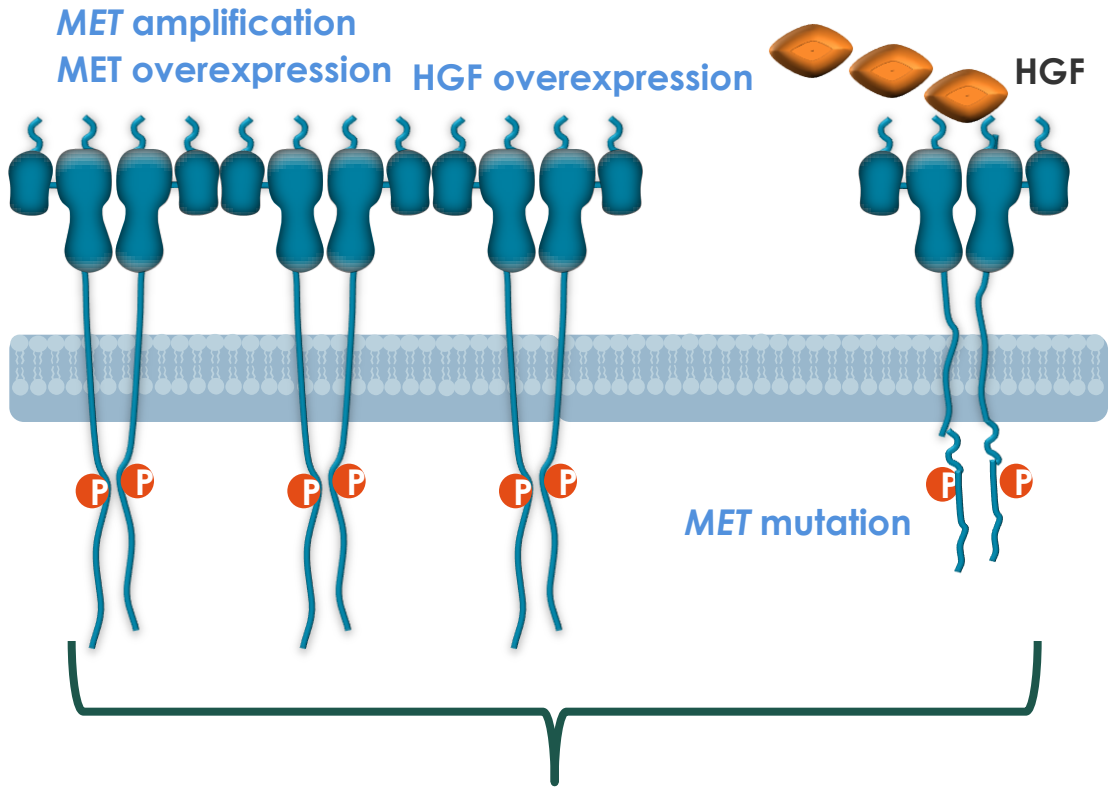


Smyth EC, et al. Onco Targets Ther. 2014;7:1001-14.

Dysregulated MET signaling in NSCLC

- Dysregulation of MET/HGF signaling leads to malignant cellular transformation, proliferation, survival, angiogenesis, invasion, and metastasis[1]
- *MET*-dysregulated NSCLC is an umbrella term for NSCLC with alterations to the *MET* receptor gene
- Genetic aberrations in *MET*, including overexpression, amplification, mutation, and alternative splicing, are recognized as oncogenic driver mutations in NSCLC[2]

Dysregulated MET signaling in NSCLC may occur de novo or as a resistance mechanism[3,4]



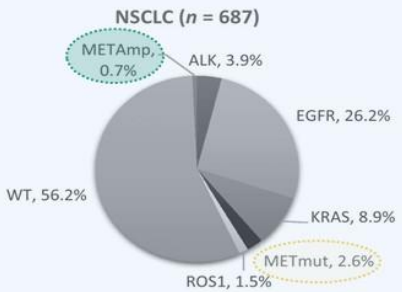
1. Gherardi E, et al. Nat Rev Cancer. 2012;12:89-103.
2. Luo SY, Lam DC. Transl Respir Med. 2013;1:6.
3. Smyth EC, et al. Onco Targets Ther. 2014;7:1001-14.
4. Sadiq AA, Salgia R. J Clin Oncol. 2013;31:1089-96.

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

Classification of MET Tyrosine Kinase Inhibitors

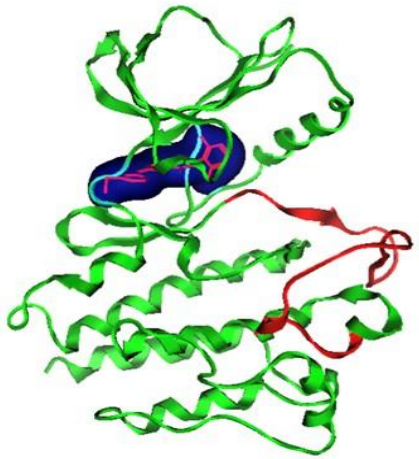
Type I a/b TKIs

Crizotinib
Savolitinib
Tepotinib

Capmatinib

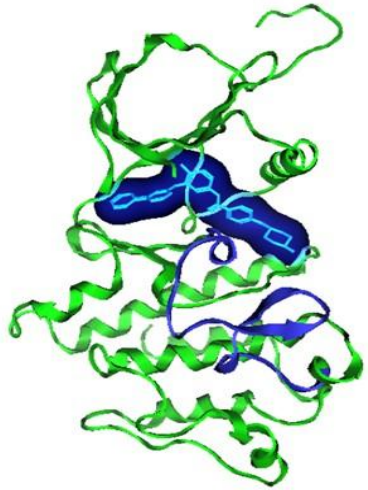
FDA approved
5/6/20

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

Tab 1 TKIs targeting *MET* gene mutation

Drugs	Targets	Types of TKI	Current status	Clinical trial number	Affiliated company
Crizotinib	*MET, ALK, ROS-1*	Ia	On the market	NCT0058519 NCT02465060 NCT02499614 NCT02664935	Pfizer
Cabozantinib	*MET, VEGFR2, RET, KIT, AXL*	II	On the market	NCT01639508	Elexis
Savolitinib	*MET*	Ib	In the process of marketing	NCT02897479	Hutchison MediPharma
Tepotinib	*MET*	Ib	On the market	NCT02864992/2015-005696-24	Merck
Capmatinib	*MET*	Ib	In the process of marketing	NCT02750215 NCT01324479	Novartis
Glesatinib	*MET, VEGFR, RON, TIE-2*	II	Clinical trials in progress	NCT02544633	Mirati Therapeutics
Merestinib	*MET, TIE-1, AXL, ROS1, DDR1/2, FLT3, MERTK, RON, MKNK1/2*	II	Clinical trials in progress	NCT02920996	Eli Lilly

EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; TKI: tyrosine kinase inhibitor; VEGFR2: vascular endothelial growth factor receptor 2.

Trial and drug	Trial design (phase, endpoints, number of patients)	Outcomes (ORR, median PFS and median OS)	All-grade toxicities	Refs.
GEOMETRY mono-1, capmatinib	• Phase II • ORR, DOR, PFS and safety • *n*=160 *MET* exon 14 (pre-treated: 100, treatment naive: 60)	• ORR: -Pre-treated: 44% -Naive: 66.7% • DOR: -Pre-treated: 9.7mo -Naive: 12.6 mo • PFS: -Pre-treated: 5.5 mo -Naive: 12.3 mo	Pre-treated/Naive • Oedemas (54/75%) • Nausea (46/46%) • Blood creatinine increase (33/36%) • Dyspnoea (28/21%)	16,50
VISION, tepotinib	• Phase II • ORR, DOR, PFS, OS and safety • *n*=146 *MET* exon 14	• ORR: 45.2% • DOR: 11.1 mo • PFS: 8.5 mo • OS: 17.1 mo	• Oedemas (63%) • Nausea (26%) • Diarrhoea (22%)	15,51
NCT02897479, savolitinib	• Phase II • ORR, DOR, TTR, PFS, OS and safety • *n*=70 *MET* exon 14 (25 sarcomatoid carcinoma)	• ORR: 42.9% • DOR: 8.3 mo • TTR: 1.4 mo • PFS: 6.8 mo • OS: 12.5 mo	• Oedemas (56%) • Nausea (53%) • Hypoalbuminaemia (41%)	52
PROFILE 1001, crizotinib	• Phase I • ORR, DOR, PFS, OS and safety • *n*=69 *MET* exon 14	• ORR: 32% • DOR: 9.1 mo • PFS: 7.3 mo • OS: 20.5 mo	• Oedemas (51%) • Vision disorders (45%) • Diarrhoea (39%)	49
METROS, crizotinib	• Phase II • ORR, PFS, OS and safety • *n*=9 *MET* exon 14	• ORR: 20% • PFS: 2.6 mo • OS: 3.8 mo	• Cough/dyspnoea (46%) • Oedemas (31%) • Nausea (31%)	66

