Selection of 1st line therapy for *MET* amplification and *MET* exon 14 mutation in NSCLC

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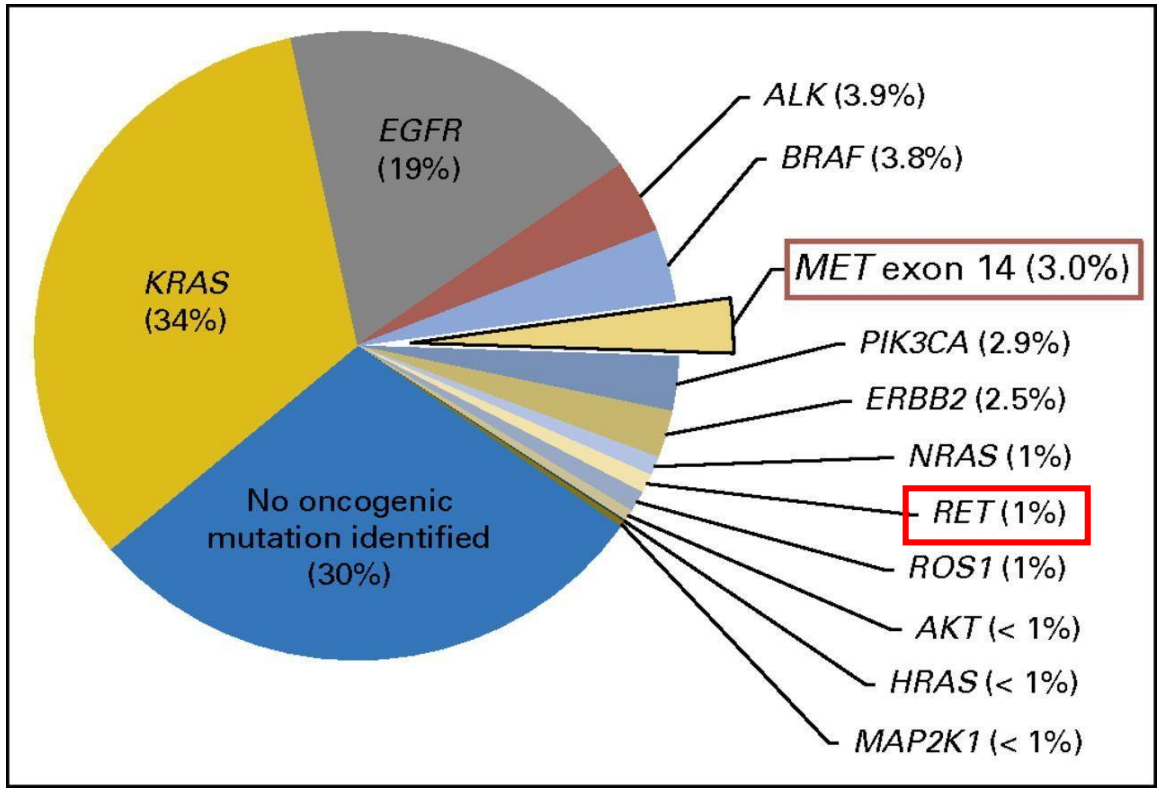


MET in NSCLC may be a:

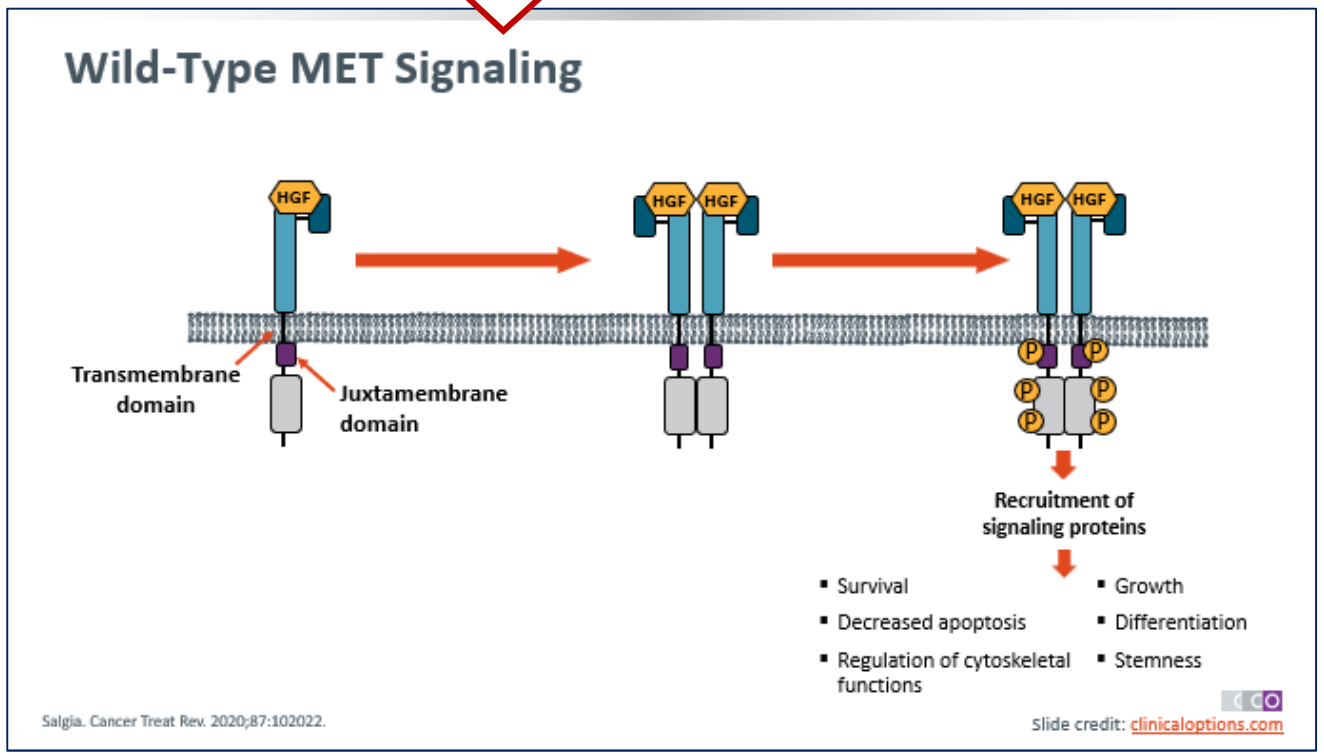
Primary oncogenic driver: exon 14 skipping mutations, high-level amplification, *MET* fusions

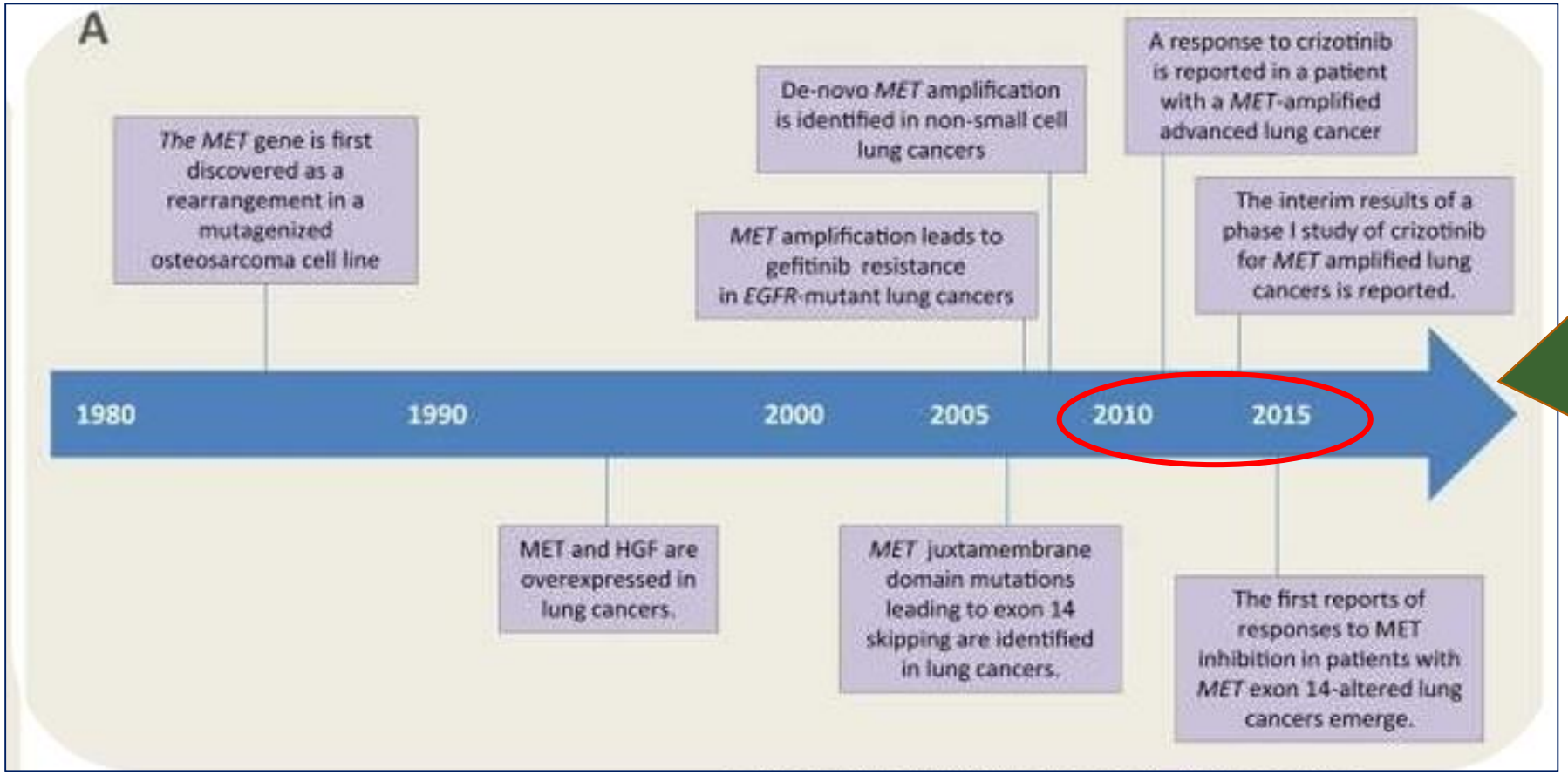
Secondary co-driver of acquired resistance in patients with NSCLC and *EGFR* mutations or other oncogenic alterations

Mesenchymal–epithelial transition (*MET*) proto-oncogene long arm of human chromosome 7

Encodes the tyrosine kinase receptor for hepatocyte growth factor (HGF)

MET signaling regulates important cell functions dysregulation may contribute to oncogenesis





- **History of MET spans > 3 decades**
  - MET proto-oncogene and its ligand HGF first discovered in the mid-1980s
  - MET found to be dysregulated in lung cancers in the mid-1990s

Drilon et al. J Thorac Oncol . 2017

The first activating mutations identified within the MET gene were discovered by genome-wide analysis of families with hereditary papillary renal cell carcinoma

Over the past two decades, alterations within and outside the MET kinase domain have been described in several solid tumours, including NSCLC, glioblastoma, breast, renal and colon cancers, as well as cancers of unknown primary origin

Suggests that activated MET plays a significant role in the tumourigenic process in a wide range of cell types