DOR, duration of response; mo, months; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTR,

MET inhibitors: the story so far

MET exon 14sk	N of patients	Line of treatment	RR (%)	DOR (months)	icRR (%)	PFS (months)	OS (months)	TR-AEs discontinuation
CRIZOTINIB	65	1 >1	25 36.6	9.1 (overall)	20[§]	7.3 (overall)	20.5 (overall)	7%
CAPMATINIB	63	1 2	65.6 51.6	12.6 9.7	54	10.8 6.9	20.8* 13.6*	11%
TEPOTINIB	152	1 >1	43 43	10.8 11.1	55	8.5 (overall)	17.1 (overall)	11%
SAVOLITINIB	70	1 >1	54.4 46	6.8 NR	NA	5.6 13.8	NA	14.3%

MET *de novo* amplification	N of patients	Line of treatment	RR (%)	DOR (months)	PFS (months)	OS (months)	TR-AEs discontinuation
CRIZOTINIB	21	≥1	38.1	5.2	6.7	11.4	10.5%
CAPMATINIB	84	1 >1	40 29	7.5 8.3	4.2 4.1	NA	11%
TEPOTINIB	24	1 >1	71.4 28-30	NR	4.2 (overall)	NA	0%

*Data not mature for expansion cohorts; [§] retrospective data, not reported in Profile 1001

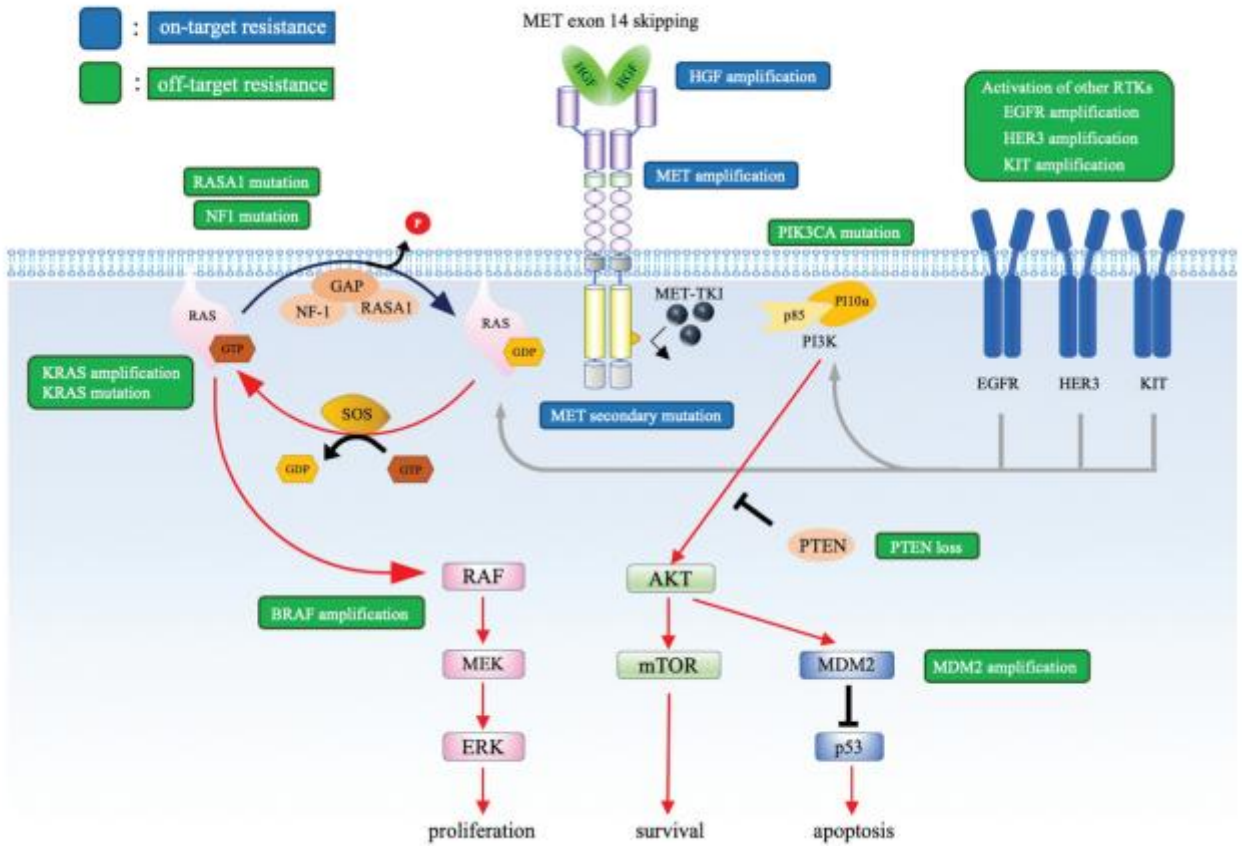
Inherent resistance

- Presence of concurrent mutations:
- Gene amplifications of MDM2 (25–34.6%), CDK4 (3.3–21%), and EGFR (6.4–29%)
- Amplification of or mutations in KRAS (3–7%) and PIK3CA (3– 9.8%)
- Loss of PTEN protein expression (23%)

Acquired resistance

- On target resistance mechanism-

- Off target resistance mechanism



Acquired resistance is inevitable in MET-targeted therapy

- Multiple secondary mutations could occur simultaneously in one patient, which indicates the possibility of heterogeneous resistance mechanisms
- Difficult to treat patients based on the resistance mechanisms identified from a biopsied lesion because other lesions might harbor different secondary mutations

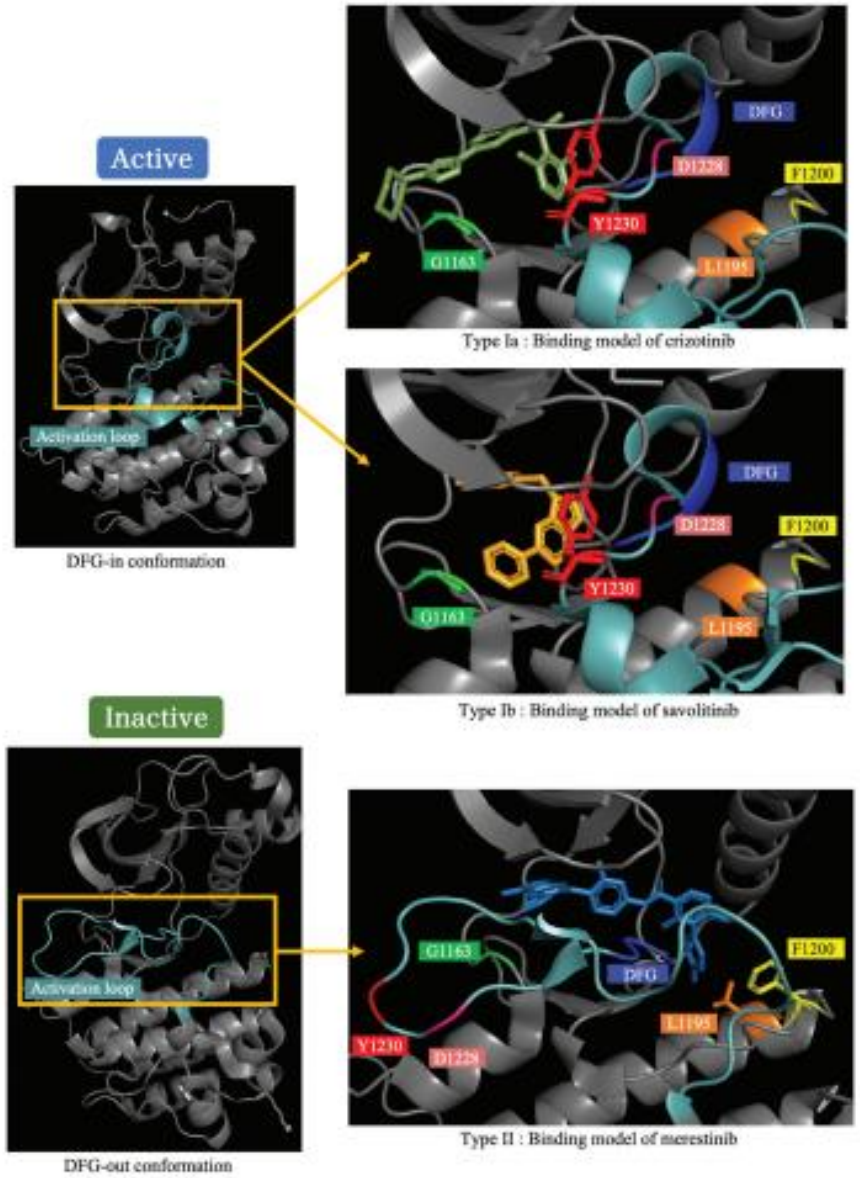
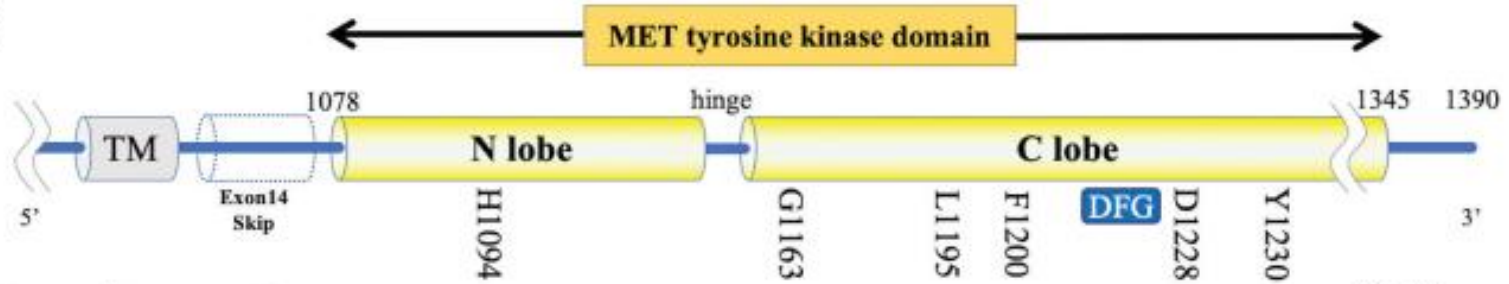


Figure 3. Difference in the binding mode between type I and type II MET-TKIs.

Type I inhibitors are ATP competitors that bind to the ATP-binding pocket of the active state ('DFG-in') and interact with the Y1230 residue in the activation loop and hinge. The type Ia inhibitor crizotinib also interacts with the solvent front residue G1163, while type Ib inhibitors do not interact with this residue. Type II TKIs are also ATP competitors that bind to the

(a)

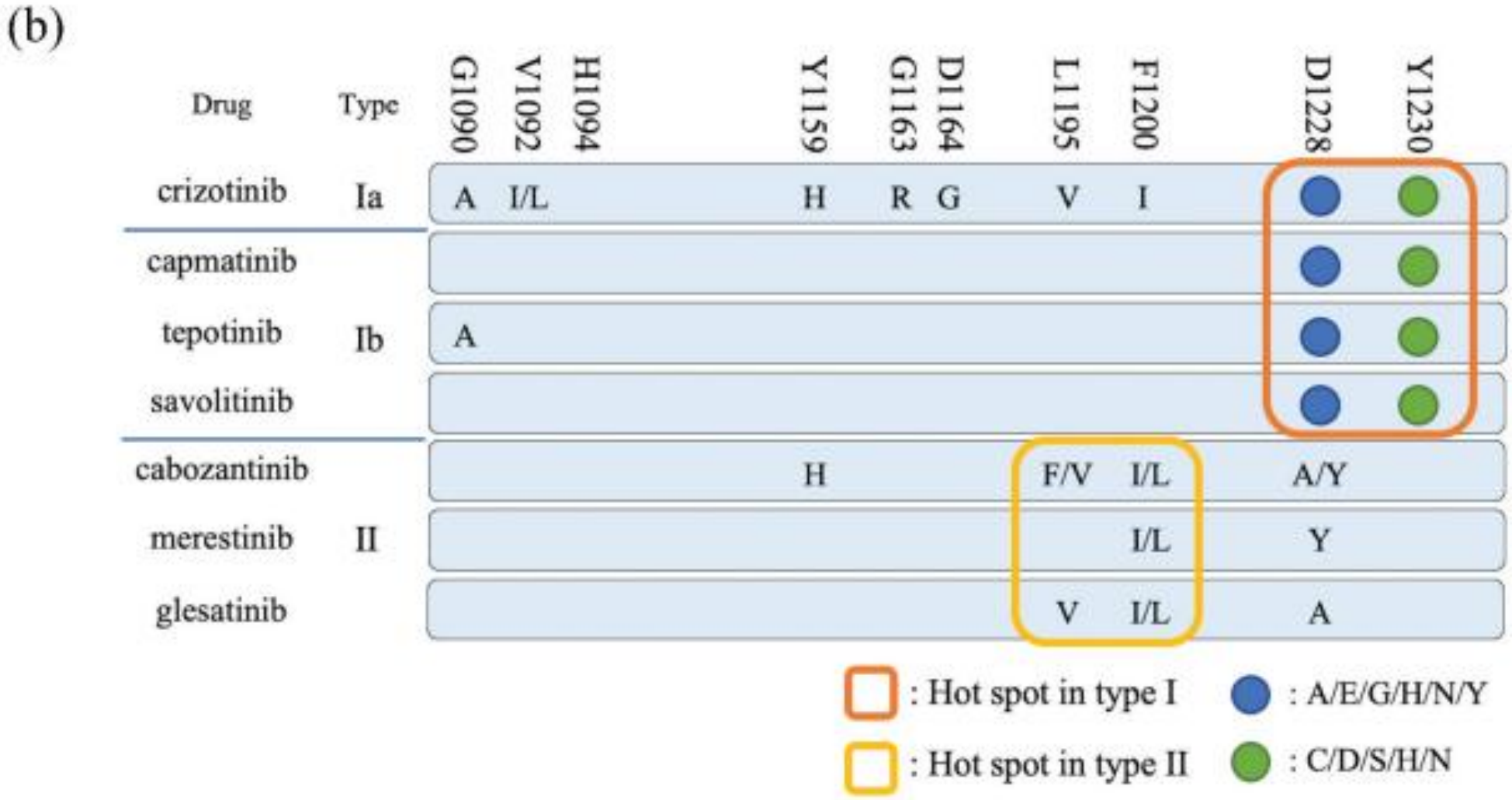


Patient	Drug	Type	Biopsy	H1094	G1163	L1195	F1200	DFG	D1228	Y1230	Reference
1			T & L		R	V			H/N	H/S	[132]
2			L		R				A/H	H	[149]
3			T & L		R				N	H/S	[133]
4			L				I			S	[146]
5			L						H/N	H	[142]
6			L						N	H	[145]
7			L			V					[142]
8			T						H		[132]
9	crizotinib	Ia	L						H		[142]
10			T						N		[150]
11			L						N		[32]
12			L						N		[32]
13			N/A						N		[146]
14			N/A						N		[132]
15			T & L							C	[132]
16			T							H	[148]
17	capmatinib	Ib	T & L						N		[132]
18	glesatinib	II	T & L	Y		V					[132]

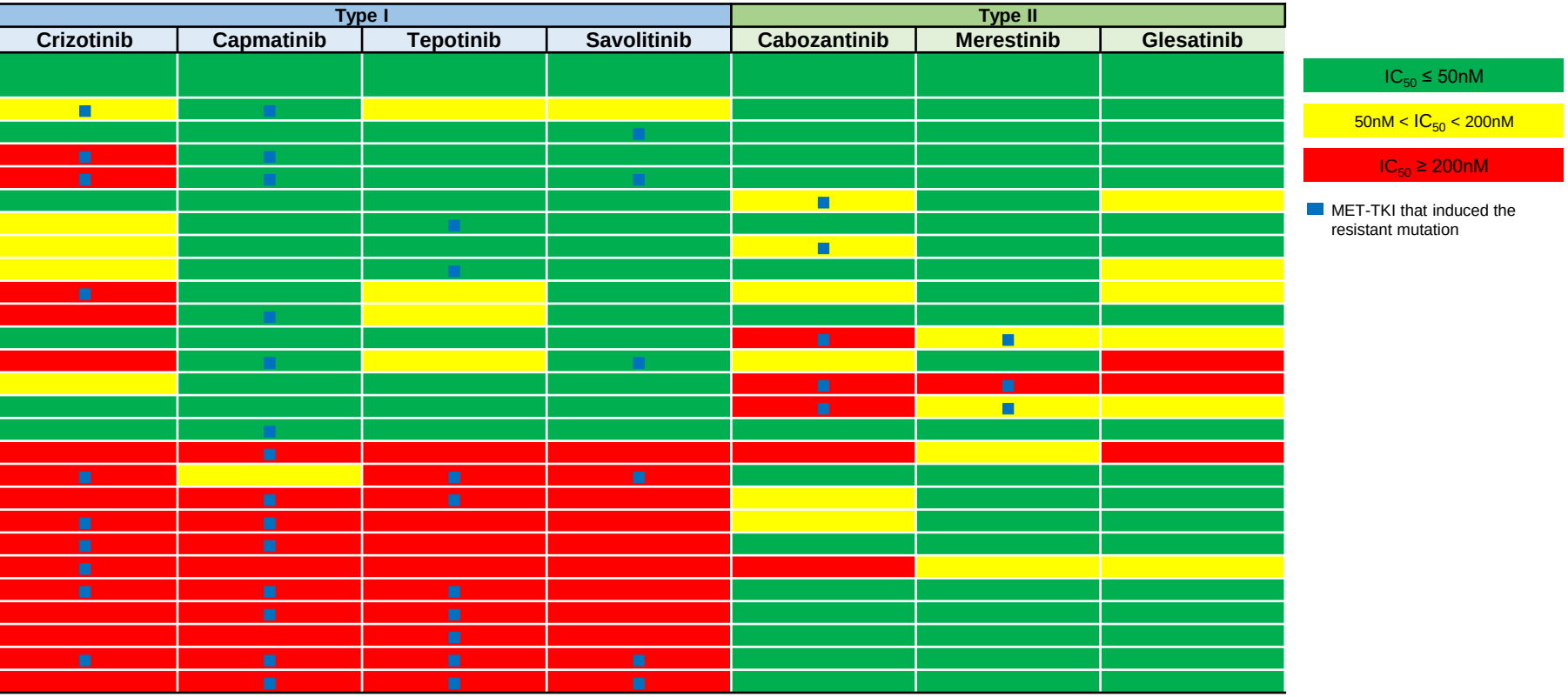
- Tissue and liquid biopsy NGS are complementary
- Multiple mutations can co-exist