Prevalence of *MET* Alterations

	METex14 mut	*MET* Amp
Molecular	~3% NSCLC 15% co-occurring *MET* amp	<10% NSCLC ~10% resistance mechanism in *EGFR* ~15% resistance 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 y Smokers, also in never-smokers Female Poor survival	Median age ~60 y Smokers Male Poor survival

METex14 mut

Occur in NSCLC mostly independently of other oncogenes

Mutually exclusive with these molecular drivers

1% of patients with squamous cell carcinoma lung

MET Amp

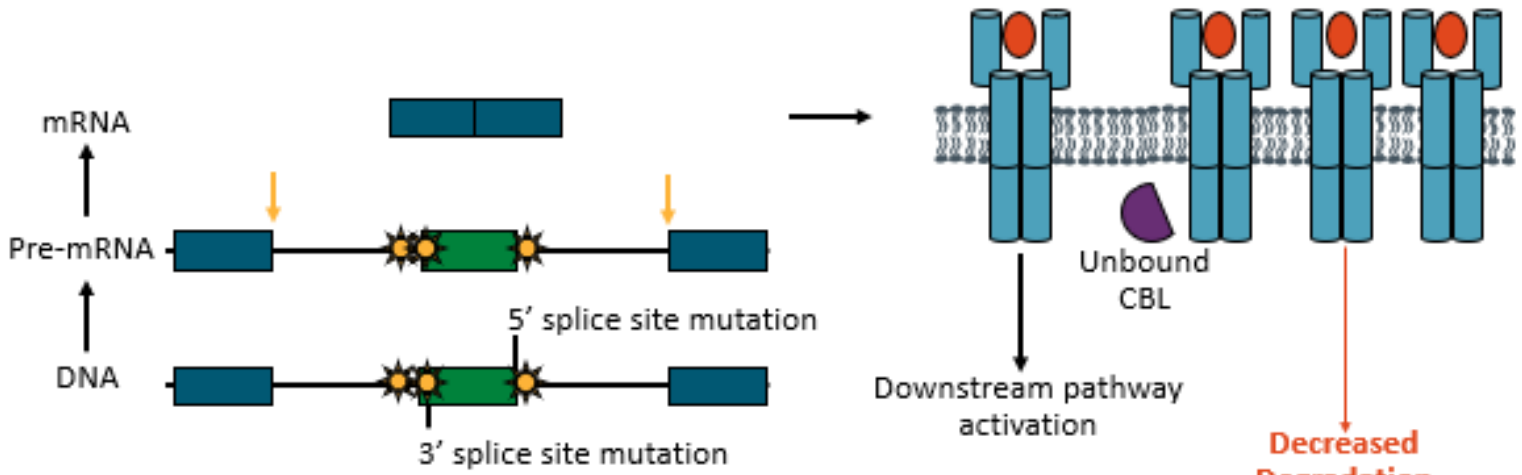
often co-occur with other pathogenic mutations (NRAS, KRAS and TP53)

Squamous cell ca:

Former or current smokers- over 50% of patients

*MET*ex14 Splice Site Alterations: Alternative Splicing Can Be Oncogenic

***MET* Mutations Cause Aberrant Splicing and Exon 14 Skipping**



MET shorter exon 14– spliced protein: increased stability increases MET signaling

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

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

Slide credit: clinicaloptions.com

High frequency in non- squamous subtype of pulmonary sarcomatoid carcinoma: 5–32%

Heterogeneous group of indels and missense mutations: post-translational modifications detectable at the RNA level

older patients (median age of 72 years)

Higher percentage of eversmokers compared to patients with tumours harbouring other oncogenic alterations

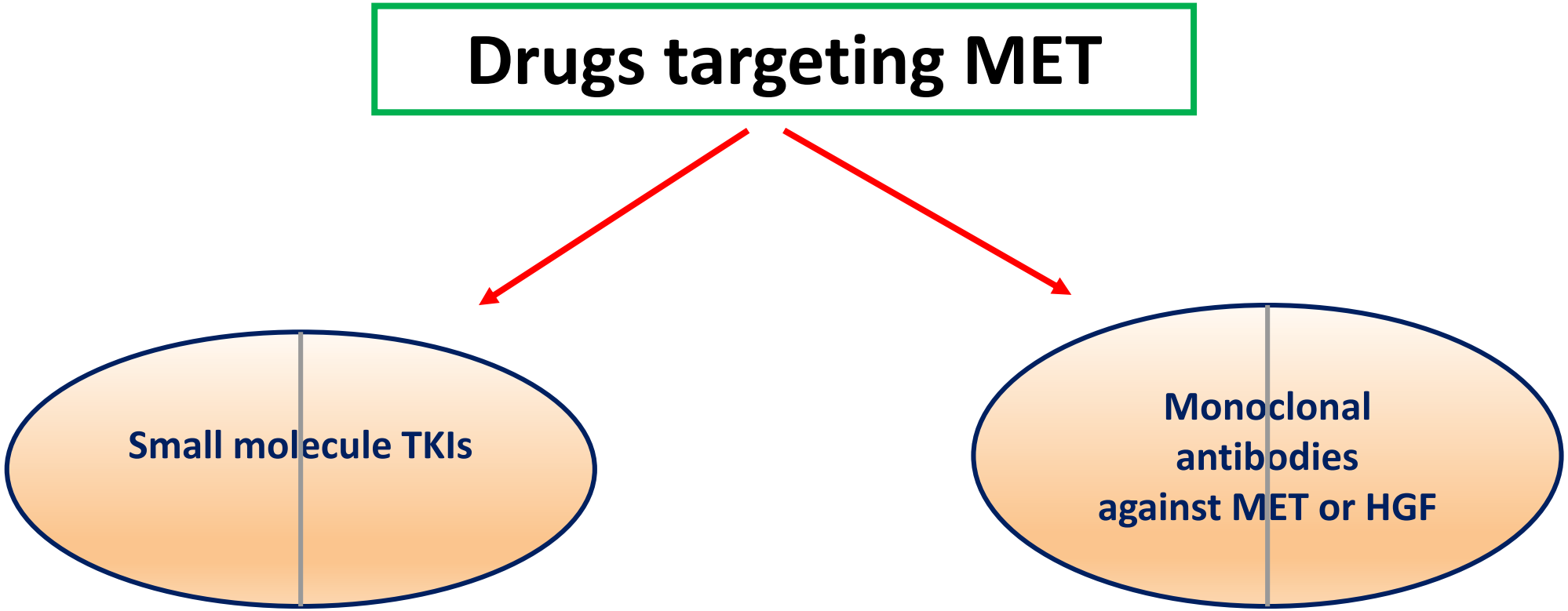
aggressive disease, resistance to anticancer therapies, and poor prognosis when not treated with MET inhibitors

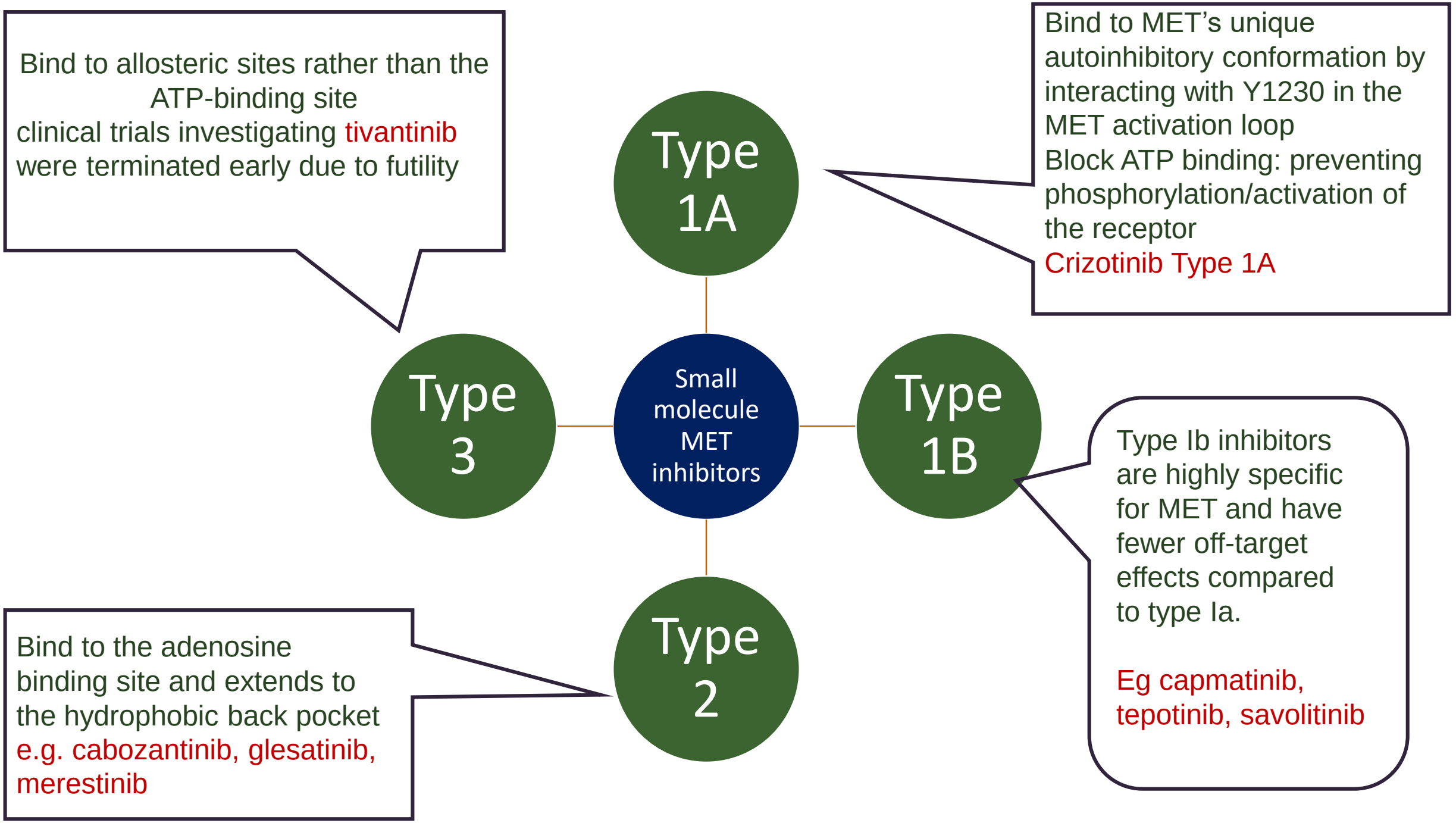
Testing Strategies

- Dysregulated MET expression and activity can be detected at the DNA, RNA, and protein levels

- IHC detects protein overexpression: poor correlation between IHC and METex14 skipping mutations and MET amplification, Guidelines do not support the use of MET IHC as a surrogate marker or screening for genomic MET alterations
- Fluorescence in situ hybridization (FISH) identify gene amplification- can be utilized in select scenarios
- Reverse transcription polymerase chain reaction (RT-PCR) detect gene mutations
- Next-generation sequencing (NGS) detect both amplifications and mutations, depending on the sample used (i.e., DNA and/or RNA)
  - More *MET*-ex14 mutations identified by RNA NGS than DNA NGS, DNA NGS: 16/644 (2.5%), RNA NGS: 25/644 (3.9%)* * Jurkiewicz. ASCO 2020. Abstr 9036.
  - Due to a high risk of poor sensitivity, caution is needed when amplicon-based DNA panels are used to capture some genomic METex14 skipping mutations without combined RNA sequencing.