- . The development of strategies for overcoming this resistance depending on the resistance mechanism is awaited
- These will include the optimal sequencing of different MET-TKIs
- Development of new MET-TKIs
- Combination therapies

In vitro analysis: Fujino et al. in JTO in 2019



Resistant mutations against type I TKIs were sensitive to type II TKIs and vice versa in an in vitro model

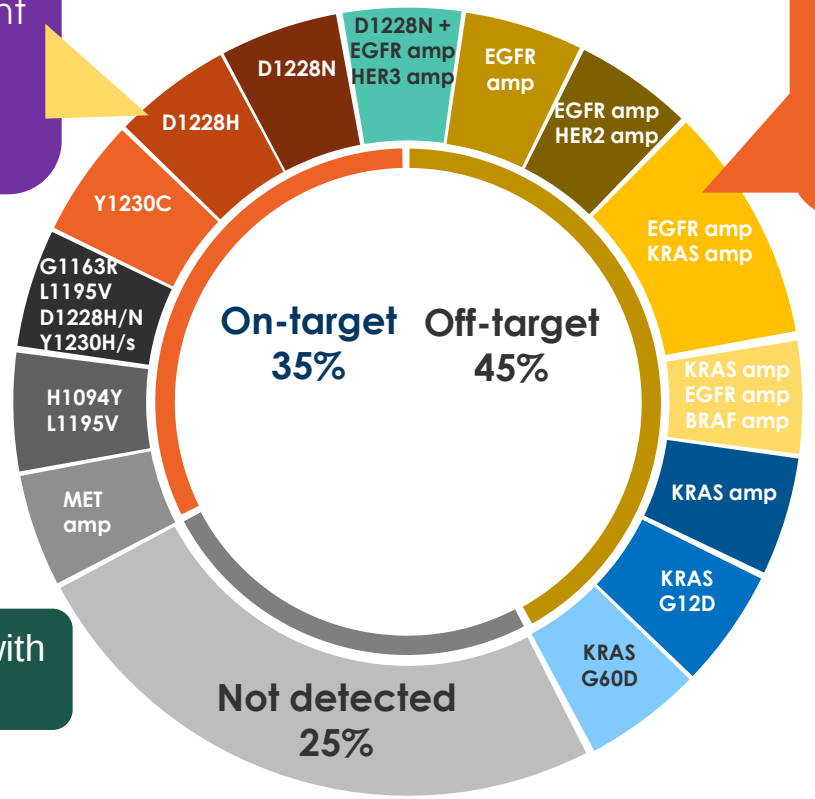


- D1228 and Y1230 mutations, which commonly occurred with type I TKIs, were generally highly resistant to all type I inhibitors, but were still sensitive to type II
- L1195 and F1200 mutations which commonly occurred with type II TKIs, had moderate to high resistance to all type II inhibitors, while they were still sensitive to type I, except for crizotinib

Resistance mechanisms to MET TKIs

MET-dependent resistance (on target) included single and multiple kinase domain mutations in different residues and amplification of the *MET* exon 14 mutant allele

Results from 15 paired samples



Genomic bypass mechanisms of resistance (off-target) involved recurrent gene amplification in *EGFR, HER2, HER3, and* MAPK pathway genes *(KRAS/ BRAF)* and *KRAS* mutations

15 patients treated with MET TKIs

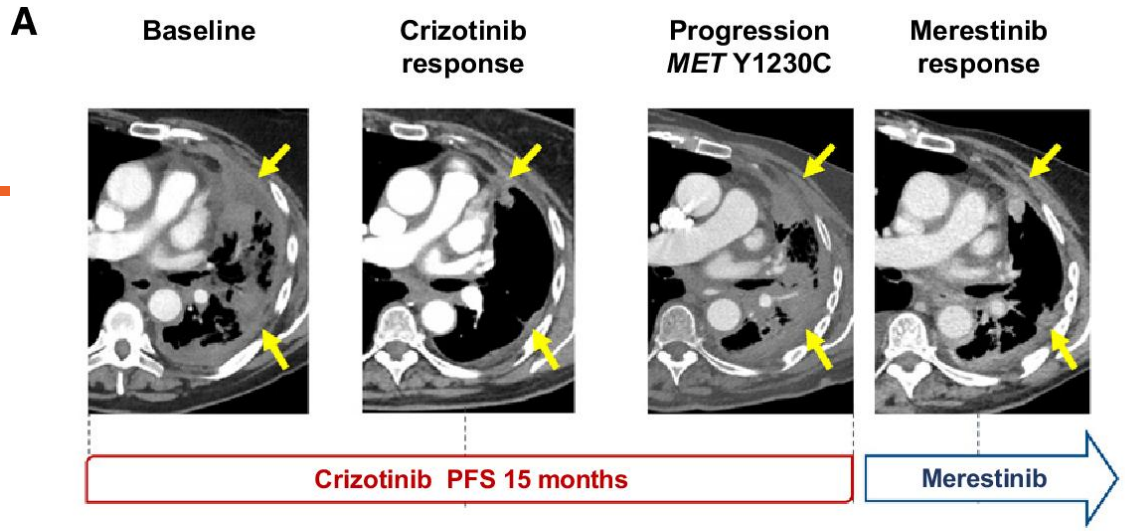
Recondo G, et al. Clin Cancer Res. 2020; doi: 10.1158/1078-0432.CCR-19-3608.

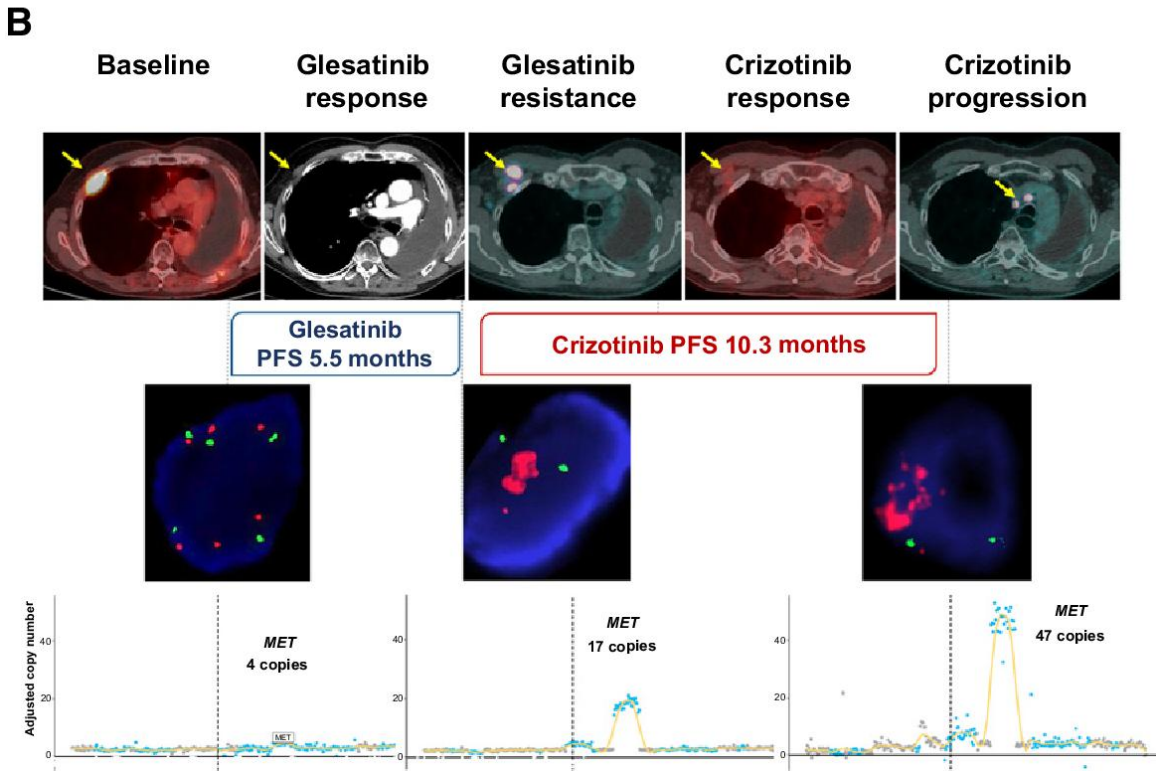
MET TKI	Resistance mutations
Type Ia: crizotinib	G1163R D1228H/N Y1230C/H/S L1195V
Type Ib: capmatinib	D1228N
Type II: glesatinib	H1094Y L1195V