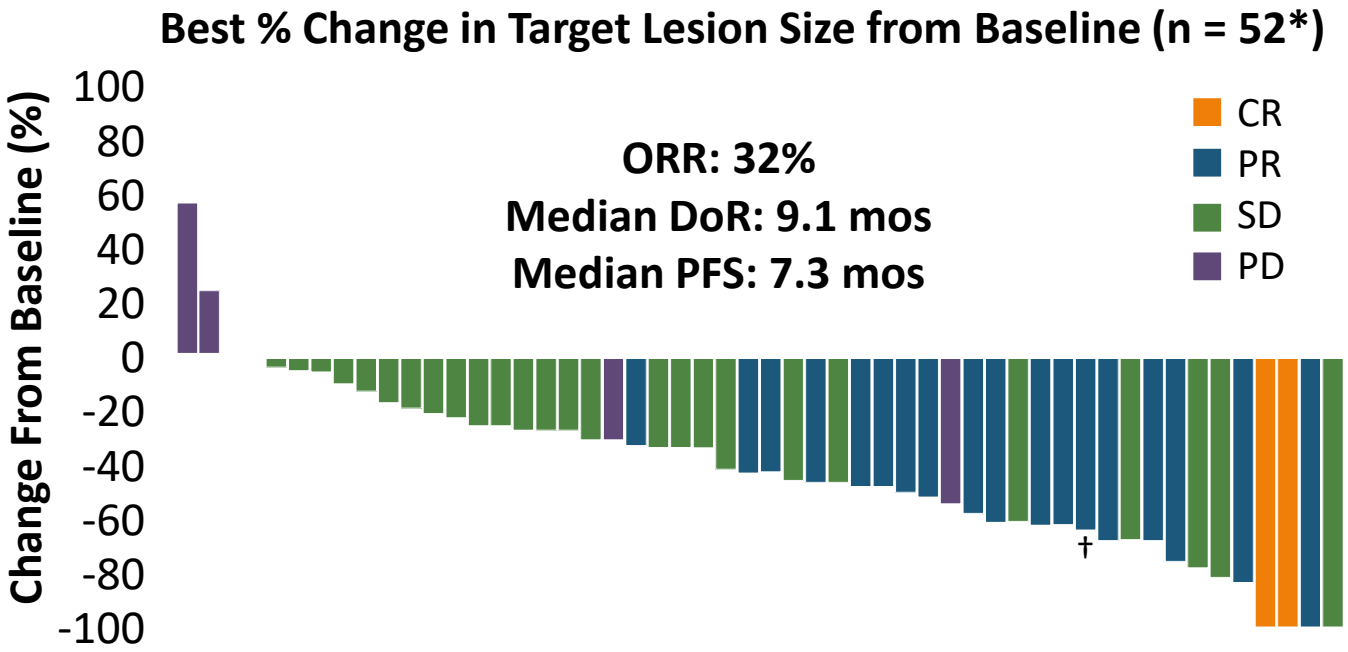
- Guidelines recommend broad based multi-target testing, rather than single gene testing


Drugs targeting MET
Small molecule TKIs
Monoclonal antibodies against MET or HGF


Bind to allosteric sites rather than the ATP-binding site
clinical trials investigating tivantinib were terminated early due to futility
Type 1A
Bind to MET's unique autoinhibitory conformation by interacting with Y1230 in the MET activation loop
Block ATP binding: preventing phosphorylation/activation of the receptor
Crizotinib Type 1A
Type 3
Small molecule MET inhibitors
Type 1B
Type Ib inhibitors are highly specific for MET and have fewer off-target effects compared to type Ia.
Eg capmatinib, tepotinib, savolitinib
Type 2
Bind to the adenosine binding site and extends to the hydrophobic back pocket
e.g. cabozantinib, glesatinib, merestinib

PROFILE 1001: Crizotinib in *MET* Exon 14–Altered NSCLC

- Crizotinib: multikinase TKI approved for treatment of *ALK*+ and *ROS*+ NSCLC
- 250 mg twice daily
- Open-label, multicohort phase I study evaluating efficacy, safety of crizotinib in NSCLC, including a *MET*ex14 expansion cohort (n = 69)
- No difference in ORR by type of MET alteration, either by splice-site region or by mutation type
- Estimated mOS: 20.5 months, 12-month rates of 70%
- Intracranial efficacy: poor brain penetration



*Of 65 response-evaluable patients, 13 excluded from waterfall plot.
†*MET*ex14 alteration by local testing; *ROS1*+, WT *MET* by central testing.

Drilon. Nat Med. 2020;26:47. Paik. ASCO 2019. Abstr 9005. Wolf. ASCO 2019. Abstr 9004.

Slide credit: clinicaloptions.com

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Capmatinib in *MET* Exon 14–Mutated or *MET*-Amplified Non–Small-Cell Lung Cancer

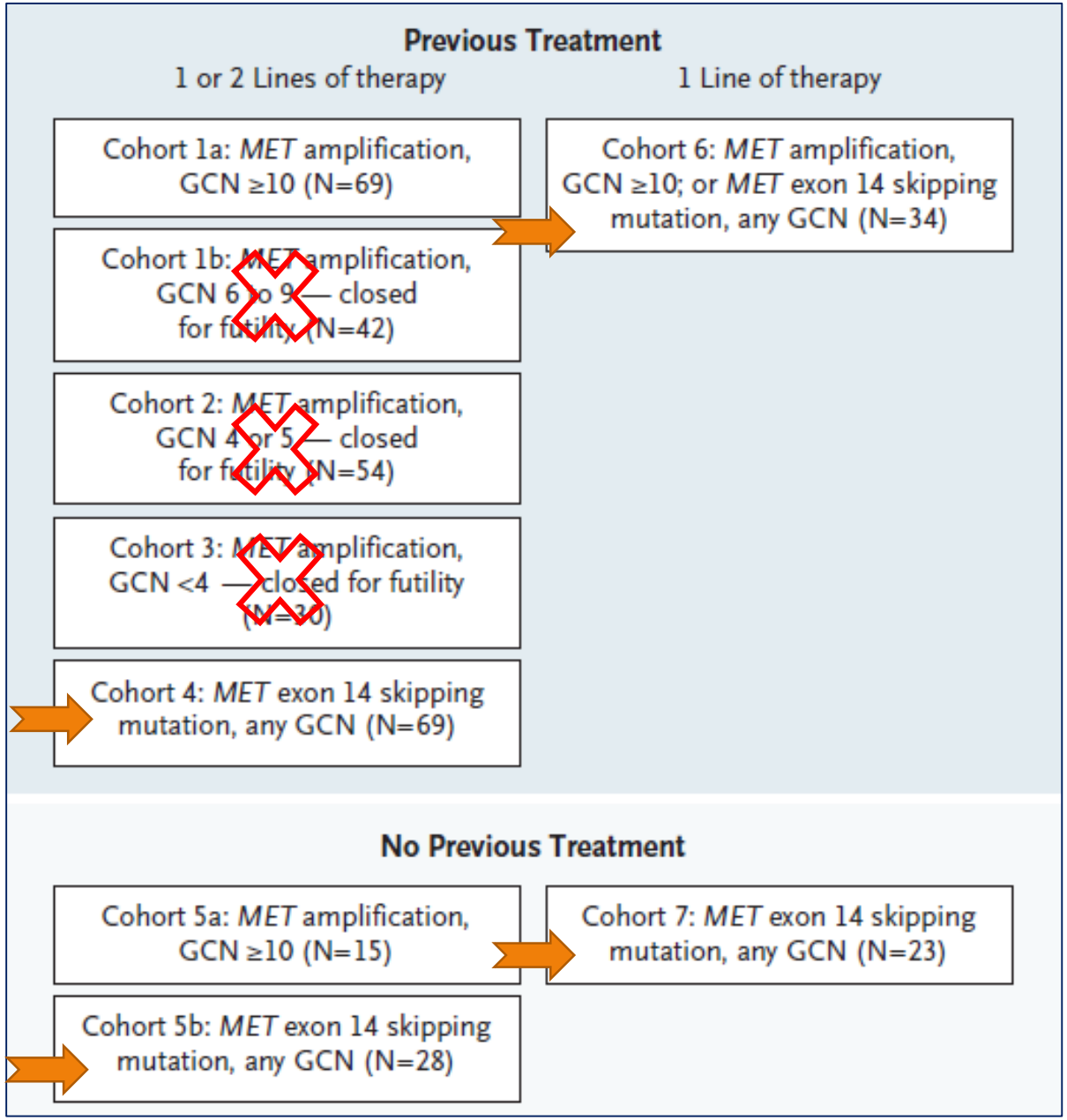
J. Wolf, T. Seto, J.-Y. Han, N. Reguart, E.B. Garon, H.J.M. Groen, D.S.W. Tan, T. Hida, M. de Jonge, S.V. Orlov, E.F. Smit, P.-J. Souquet, J. Vansteenkiste, M. Hochmair, E. Felip, M. Nishio, M. Thomas, K. Ohashi, R. Toyozawa, T.R. Overbeck, F. de Marinis, T.-M. Kim, E. Laack, A. Robeva, S. Le Mouhaer, M. Waldron-Lynch, B. Sankaran, O.A. Balbin, X. Cui, M. Giovannini, M. Akimov, and R.S. Heist, for the GEOMETRY mono-1 Investigators*

prospective, international, open label, multiple-cohort, phase 2 study

Patients with advanced stage NSCLC were assigned to cohorts on the basis of *MET* status and previous lines of therapy

Stable brain metastases allowed

400 mg twice daily fasting in cohorts 1 - 5
without fasting restrictions in cohorts 6 and 7 (now no food restrictions!!)



GEOMETRY mono-1: Best Overall Response in Pretreated Cohort 4

Response per RECIST v1.1, n (%)	2/3L Cohort 4 (n = 69)	
	BIRC	Investigator
Best overall response		
▪ CR	0	1 (1.4)
▪ PR	28 (40.6)	28 (40.6)
▪ SD	25 (36.2)	22 (31.9)
▪ Non-CR/non-PD	1 (1.4)	2 (2.9)
▪ PD	6 (8.7)	7 (10.1)
▪ Not evaluable*	9 (13.0)	9 (13.0)
ORR, % (95% CI)	40.6 (28.9-53.1)	42.0 (30.2-54.5)
DCR, % (95% CI)	78.3 (66.7-87.3)	76.8 (65.1-86.1)

*Not qualifying for confirmed CR/PR and no SD achieved after ≥ 6 wks or PD within first 12 wks.

- Response rates comparable by BIRC and investigator assessment

GEOMETRY mono-1: Best Overall Response in Treatment-Naive Cohort 5B

Response per RECIST v1.1, n (%)	1L Cohort 5B (n = 28)	
	BIRC	Investigator
Best overall response		
▪ CR	1 (3.6)	0
▪ PR	18 (64.3)	17 (60.7)
▪ SD	8 (28.6)	10 (35.7)
▪ 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)

- Response rates comparable by BIRC and investigator assessment

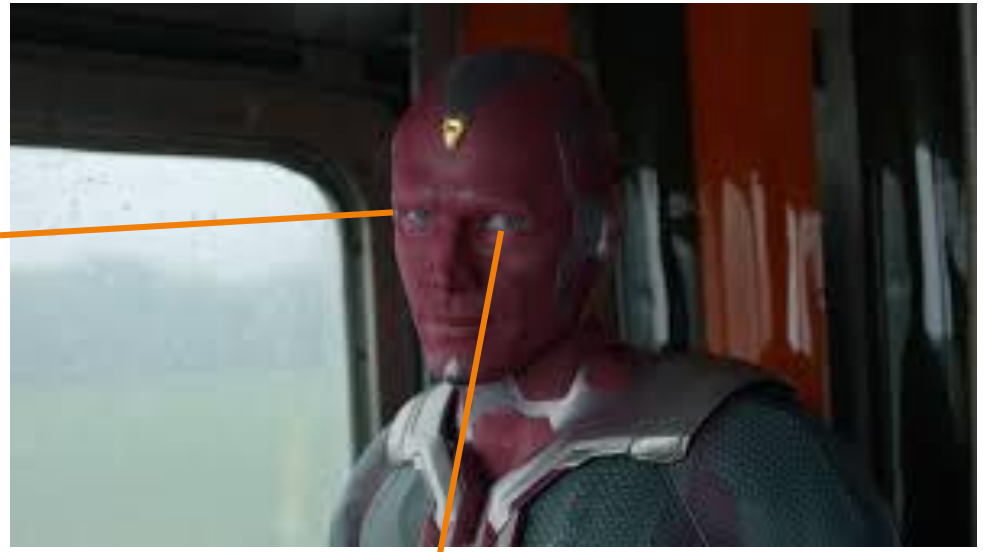
mPFS: 5.4 months among previously treated patients and 12.4 months among treatment naïve patients

Clinically meaningful median OS of 20.8 months in first-line (Cohort 5b) and of 13.6 months in relapse settings (Cohort 4)

no considerable differences in response according to the type of genetic alteration causing *MET* exon 14 skipping mutations or the co-occurrence of *MET* amplification

Intracranial responses: 54%, CR in four patients.

Tepotinib: highly selective oral MET inhibitor



Open-label, phase 2 study : VISION study
Tepotinib 500 mg OD
patients with advanced or metastatic NSCLC

3 cohorts:
Cohort A: MET exon 14 skipping mutations were enrolled
Cohort B: MET-amplified disease (but without *MET* exon 14 skipping mutations)
Cohort C: patients with *MET* exon 14 skipping mutations
for confirmatory analysis of the results in cohort A

Prospective testing of *MET* exon 14 skipping mutations:
Circulating free DNA (cfDNA) obtained from plasma (liquid biopsy)Guardant360
Or
RNA obtained from fresh or archival tumor-biopsy tissue: Oncomine Focus Assay

ASCO 2020: Update of Phase II VISION Study of Tepotinib in *MET*ex14 Mutation–Positive NSCLC

Efficacy Outcomes*	Liquid Biopsy (L+) (n = 66)		Tissue Biopsy (T+) (n = 60)	
	IRC	Investigator	IRC	Investigator
ORR, % (95% CI)	44 (32-57)	56 (43-68)	47 (34-60)	62 (48-74)
Median DoR, mos (95% CI)	11.1 (8.3-NE)	16.4 (7.3-21.5)	12.4 (9.7-NE)	16.4 (7.0-21.5)
DCR, % (95% CI)	64 (51-75)	70 (57-80)	70 (57-81)	78 (66-88)
Median PFS, mos (95% CI)	8.5 (5.1-11.0)	8.5 (5.6-11.2)	11.0 (7.8-17.1)	12.2 (6.3-17.7)
Median OS*, mos (95% CI)	19.1 (9.5-NE)		19.7 (12.8-NE)	

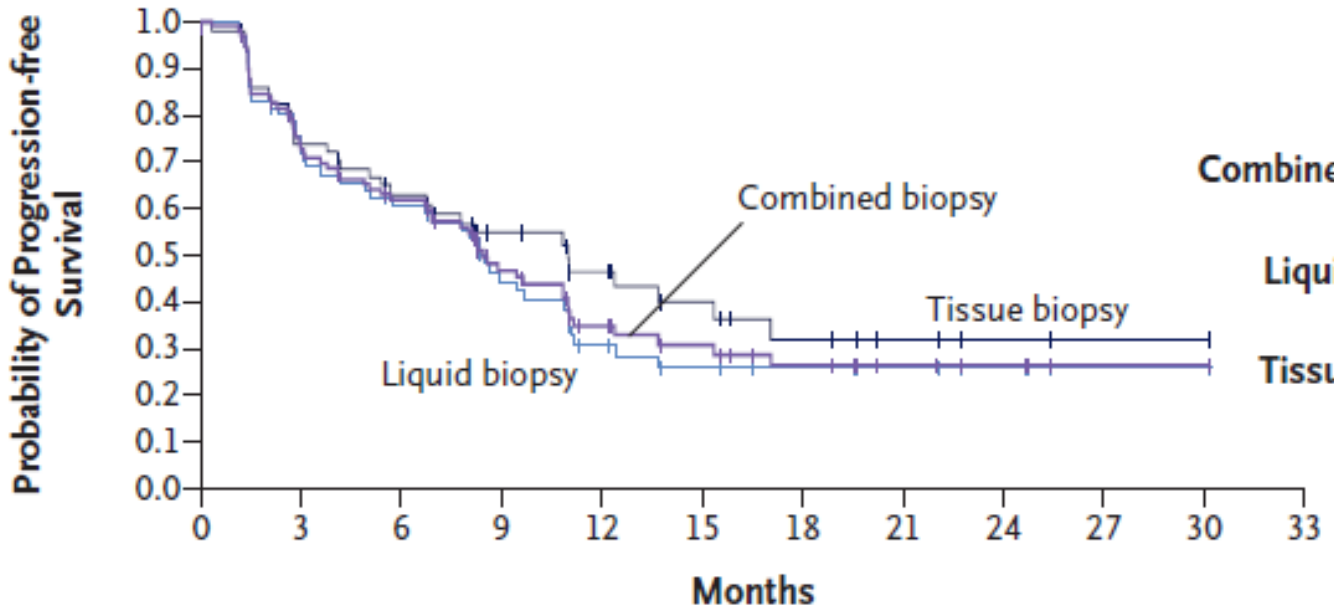
*Immature.

- Comparable outcomes in patients with brain mets (n = 11)
  - ORR by IRC: 55% (95% CI: 23-83)
  - Median PFS: 10.9 mos (95% CI: 8.0-NE)

- Grade ≥ 3 AEs in 37/151 (25%)
  - 13 patients (9%) d/c due to TRAEs
- Analysis of PROs showed clinical improvement in coughing, while maintaining HRQoL

Le. ASCO 2020. Abstract 9556. Paik. ASCO 2020. Abstract 9575.

Slide credit: clinicaloptions.com



	No. of Events	Median Duration (95% CI)
		mo
Combined Biopsy (N=99)	60	8.5 (6.7–11.0)
Liquid Biopsy (N=66)	43	8.5 (5.1–11.0)
Tissue Biopsy (N=60)	32	11.0 (5.7–17.1)

No. at Risk

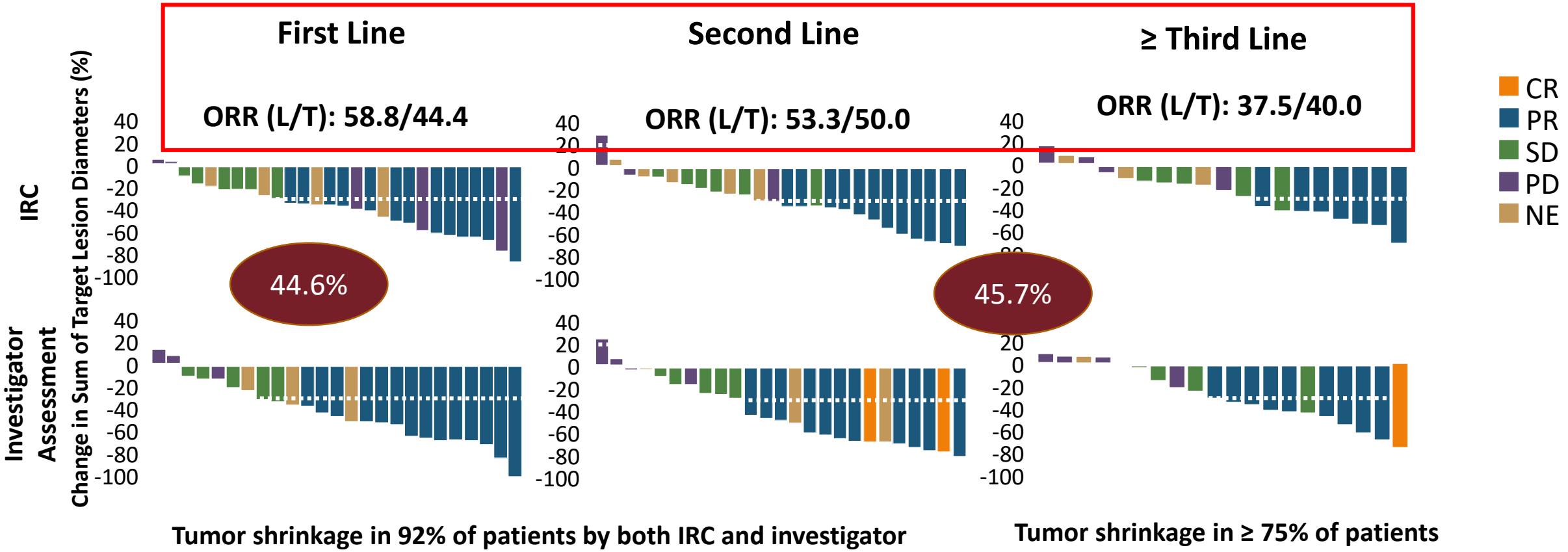
Combined biopsy	99	67	53	33	20	15	10	6	4	1	1	0
Liquid biopsy	66	44	36	23	14	10	8	6	4	1	1	0
Tissue biopsy	60	42	32	22	16	11	7	4	2	1	1	0

Figure 2. Progression-free Survival, According to Biopsy Group.

Outcomes were similar in the two biopsy categories

No association was noted between the location or type of the *MET* exon 14 alteration and outcome

VISION: Tumor Response



response rates were similar regardless of baseline characteristics and the number of lines of previous therapies

Paik. ASCO 2019. Abstr 9005.

Once-daily savolitinib in Chinese patients with pulmonary sarcomatoid carcinomas and other non-small-cell lung cancers harbouring *MET* exon 14 skipping alterations: a multicentre, single-arm, open-label, phase 2 study

.ancet Respir Med 2021

Shun Lu, Jian Fang, Xingya Li, Lejie Cao, Jianying Zhou, Qisen Guo, Zongan Liang, Ying Cheng, Liyan Jiang, Nong Yang, Zhigang Han, Jianhua Shi, Yuan Chen, Hua Xu, Helong Zhang, Gongyan Chen, Rui Ma, Sanyuan Sun, Yun Fan, Jing Li, Xian Luo, Linfang Wang, Yongxin Ren, Weiguo Su

Multicentre, single-arm, open-label, phase 2 study
70 patients

Savolitinib: **600 mg (bodyweight ≥50 kg) or 400 mg (bodyweight <50 kg) once a day**
Cohort 1: MET inhibitor-naïve
Cohort 2: MET inhibitor-treated
Cohort 3: An exploratory study cohort was added after the completion of cohort 1 enrolment to investigate the efficacy, safety, and pharmacokinetic characteristics of savolitinib when administered through different methods

21% patients had brain metastases

	IRC-assessed (n=70)	Investigator-assessed (n=70)
Best overall response		
Confirmed complete	0	0
Confirmed partial	30 (42·9%, 31·1–55·3)	33 (47·1%, 35·1–59·5)
Objective response rate	30 (42·9%, 31·1–55·3)	33 (47·1%, 35·1–59·5)
Disease control rate	58 (82·9%, 72·0–90·8)	57 (81·4%, 70·3–89·7)
Median time to response, months	1·4 (1·4–1·5)	1·4 (1·4–1·5)
Median duration of response, months	8·3 (5·3–16·6)	6·9 (4·9–12·5)
Median progression-free survival, months	6·8 (4·2–9·6)	6·9 (4·6–8·3)
6-month progression-free survival (95% CI)	52·0% (38·6–63·8)	54·6% (41·3–66·1)
12-month progression-free survival (95% CI)‡	31·9% (20·3–44·2)	30·7% (19·6–42·6)

15 patients with brain metastases showed stable or decreased brain lesions after savolitinib treatment

Three patients who had brain metastases selected as target lesions by investigators had intracranial partial responses.