- MET mutations in residues D1228 and Y1230 confer resistance to type I MET TKI by weakening the chemical bonds between the drug and its receptor.

- The solvent front mutation G1163R mediates resistance only to crizotinib but not to type Ib or type II MET inhibitors.

- In contrast, mutations in residues L1195 and F1200 confer resistance to type II MET inhibitors


A
Baseline
Crizotinib response
Progression MET Y1230C
Merestinib response
Crizotinib PFS 15 months
Merestinib


B
Baseline
Glesatinib response
Glesatinib resistance
Crizotinib response
Crizotinib progression
Glesatinib PFS 5.5 months
Crizotinib PFS 10.3 months
Adjusted copy number
MET 4 copies
MET 17 copies
MET 47 copies

- The complementary activities against those mutations, i.e., type II MET-TKIs can overcome acquired resistance due to secondary mutations caused by type I MET-TKIs, and vice versa.
- Indeed, glesatinib (type II) shows antitumor activity for Y1230H/S, which appears after crizotinib (type Ia)
- Merestinib (type II) can overcome D1228N, which appears after capmatinib (type Ib)
- However, some mutations, such as D1228A/Y, confers resistance to both type I and type II MET-TKIs
- Mutation-induced conformational change in A-loop reshapes kinase active site and then influences the site interactions with inhibitor ligands, thus conferring different selectivity to the type I and type II TKI

Fujino *et al.*
Journal of Hematology & Oncology (2022) 15:79
https://doi.org/10.1186/s13045-022-01299-z

Journal of
Hematology & Oncology

RESEARCH Open Access

Foretinib can overcome common on-target resistance mutations after capmatinib/tepotinib treatment in NSCLCs with MET exon 14 skipping mutation

Toshio Fujino, Kenichi Suda, Takamasa Koga, Akira Hamada, Shuta Ohara, Masato Chiba, Masaki Shimoji, Toshiki Takemoto, Junichi Soh and Tetsuya Mitsudomi*

Abstract

Background: Capmatinib and tepotinib are guideline-recommended front-line treatments for non-small-cell lung cancer (NSCLC) patients with *MET* exon 14 skipping mutations (*METex14*). However, the emergence of acquired resistance to capmatinib/tepotinib is almost inevitable partially due to D1228X or Y1230X secondary mutations of the MET. In this study, we explored agents that are active against both D1228X and Y1230X MET to propose an ideal sequential treatment after capmatinib/tepotinib treatment failure in NSCLC patients with *METex14*.

Methods: The inhibitory effects of 300 drugs, including 33 MET-TKIs, were screened in Ba/F3 cells carrying *METex14* plus *MET* D1228A/Y secondary mutations. The screen revealed four-candidate type II MET-TKIs (altiratinib, CEP-40783, foretinib and sitravatinib). Therefore, we performed further growth inhibitory assays using these four MET-TKIs plus