	All-cause adverse events		Treatment-related adverse events	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any event	70 (100%)	45 (64%)	70 (100%)	32 (46%)
Event occurring in ≥25% of patients				
Peripheral oedema	39 (56%)	6 (9%)	38 (54%)	6 (9%)
Nausea	37 (53%)	0	32 (46%)	0
Hypoalbuminaemia	29 (41%)	1 (1%)	16 (23%)	0
Increased aspartate aminotransferase	27 (39%)	9 (13%)	26 (37%)	9 (13%)
Increased alanine aminotransferase	27 (39%)	7 (10%)	27 (39%)	7 (10%)
Vomiting	23 (33%)	0	18 (26%)	0
Decreased appetite	22 (31%)	0	14 (20%)	0
Pyrexia	20 (29%)	1 (1%)	10 (14%)	1 (1%)
Hypokalaemia	18 (26%)	5 (7%)	7 (10%)	2 (3%)
Anaemia	18 (26%)	1 (1%)	10 (14%)	1 (1%)
Cough	18 (26%)	0	0	0

Data are n (%).

14% treatment related discontinuation

Table 3: Adverse events in the full an

SAFETY

Tepotinib (Phase 2 VISION)[1]	Patients (N = 255)
	All Grades, ≥20%
Peripheral oedema	54.1
Nausea	20.0

Grade 3-4 AEs, 24.3%
Discontinuation, 10.6%

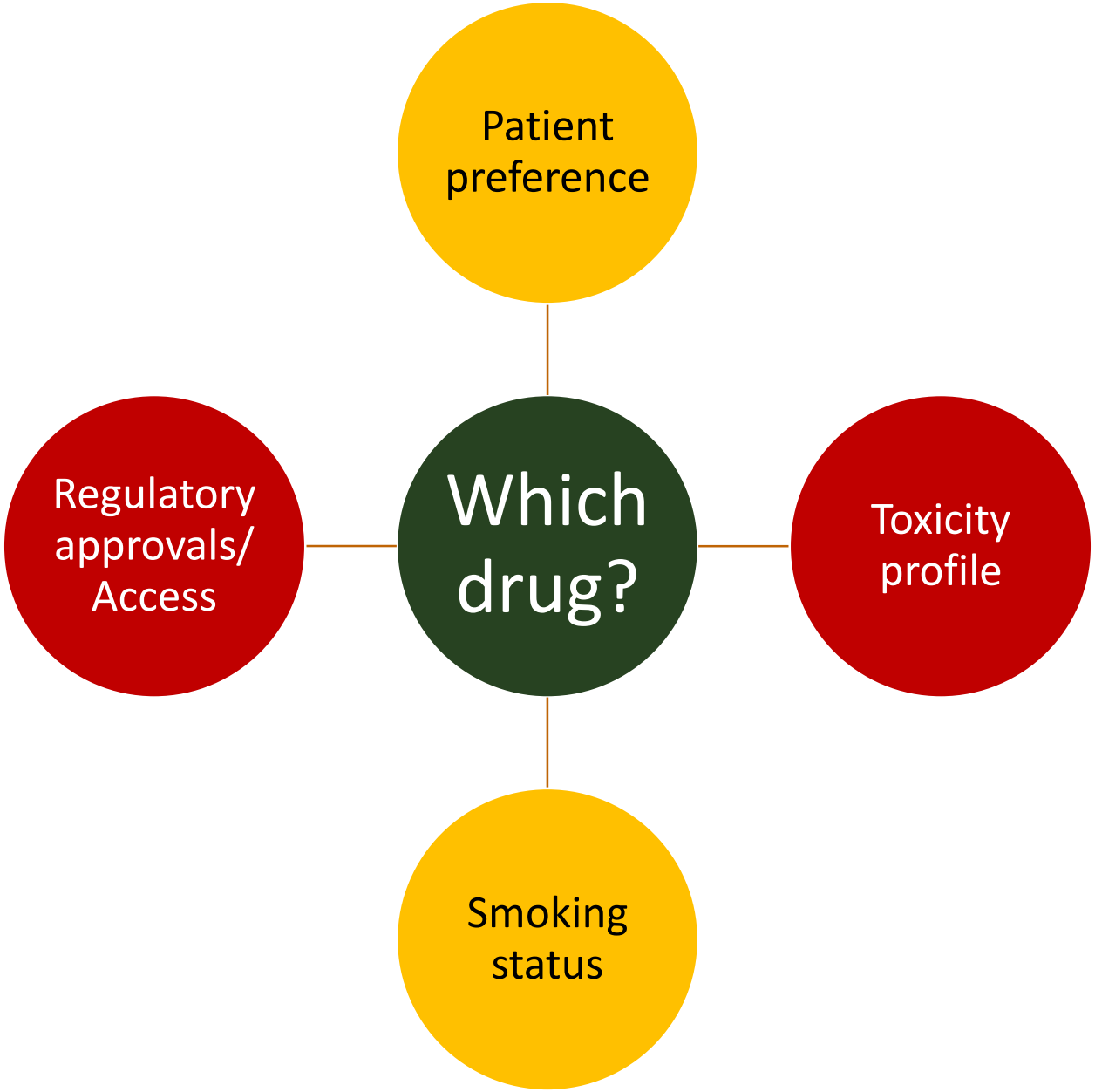
Grade 3 peripheral edema approx. 8%

Capmatinib (Phase 2 GEOMETRY mono-1)[2]	Patients (N = 373)
	All Grades, ≥20%
Peripheral oedema	54.2
Nausea	45.0
Vomiting	28.2
Increased blood creatinine	26.5
Dyspnoea	23.3
Fatigue	22.3
Decreased appetite	21.2

Grade 3-4 AEs, 68.6%
Discontinuation, 16.1%

Pseudo Acute Kidney Injury/ rise in serum creatinine: inhibition of renal transporters—multidrug and toxic extrusion protein 1 and 2-K (MATE1 and MATE2-K)

Monitor for ILD and pneumonitis during treatment; monitor LFTs; counsel patients to limit direct UV exposure due to potential photosensitivity and to use effective contraception due to potential risk to fetus


Patient preference
Regulatory approvals/ Access
Which drug?
Toxicity profile
Smoking status

Cross Trial comparison of the small molecule MET inhibitors

Tepotinib
VISION Confirmatory Analysis[1]

	First-Line	Second-Line and Beyond
Median DOR,	NR	12.6
Median PFS, mo	15.9	12.1
Median OS, mo	21.1	18.8

First-Line vs Second-Line+ ORR, 60% vs 47%

Capmatinib
Confirmatory Analysis[2]

	Previously Treated	Treatment-Naïve
Median DOR, mo	17.2	NR
Median PFS, mo	9.1	10.6

Treatment-Naïve vs Previously Treated ORR, 68% vs 50%

Savolitinib
Phase 2 Open-Label Single-Arm Trial[1]

	Previously Treated (n = 42)	Treatment-Naïve (n = 28)
Median PFS, mo	6.9	6.9
Median OS, mo	19.4	10.9

ORR (N = 61), 49.2%

Reference(s): 1. Thomas M et al. IASLC 2022 WCLC World Conference on Lung Cancer (WCLC 2022). Abstract OA03.05.
2. Illini O et al. *Ther Adv Med Oncol*. 2022;14:17588359221103206.

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 and pretreated (n = 31)	Tumor	51.6	--	--

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. AACR 2019. Abstr CT031. 8. NCT02897479.

Slide credit: clinicaloptions.com

Crizotinib: lower ORR

ORR: 45-68% in 1st line (capmatinib highest)

ORR: 40-45% in 2nd or later lines of therapy

MET TKI Potency Comparison[2,3]

	Crizotinib	Cabozantinib	Savolitinib	Tepotinib	Capmatinib
IC_{50}, nM	22.5	7.8	2.1	~ 1.7-3.0	0.6

Emerging Targeted therapy for NSCLC with MET exon 14 skipping mutations

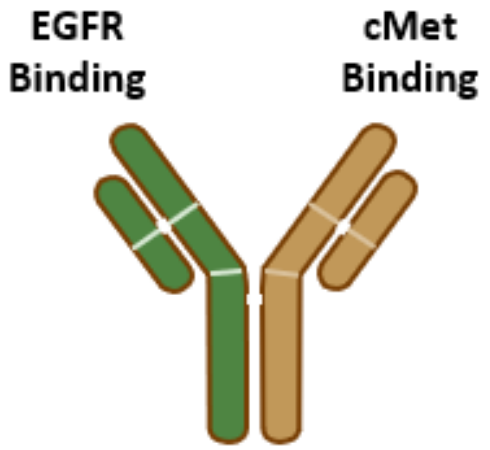
Amivantamab (JNJ-372): EGFR-MET Bispecific Antibody

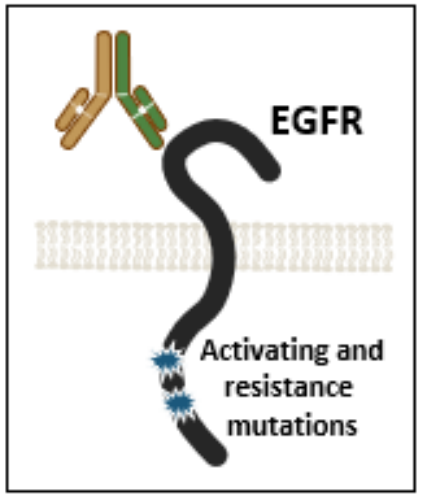
- Fully humanized, bispecific IgG1 Ab targeting *EGFR* mutations and *MET* mutations/amplifications via unique MoA[1,2]
  - 3 MoAs: **receptor degradation, immune cell–directing activity,** inhibition of ligand binding

CHRYSALIS: Open-label phase I multicohort dose escalation (140-1750 mg) and dose expansion study

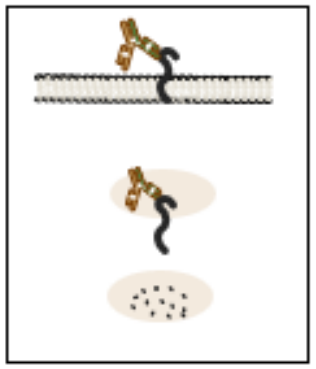
Patients with metastatic/unresectable NSCLC with primary *MET*ex14 mutation by NGS of tumor or ctDNA who progressed after or declined standard of care treatment (n = 19)

42% patients had received prior MET inhibitors, 21% were treatment naïve

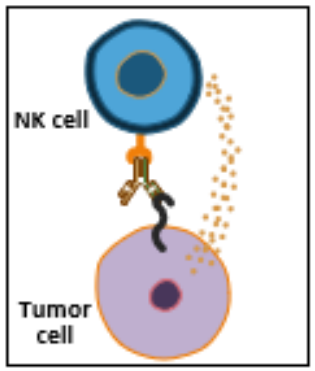




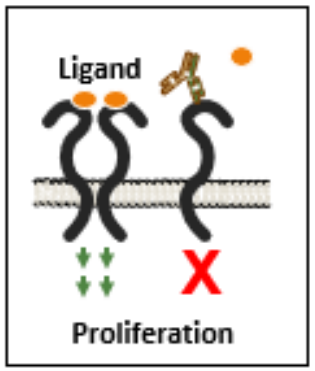
EGFR/MET Receptor Degradation



Immune Cell–Directing Activity



Inhibition of Ligand Binding



1. Moores. Cancer Res. 2016;76:3942. 2. Vijayaraghavan. Mol Cancer Ther. 2020;19:2044.
3. Yun. Cancer Discov. 2020;10:1194. 4. Cho. ESMO 2018. Abstr. 1497P. 5. Haura. ASCO 2019. Abstr 9009.