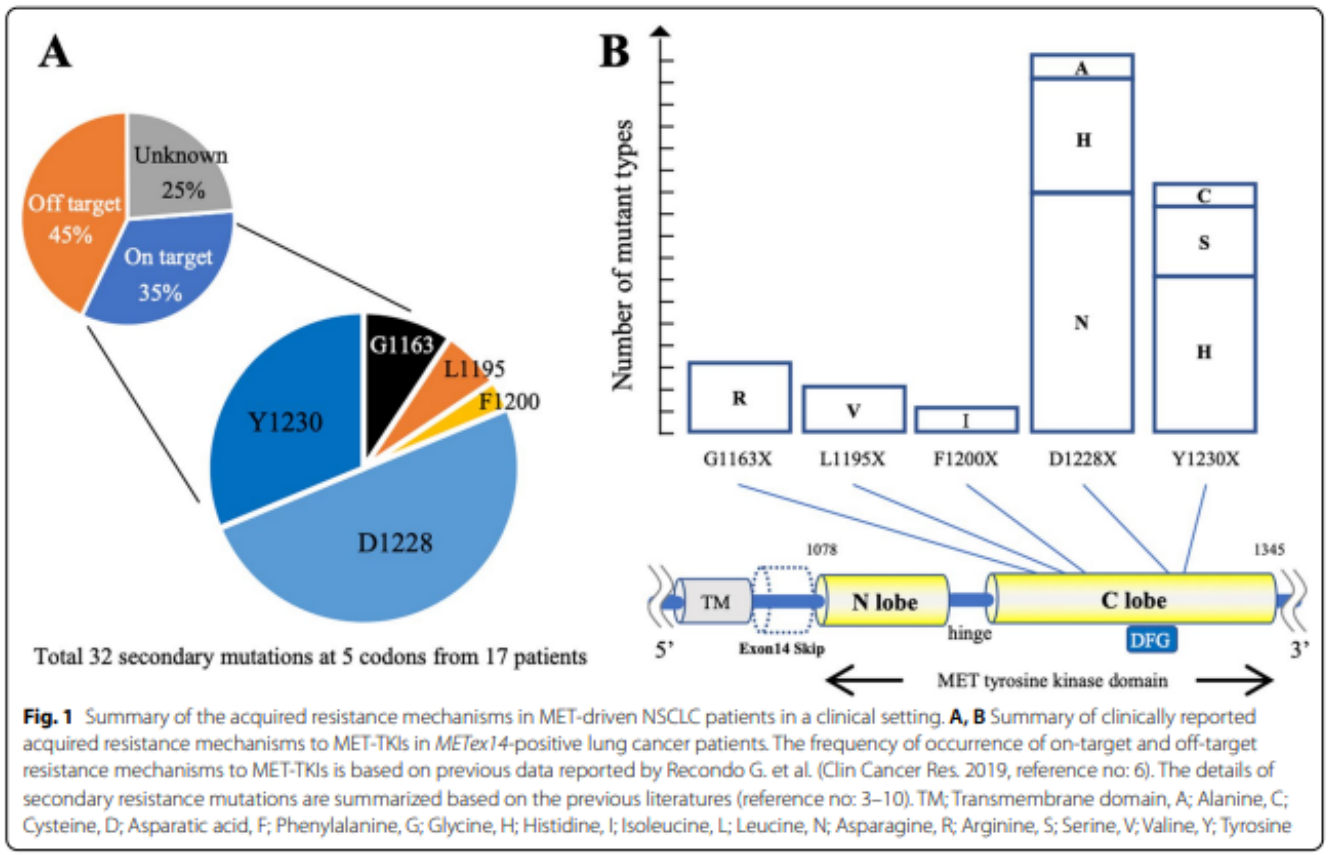


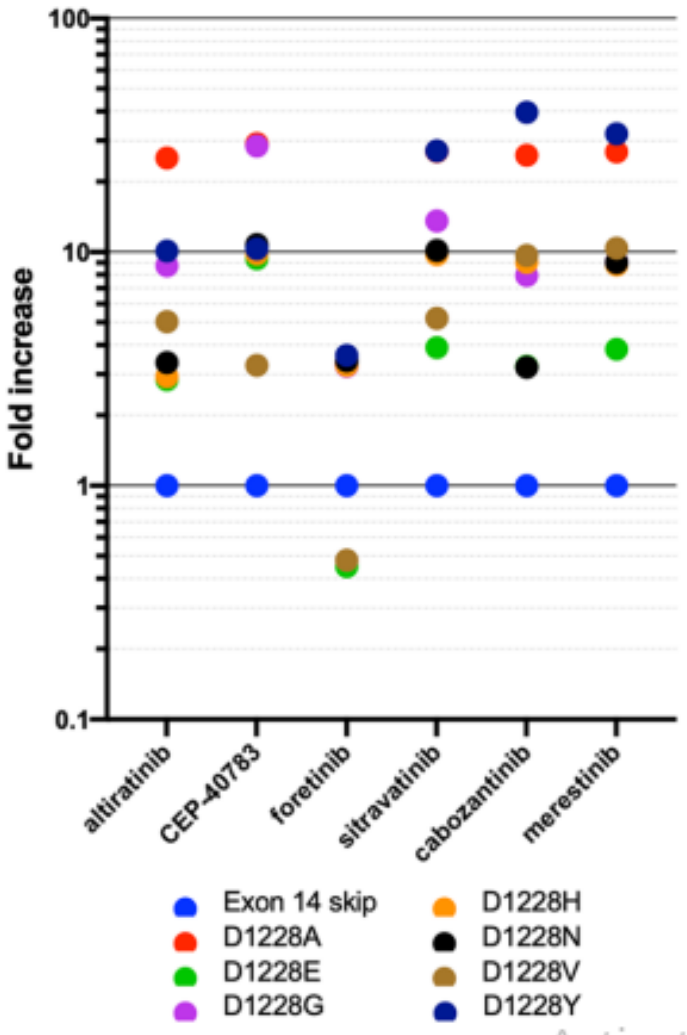
Fig. 1 Summary of the acquired resistance mechanisms in MET-driven NSCLC patients in a clinical setting. **A, B** Summary of clinically reported acquired resistance mechanisms to MET-TKIs in *METex14*-positive lung cancer patients. The frequency of occurrence of on-target and off-target resistance mechanisms to MET-TKIs is based on previous data reported by Recondo G. et al. (Clin Cancer Res. 2019, reference no: 6). The details of secondary resistance mutations are summarized based on the previous literatures (reference no: 3–10). TM; Transmembrane domain, A; Alanine, C; Cysteine, D; Asparatic acid, F; Phenylalanine, G; Glycine, H; Histidine, I; Isoleucine, L; Leucine, N; Asparagine, R; Arginine, S; Serine, V; Valine, Y; Tyrosine

A

IC_{50} (nM)		Type I		Type II					
Mutation		capmatinib	tepotinib	altiratinib	CEP-40783	foretinib	sitravatinib	cabozantinib	merestinib
MET WT + IL3 *		>1000	>1000	>1000	>1000	906	>1000	>1000	452
Exon 14 skip *		0.4	3.5	3.6	1.1	3.2	3.6	11	3.7
D1228	A	>1000	>1000	92	32	11	98	295	99
	E	50	>1000	10	10	1.4	14	37	14
	G	348	>1000	32	31	10	49	90	34
	H	>1000	>1000	11	11	10	35	103	33
	N	>1000	>1000	12	12	11	37	37	34
	V*	>1000	>1000	18	3.6	1.5	19	110	39
	Y	402	>1000	37	11	12	98	451	119
Y1230	C	>1000	>1000	1.3	4.1	0.4	10	18	10
	D	>1000	>1000	3.7	10	0.4	10	31	4.3
	H	470	>1000	4.6	12	3.6	32	18	11
	N	>1000	>1000	11	35	3.6	33	36	4.1
	S	>1000	>1000	0.2	4	0.1	0.8	32	12

$IC_{50} \leq 50nM$ | $50 < IC_{50} < 200nM$ | $IC_{50} \geq 200nM$

B



› Mol Cancer Ther. 2022 Feb;21(2):322-335. doi: 10.1158/1535-7163.MCT-21-0344.
Epub 2021 Nov 17.

Combination of Type I and Type II MET Tyrosine Kinase Inhibitors as Therapeutic Approach to Prevent Resistance

Magda Bahcall [1], Cloud P Paweletz [2], Yanan Kuang [2], Luke J Taus [2], Taebo Sim [3 4], Nam Doo Kim [5], Kshiti H Dholakia [1], Christie J Lau [2], Prafulla C Gokhale [2], Pratik R Chopade [2], Fangxin Hong [6 7], Zihan Wei [6], Jens Köhler [1], Paul T Kirschmeier [2], Jiannan Guo [8], Sujuan Guo [2], Stephen Wang [2], Pasi A Jänne [9 2 10]

Affiliations + expand

PMID: 34789563 PMCID: PMC8828669 (available on 2022-08-01)
DOI: 10.1158/1535-7163.MCT-21-0344

Abstract

MET-targeted therapies are clinically effective in *MET*-amplified and *MET* exon 14 deletion mutant (*MET*ex14) non-small cell lung cancers (NSCLCs), but their efficacy is limited by the development of drug resistance. Structurally distinct MET tyrosine kinase inhibitors (TKIs) (type I/II) have been developed or are under clinical evaluation, which may overcome MET-mediated drug resistance mechanisms. In this study, we assess secondary MET mutations likely to emerge in response to treatment with single-agent or combinations of type I/type II MET TKIs using TPR-MET transformed Ba/F3 cell mutagenesis assays. We found that these inhibitors gave rise to distinct secondary MET mutant profiles. However, a combination of type I/II TKI inhibitors (capmatinib and merestinib) yielded no resistant clones *in vitro* The combination of capmatinib/merestinib was evaluated *in vivo* and led to a significant reduction in tumor outgrowth compared with either MET inhibitor alone. Our findings demonstrate *in vitro* and *in vivo* that a simultaneous treatment with a type I and type II MET TKI may be a clinically viable approach to delay and/or diminish the emergence of on target MET-mediated drug-resistance mutations.

Published in final edited form as:

Cancer Discov. 2016 December ; 6(12): 1334–1341. doi:10.1158/2159-8290.CD-16-0686.

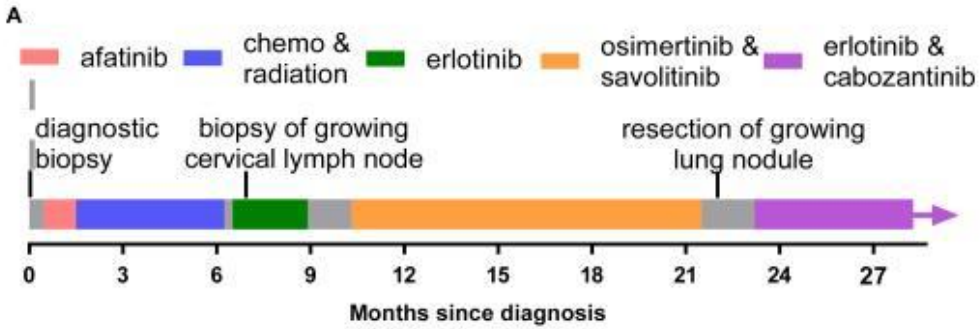
Acquired *MET* D1228V mutation and resistance to MET inhibition in lung cancer

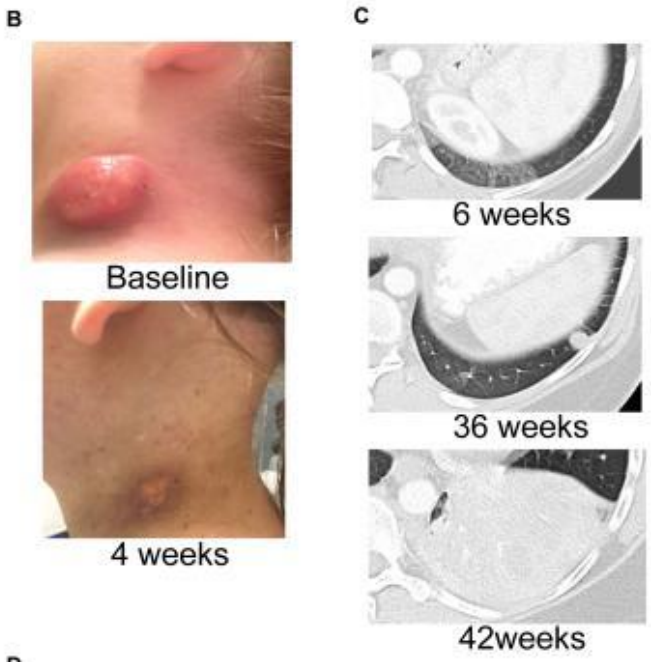
Magda Bahcall[1], **Taebo Sim**[2,3], **Cloud P. Paweletz**[4], **Jyoti D. Patel**[5], **Ryan S. Alden**[1], **Yanan Kuang**[4], **Adrian G. Sacher**[1], **Nam Doo Kim**[6], **Christine A. Lydon**[1], **Mark M. Awad**[1,7], **Michael T. Jaklitsch**[8], **Lynette M. Sholl**[9], **Pasi A. Jänne**[1,4,7,*], and **Geoffrey R. Oxnard**[1,7,*]