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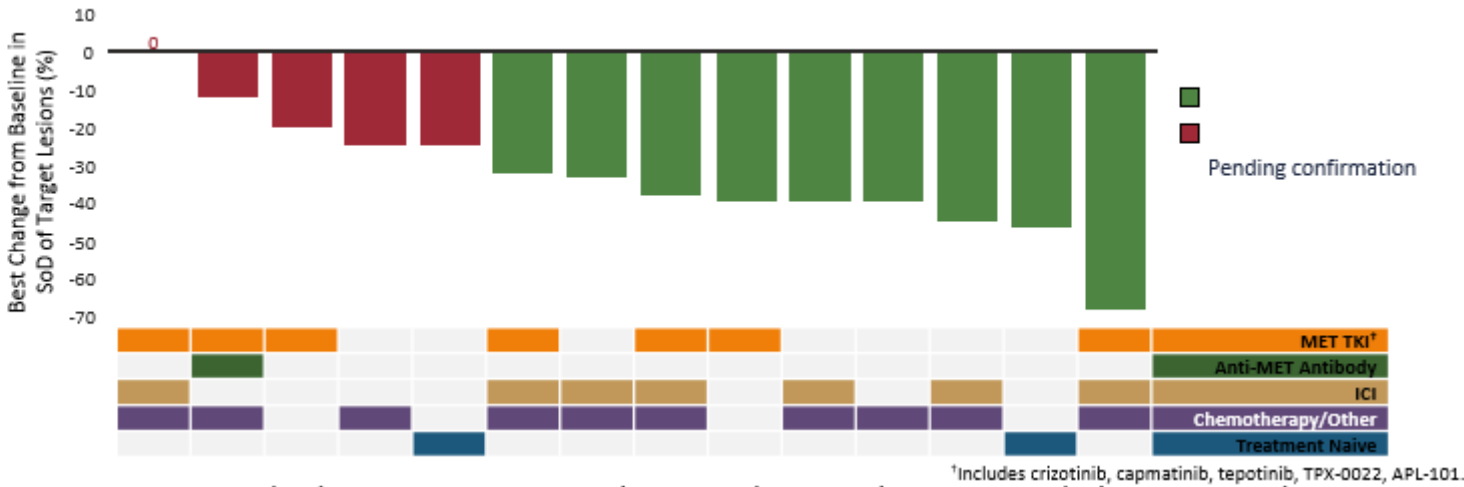
Amivantamab
Phase 1 Dose Expansion CHRYSALIS

	Entire Cohort (N = 46)	Prior MET Inhibitor (n = 24)	No Prior MET Inhibitor (n = 15)	Treatment-Naïve (n = 7)
ORR, %	33	17	47	57
Median PFS, mo	6.7	4.2	8.3	NE

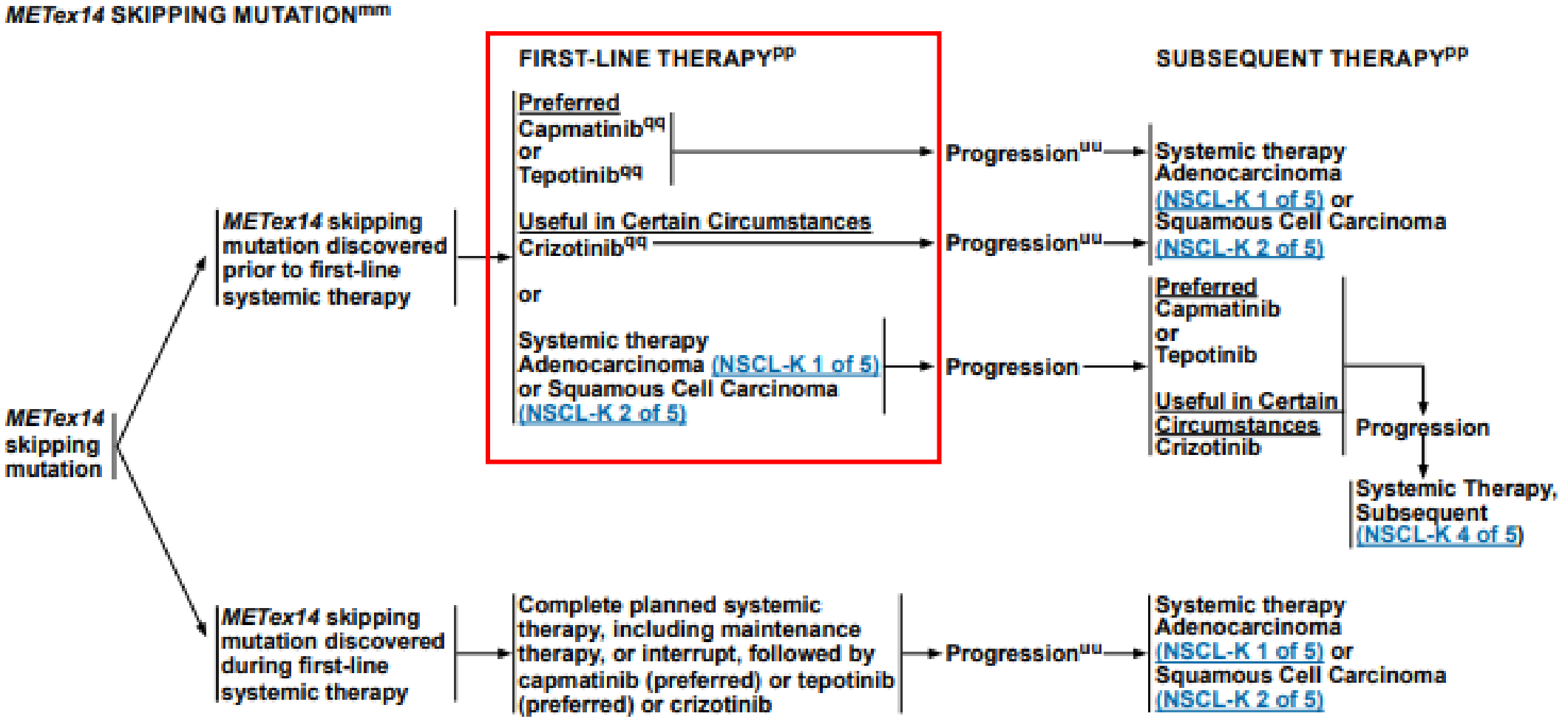
CHRYSALIS METex14 Cohort: Antitumor Activity

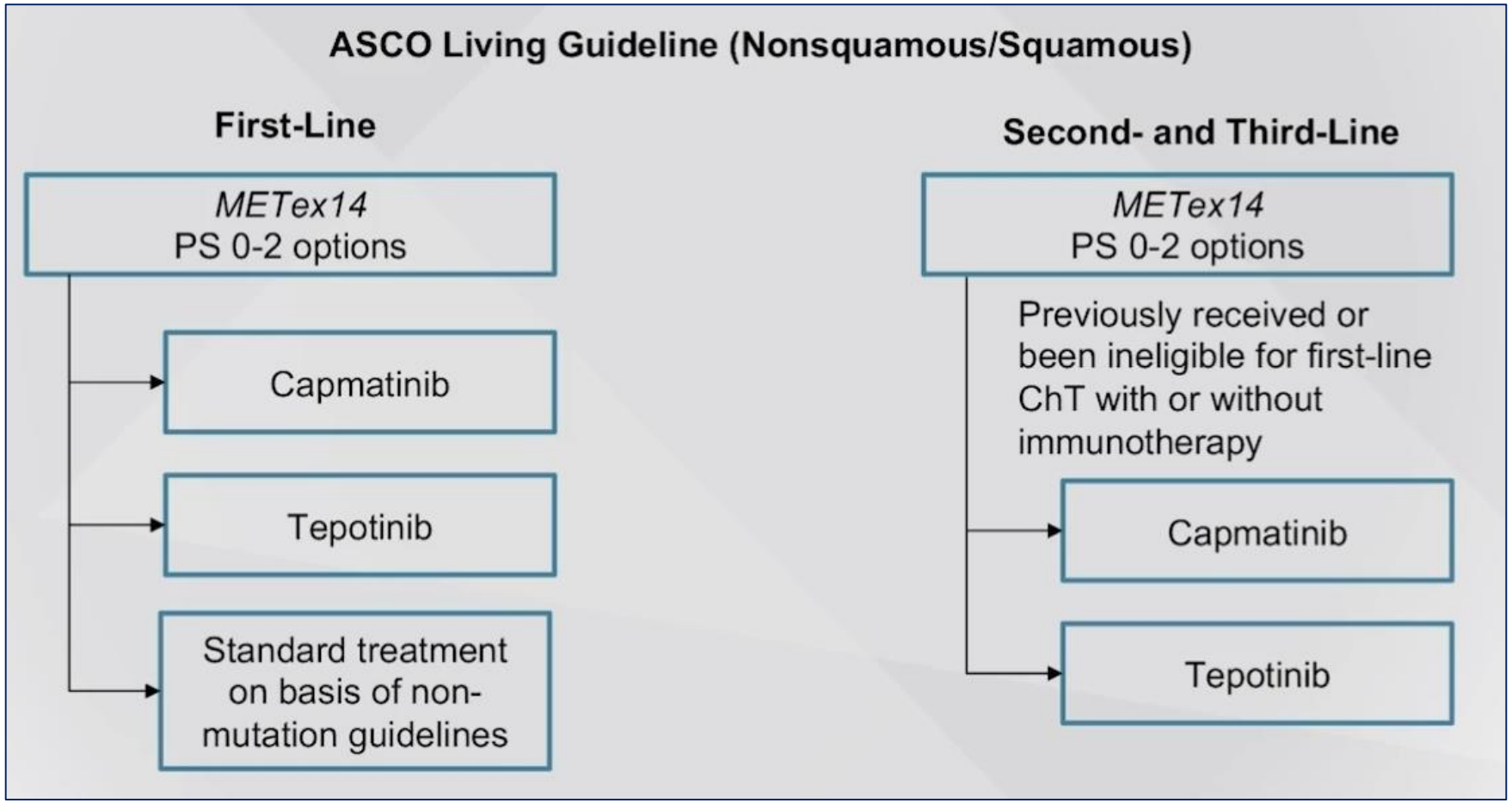


†Includes crizotinib, capmatinib, tepotinib, TPX-0022, APL-101.