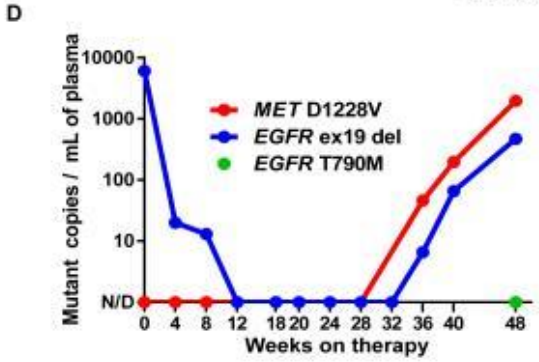
[1]Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA

[2]Chemical Kinomics Research Center, Korea Institute of Science and Technology, Seoul, Republic of Korea

[3]KU-KIST Graduate School of Converging Science and Technology, Korea University, Seoul,







Most common AEs regardless of causality (≥20%, all grades): All patients[a- GEOMETRY] MONO-1

	N=373	
	All grades	**Grade 3/4**
Any event, n (%)	367 (98.4)	256 (68.6)
Most common events, n (%)		
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	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)

[a]All patients with MET-dysregulated advanced NSCLC in the trial (includes *MET*ex14 and MET amplification)
AEs, adverse events; *MET*ex14, *MET* exon 14 skipping mutation; NSCLC, non-small cell lung cancer

MET Inhibitor Safety Overview

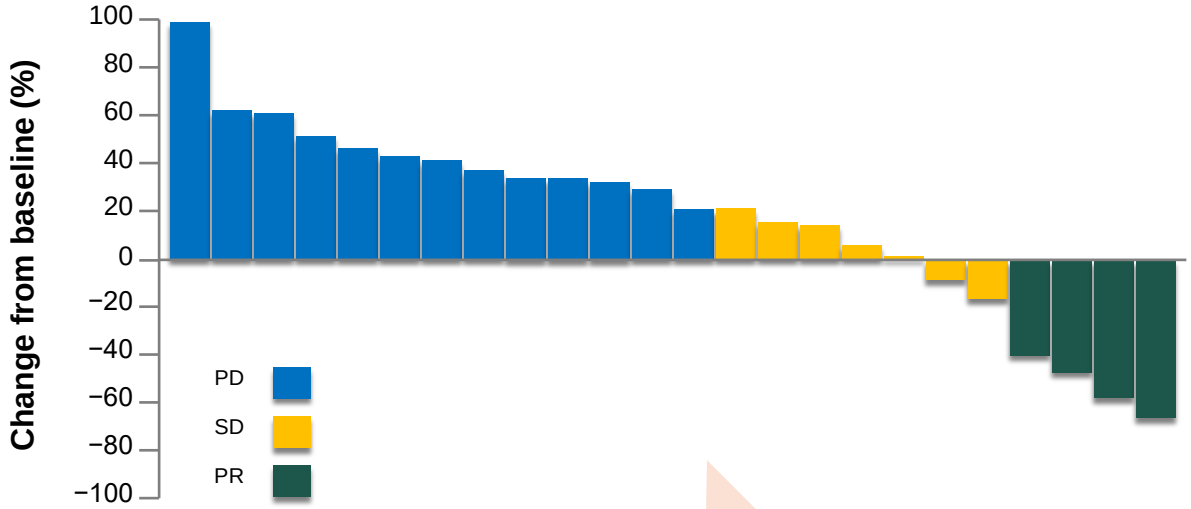
TRAEs With Capmatinib,* n (%)	All Patients (N = 334)	
	Any Grade	Grade 3/4
Any	282 (84.4)	119 (35.6)
Peripheral edema	139 (41.6)	25 (7.5)
Nausea†	111 (33.2)	6 (1.8)
Creatinine increased‡	65 (19.5)	0
Vomiting†	63 (18.9)	6 (1.8)
Fatigue	46 (13.8)	10 (3.0)
Appetite decreased†	42 (12.6)	3 (0.9)
Diarrhea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

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

*MET*ex14 mutation: 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)

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]

Annals of Oncology 30: 1321–1328, 2019
doi:10.1093/annonc/mdz167
Published online 24 May 2019

ORIGINAL ARTICLE

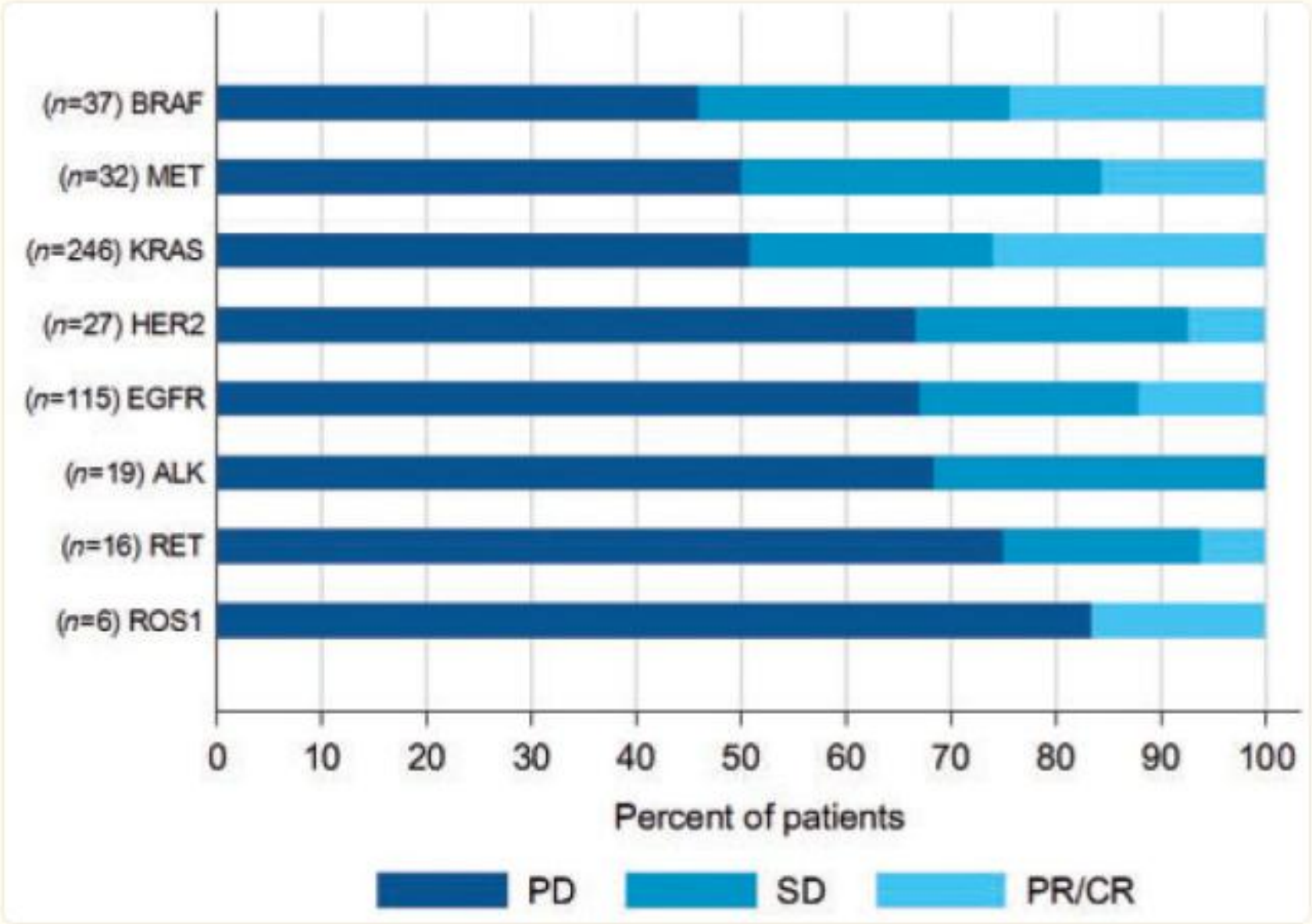
Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry

J. Mazieres[1*], A. Drilon[2], A. Lusque[3], L. Mhanna[1], A. B. Cortot[4], L. Mezquita[5], A. A. Thai[6], C. Mascaux[7], S. Couraud[8], R. Veillon[9], M. V S. Popat[16], J. Diebold[17], J. Sa A. Curioni-Fontecedro[22], R. F. Barlesi[7], R. D. Schouten[10], J. Milia[1] & O. Gautschi[27]

Background: Anti-PD1/PD-L1 directed immune checkpoint inhibitors (ICI) are widely used to treat patients with advanced non-small-cell lung cancer (NSCLC). The activity of ICI across NSCLC harboring oncogenic alterations is poorly characterized. The aim of our study was to address the efficacy of ICI in the context of oncogenic addiction.