- Activity seen in both treatment-naive and previously treated patients, including 4 PRs in those previously treated with MET TKIs
  - 14 of 19 patients response evaluable: 9 (64%) PRs (5 confirmed, 4 pending), 4 SDs
  - Median time to first confirmed response: 4.1 mo (range: 1.6-9.9)

Reference(s): Krebs M et al. *J Clin Oncol*. 2022;40(16_suppl):9008-9008.


METex14 SKIPPING MUTATION[mm]
FIRST-LINE THERAPY[pp]
SUBSEQUENT THERAPY[pp]
METex14 skipping mutation
METex14 skipping mutation discovered prior to first-line systemic therapy
Preferred
Capmatinib[qq] or Tepotinib[qq]
Useful in Certain Circumstances
Crizotinib[qq]
or
Systemic therapy Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5)
Progression[uu]
Systemic therapy Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5)
Progression[uu]
Systemic therapy Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5)
Progression
Preferred
Capmatinib
or
Tepotinib
Useful in Certain Circumstances
Crizotinib
Progression
Systemic Therapy, Subsequent (NSCL-K 4 of 5)
METex14 skipping mutation discovered during first-line systemic therapy
Complete planned systemic therapy, including maintenance therapy, or interrupt, followed by capmatinib (preferred) or tepotinib (preferred) or crizotinib
Progression[uu]
Systemic therapy Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5)


ASCO Living Guideline (Nonsquamous/Squamous)
First-Line
METex14
PS 0-2 options
Capmatinib
Tepotinib
Standard treatment on basis of non-mutation guidelines
Second- and Third-Line
METex14
PS 0-2 options
Previously received or been ineligible for first-line ChT with or without immunotherapy
Capmatinib
Tepotinib

MET amplification

- 2 different quantification FISH criteria used:
  - increase in absolute copy number (e.g. mean copy number of the gene per cell)
  - Increase in the ratio of gene copies relative to other areas on the same chromosome (MET/CEP7 ratio)

- Recent clinical trials with MET inhibitors define different cut-offs for MET amplification positivity

- Consensus on the definition of MET positivity yet to be reached

Table 3. Trials with *MET* inhibitors in NSCLC with *MET* amplification.

Drug	Trial	*MET* Amplification Cut Offs	*n*	Type of Biopsy	ORR, % (95% CI)	Median DOR Months (95% CI)	Median PFS Months (95% CI)
Crizotinib	PROFILE 1001	*MET/CEP7* ratio: ≥ 4—High	21	Tumour tissue	38 (18.1–61.6)	5.2 (3.3–25.8)	6.7 (3.4–9.2)
		MET/CEP7 ratio: >2.2 to <4—Medium	14		14.3 (1.8–42.8)	3.8 (3.8–3.8)	1.9 (1.3–5.6)
		MET/CEP7 ratio: ≥1.8 to ≤2.2—Low	3		33 (0.8–90.6)	12.2 (12.2–12.2)	1.8 (0.8–14.0)
		GCN ≥ 6	15		40% [a]	4.86–12.02 [b]	0.85–14.9 [b]
Capmatinib	GEOMETRY-mono-1	Cohort 1a: GCN ≥ 10	69	Tumour tissue	29 (19–41)	8.3 (4.2–15.4)	4.1 (2.9–4.8)
		Cohort 1b: GCN 6 to 9 [c]	42		12 (4–26)	24.9 (2.7–24.9)	2.7 (1.4–3.1)
		Cohort 2: GCN 4 or 5 [c]	54		9 (3–20)	9.7 (4.2–NE)	2.7 (1.4–4.1)
		Cohort 3: GCN < 4 [c]	30		7 (1–22)	4.2 (4.2–4.2)	3.6 (2.2–4.2)
Tepotinib	VISION	Cohort B: *MET* GCN >2.5	24	Liquid biopsy	41.7 (22.1, 63.4)	NE (2.8, NE)	4.2 (1.4, NE)

NE, not estimable; [a] 95% CI not reported; [b] Median not reported; [c] Closed for futility.

Preliminary evidence indicates activity of MET inhibitors in patients with NSCLC and MET amplification

The number of evaluated patients in these trials is small, duration of the follow-up is short, and the amplification thresholds are not clearly defined and vary between the trials

Some results were lower than the prespecified threshold for significance

Current Oncology

MDPI

Guidelines

Canadian Consensus Recommendations on the Management of *MET*-Altered NSCLC

Parneet K. Cheema [1,2,*], Shantanu O. Banerji [3], Normand Blais [4], Quincy S.-C. Chu [5], Patrice Desmeules [6],

and vary between the trials. On the other hand, current standard of care approaches for patients without actionable mutations (ICIs ± chemotherapy) lead to a median PFS of 8–9 months and a median OS of 16–30 months [91,119–122]. After discussing evolving data with *MET* inhibitors and evidence in support of ICIs ± chemotherapy, the panel concluded that ICIs ± chemotherapy should remain the standard of care in NSCLC with de novo *MET* amplification.

Recommendations

27. In patients with advanced NSCLC with de novo *MET* amplification, *MET*-targeted therapy could be considered through clinical trials at any line of therapy.
28. In patients with advanced NSCLC with de novo *MET* amplification, *MET*-targeted therapy could be considered after other standard therapies have been exhausted or in cases not eligible for standard therapies.


#SCIENCE
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THANK YOU!

Patients with Advanced EGFR-Mutated NSCLC with Acquired MET Amplification Progressing on EGFR Inhibitors

Phase II INSIGHT Trial

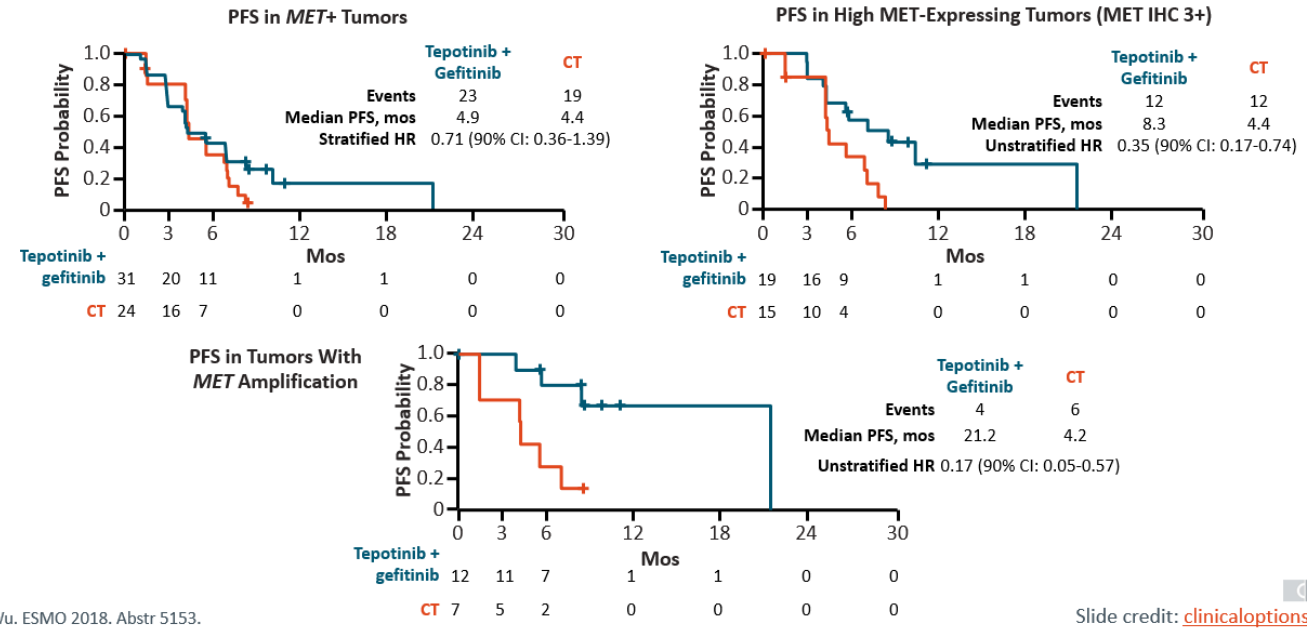
Tepotinib + Gefitinib vs Chemotherapy in MET+/EGFR+/T790M- NSCLC

Analysis Set	N	Tepotinib + Gefitinib		Chemotherapy		Odds Ratio (90% CI)
		Responder, n/N	ORR, %	Responder, n/N	ORR, %	
Overall	55	14/31	45.2	8/24	33.3	1.99 (0.56-6.87)
MET IHC 2+3+	34	13/19	68.4	5/15	33.3	4.33 (1.03-18.33)
MET amplified	19	8/12	66.7	3/7	42.9	2.67 (0.37-19.56)

- ORR higher with tepotinib + gefitinib in patients with high MET-expressing (IHC 2+/3+) or MET-amplified NSCLC (GCN ≥ 5 or *MET/CEP7* ratio ≥ 2)

phase II INSIGHT 2 study: currently investigating tepotinib plus osimertinib in patients with EGFR-mutant NSCLC with acquired resistance to prior EGFR TKIs due to MET amplification

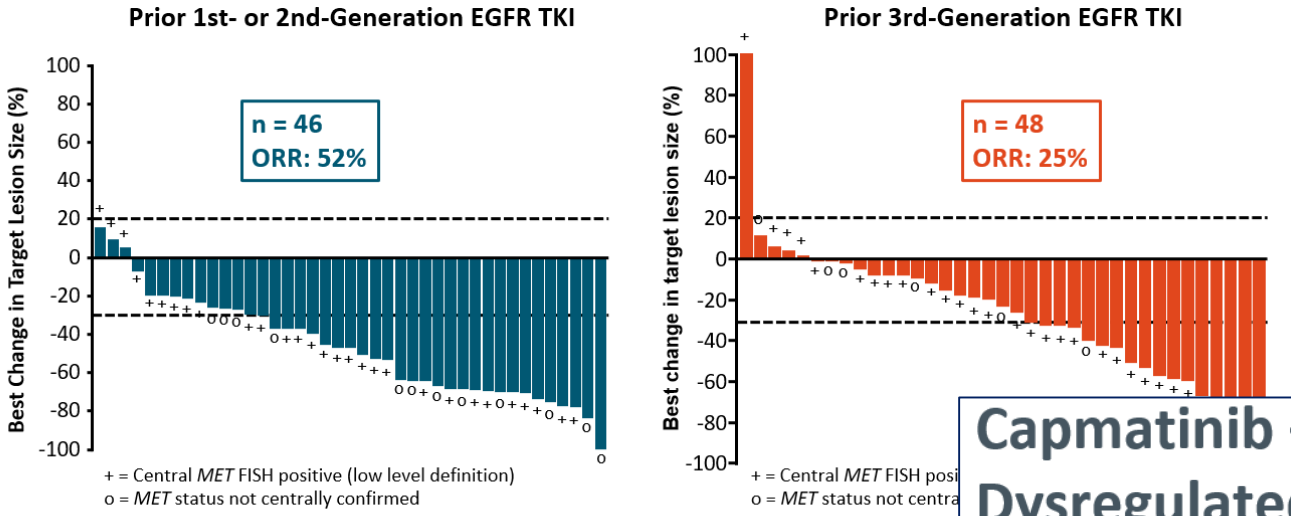
Phase II INSIGHT Trial: PFS by MET Status



Wu. ESMO 2018. Abstr 5153.