Patients and methods: We conducted a retrospective study for patients receiving ICI monotherapy for advanced NSCLC with at least one oncogenic driver alteration. Anonymized data were evaluated for clinicopathologic characteristics and outcomes for ICI therapy: best response (RECIST 1.1), progression-free survival (PFS), and overall survival (OS) from ICI initiation. The primary end point was PFS under ICI. Secondary end points were best response (RECIST 1.1) and OS from ICI initiation.

Results: We studied 551 patients treated in 24 centers from 10 countries. The molecular alterations involved *KRAS* ($n = 271$), *EGFR* ($n = 125$), *BRAF* ($n = 43$), *MET* ($n = 36$), *HER2* ($n = 29$), *ALK* ($n = 23$), *RET* ($n = 16$), *ROS1* ($n = 7$), and multiple drivers ($n = 1$). Median age was 60 years, gender ratio was 1 : 1, never/former/current smokers were 28%/51%/21%, respectively, and the majority of tumors were adenocarcinoma. The objective response rate by driver alteration was: *KRAS* = 26%, *BRAF* = 24%, *ROS1* = 17%, *MET* = 16%, *EGFR* = 12%, *HER2* = 7%, *RET* = 6%, and *ALK* = 0%. In the entire cohort, median PFS was 2.8 months, OS 13.3 months, and the best response rate 19%. In a subgroup analysis, median PFS (in months) was 2.1 for *EGFR*, 3.2 for *KRAS*, 2.5


(n=37) BRAF
(n=32) MET
(n=246) KRAS
(n=27) HER2
(n=115) EGFR
(n=19) ALK
(n=16) RET
(n=6) ROS1
0
10
20
30
40
50
60
70
80
90
100
Percent of patients
PD
SD
PR/CR

PFS according to primary oncogenic driver from initiation of ICI

	EVT/*N*	Median PFS [95% CI] (months)	6-month PFS [95% CI]	12-month PFS [95% CI]
KRAS	208/271	3.2 [2.7; 4.5]	37.9 [32.1; 49.8]	25.6 [20.2; 31.3]
EGFR	117/125	2.1 [1.8; 2.7]	18.4 [12.1; 25.6]	6.4 [2.7; 12.1]
BRAF	34/43	3.1 [1.8; 4.6]	32.1 [18.3; 46.6]	18.0 [7.2; 32.7]
HER2	23/29	2.5 [1.8; 3.5]	22.7 [8.9; 40.2]	13.6 [3.6; 30.1]
MET	26/36	3.4 [1.7; 6.2]	36.5 [20.7; 52.4]	23.4 [10.6; 39.0]
ALK	21/23	2.5 [1.5; 3.7]	11.8 [2.2; 30.2]	5.9 [0.4; 23.0]
ROS1	–	–	–	–
RET	15/16	2.1 [1.3; 4.7]	14.1 [2.3; 35.9]	7.0 [0.4; 27.1]

EVT, event; *N*, number.

TKIs under development in NSCLC with *MET* mutations

Agent	Target(s)	Company	Phase	ClinicalTrials.gov status
Small-molecule TKIs				
TPX-0022	MET/CSF1R/ SRC	Turning Point Therapeutics	Phase 1 (solid tumors, including NSCLC)	Recruiting (last updated April 14, 2020)
S49076	MET/AXL/ EGFR	Servier	Phase 1	EUDRA-CT status. Completed (last updated November 7, 2018)
Bozitinib (APL-101)	MET	Bejing Pearl Biotechnology Apollomics Inc.	Phase 1 Phase 1/2 Phase 2	Completed (last updated November 22, 2019) Recruiting (last updated March 4, 2020) Recruiting (last updated February 6, 2020)
Crizotinib	ALK/ROS/MET	Pfizer	Phase 2	Not yet recruiting (last updated September 10, 2019)
Cabozantinib (XL184)	MET/RET/ others	Exelixis	Phase 2	Recruiting (last updated April 11, 2019)
Savolitinib (AZD6094, HMPL-504, volitinib)	MET	AstraZeneca/Hutchison Medi Pharma	Phase 2	Recruiting (last updated February 17, 2020)
Tepotinib[a] (MSC2156119J)	MET	Merck KGaA	Phase 2	Recruiting (last updated May 29, 2020)
Merestinib (LY2801653)	MET/ROS1/ AXL/others	Eli Lilly	Phase 2	Active, not recruiting (last updated January 3, 2020)
Glesatinib (MGCD-265)	MET/AXL/ others	Mirati Therapeutics	Phase 2	Completed (last updated March 4, 2020)
SAR125844	MET	Sanofi	Phase 2	Completed (last updated March 23, 2016)
AMG337	MET	Amgen	Phase 2 (solid tumors, including NSCLC)	Terminated (last updated July 2, 2017)
Sitravatinib (MGCD516)	MET/VEGFR/ others	Mirati Therapeutics	Phase 3	Recruiting (last updated February 25, 2020)

[a] Approved in Japan in March 2020 for the treatment of patients with unresectable, advanced or recurrent NSCLC with *MET*ex14[1]

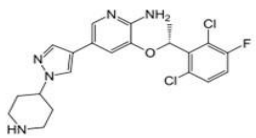
Compounds under development in NSCLC with *MET* mutations

Agent	Target(s)	Company	Phase	ClinicalTrials.gov status
Monoclonal antibodies				
Sym015	MET	Symphogen	Phase 1/2	Active, not recruiting (last updated January 18, 2020)
REGN5093	MET	Regeneron	Phase 1/2	Recruiting (last updated April 24, 2020)
Telisotuzumab vedotin (ABBV-399)	MET	AbbVie	Phase 2	Recruiting (last updated June 9, 2020)
Emibetuzumab (LY2875358)	MET	Eli Lilly	Phase 2	Completed with results (last updated September 18, 2019)

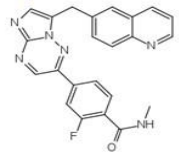
MET - targeted therapies

Tyrosine kinase Inhibitors

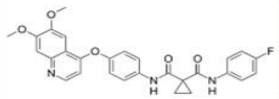
Crizotinib ●



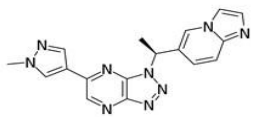
Capmatinib ●



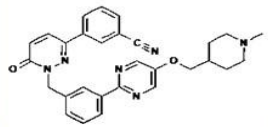
Cabozantinib ●



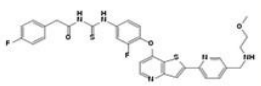
Savolitinib ●



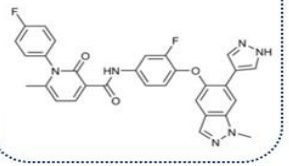
Tepotinib ●



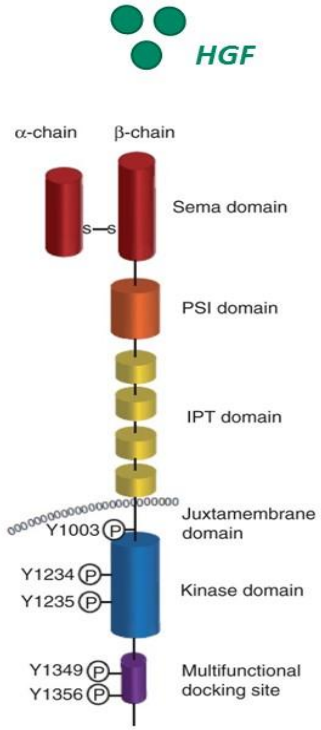
Glesatinib ●



Merestinib ●

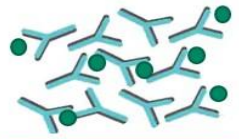


● *Multikinase*
● *Selective*



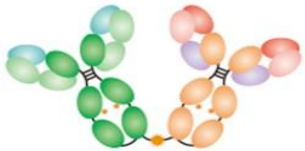
Monoclonal Antibodies

Specific HCF



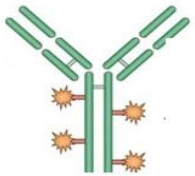
Specific-MET

Bispecific Antibody



MET-MET
MET-EGFR
MET-others

Antibody-drug conjugate



MET Lung

Conclusion

- One of the inevitable problems of targeted therapy with MET TKI is drug resistance
- Due to the presence of gene amplification, second site mutation, bypass activation, and pathological type transformation
- If type I MET inhibitors (crizotinib, capmatinib, tepotinib, savolitinib) drug resistance is developed, type II MET inhibitors (cabozantinib, glesatinib, merestinib) can be considered.