Slide credit: clinicaloptions.com

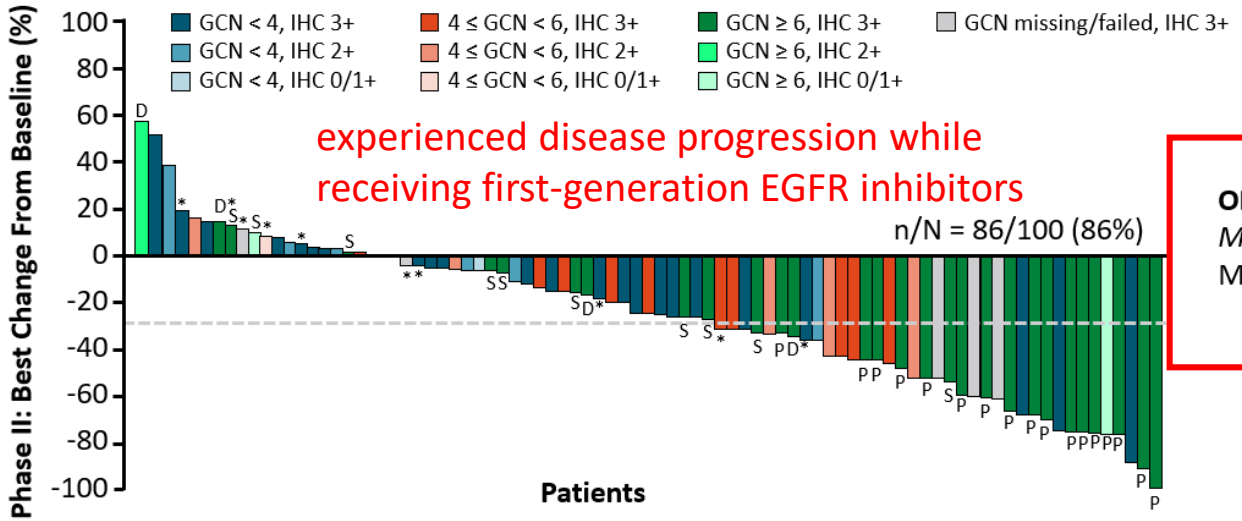
Phase Ib TATTON Trial of Osimertinib in *EGFR*-Mutant NSCLC: Efficacy in Combination With Savolitinib



Yu. AACR 2019. Abstr CT032.

phase II trials ongoing with savolitinib in patients with EGFR mutant-NSCLC with
MET amplification and progression on previous osimertinib: SAVANNAH and ORCHARD

Capmatinib + Gefitinib in *EGFR*-Mutated, *MET*-Dysregulated NSCLC: Best Change From Baseline

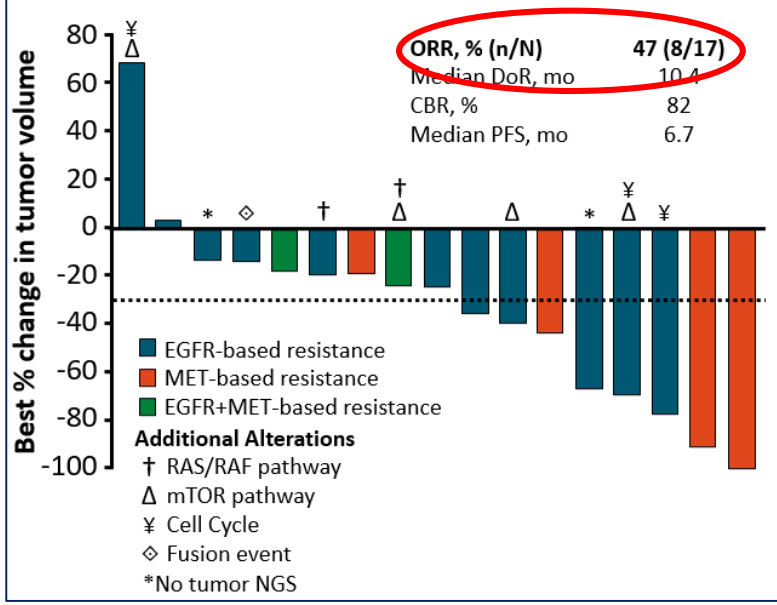


ORR by *MET* Status:
MET GCN ≥ 6: 47%
MET IHC 3+: 32%

*Change in sum of diameters of target lesion contradicted by overall lesion response of PD.
D, progressive disease. S, stable disease. P, partial response.

CHRYSALIS: Response in Patients With *EGFR/MET*-Based Resistance

- 17 patients had either *EGFR*-based or *MET*-based resistance by NGS



Metastatic/unresectable NSCLC with *EGFR* ex19del or L858R mutation and progression on osimertinib without intervening chemotherapy

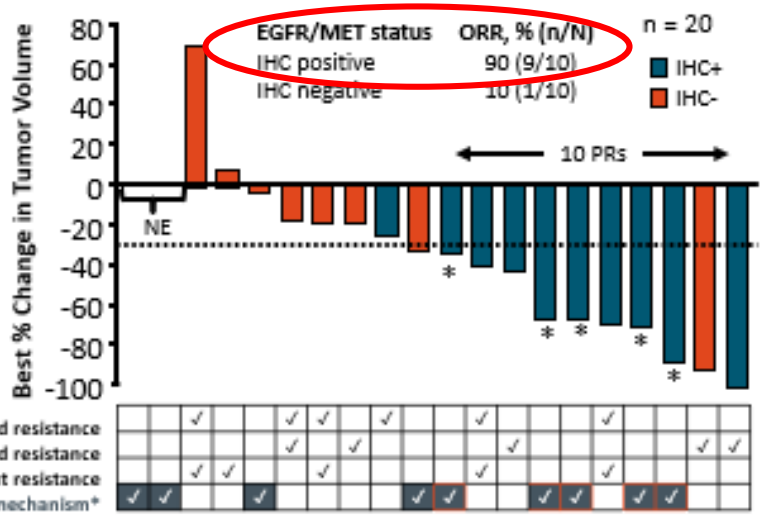
combination of amivantamab and lazertinib, a third-generation TKI

CHRYSALIS: Response in Patients With EGFR/MET Expression by IHC

- Of 20 patients with tumor biopsy available for IHC staining after tumor NGS, 10 were positive for EGFR/MET by IHC (EGFR+METH score ≥400); remainder were IHC negative

Response	IHC-Positive Patients (n = 10)
ORR, %	90
Median DoR, mos	9.7
CBR, %	100
Median PFS, mos	12.5

- 5 responding patients positive for EGFR/MET by IHC had unknown resistance mechanism

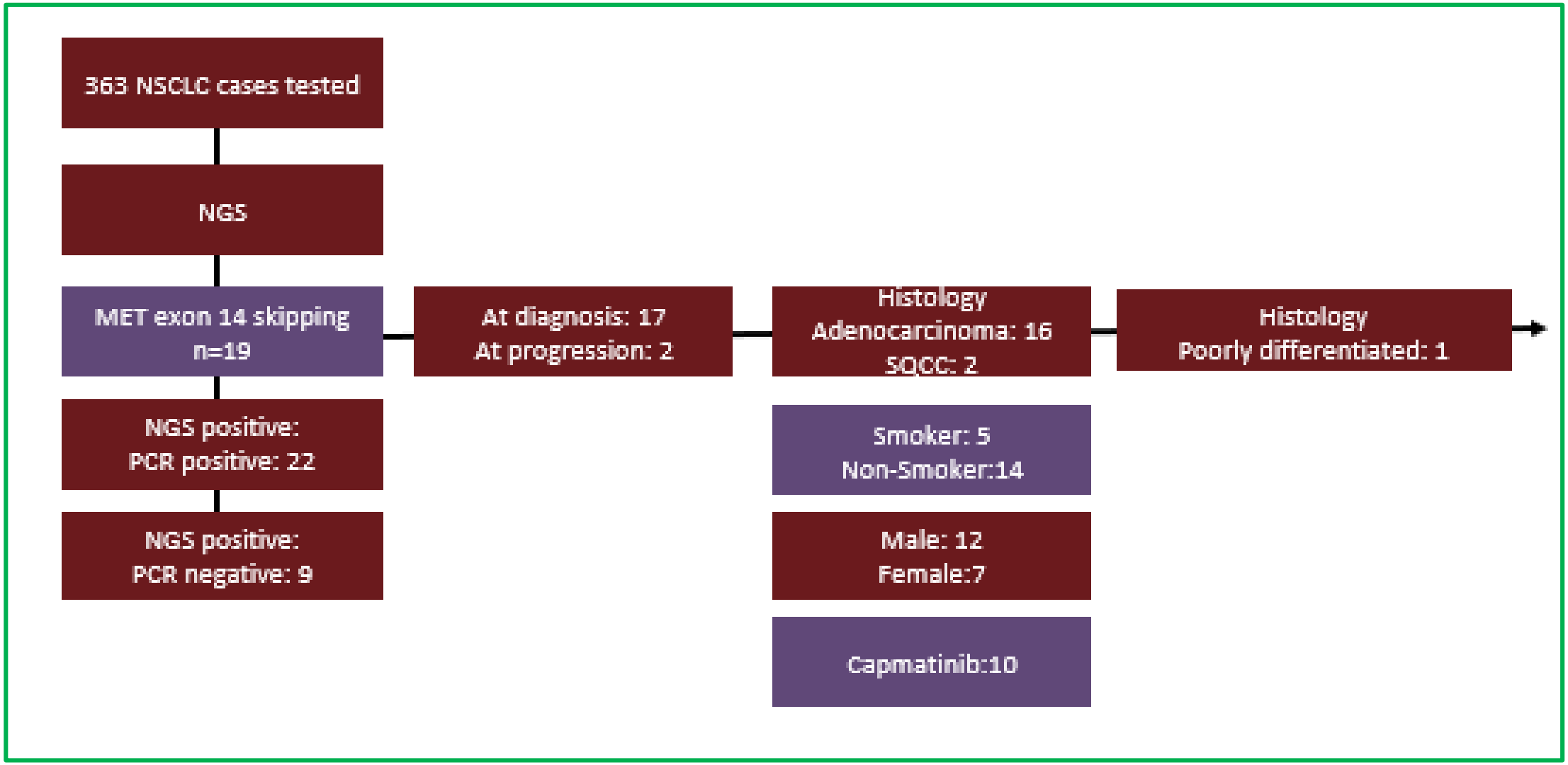


Baum. ASCO 2021. Abstr 9006. Reproduced with permission.

Slide credit: clinicaloptions.com

Additional validation analyses with both NGS and IHC needed to confirm these promising preliminary data

MET exon 14 skipping mutation: our experience



Capmatinib experience

Features	1	2	3	4	5	6	7	8	9
Age/Sex	76/F	68/F	69/M	64/M	60/F	60/M	70/M	75/M	59/F
Met 14	At diagnosis	At diagnosis	At diagnosis	At diagnosis	At diagnosis	At diagnosis	At diagnosis	After progression	At diagnosis
Smoking	No	No	Yes	No	No	No	No	No	No
Capmatinib	After CT, developed ILD after 17 days of treatment, died	After CT, 6 months capmatinib, alive	After CT, ongoing since 5 months	After CT, took capmatinib for 7 months, now on nivolumab	After CT, alive on capmatinib since 15 months	After CT, on capmatinib since 3 months	After CT, capmatinib since 4 months	After Chemo, capmatinib since 3 months	After chemo, started capmatinib this month