CURRENT AND FUTURE PRACTICE FOR MET EXON 14 SKIPPING

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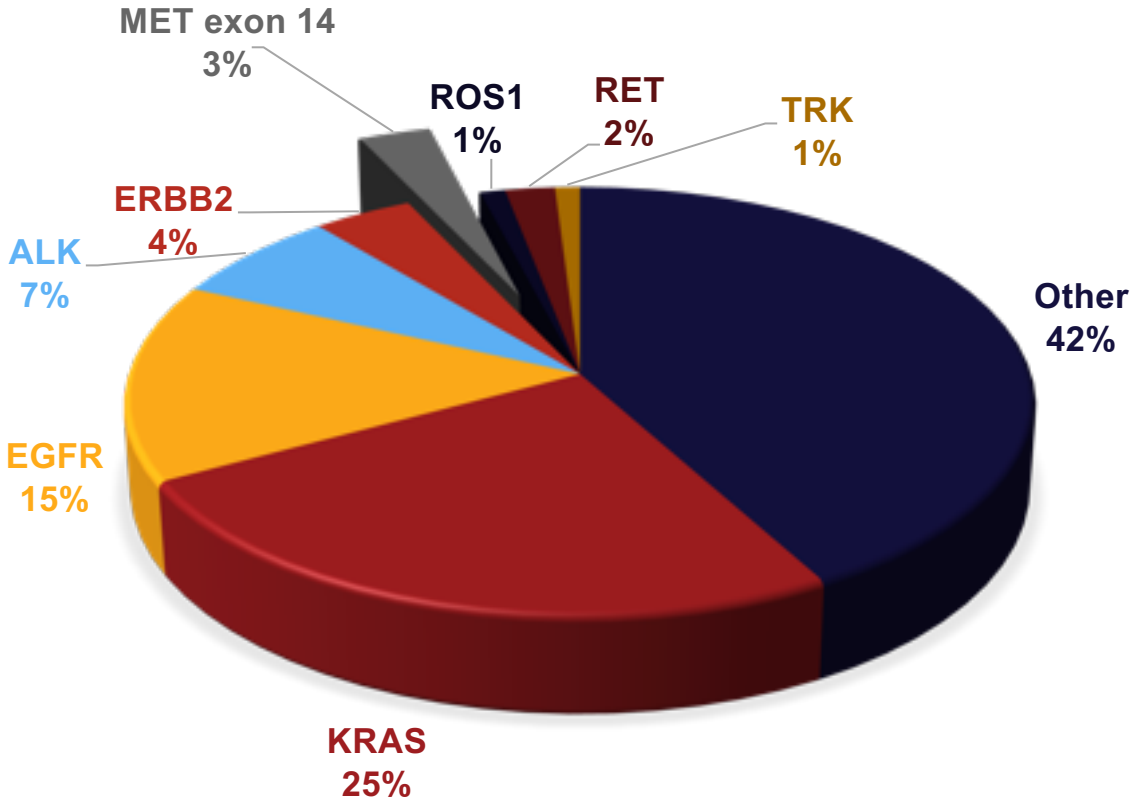
Overview

- MET exon 14 skipping mutations and patient characteristics
  - Unique population
  - Different testing methodologies
- MET inhibitors in patients with MET exon 14 skipping mutations
  - Efficacy and safety
  - Quality of life
  - Resistance mechanisms
- What should the standard of care be for these patients?

MET exon 14 skipping: the newest (arguably) actionable oncogenic alteration

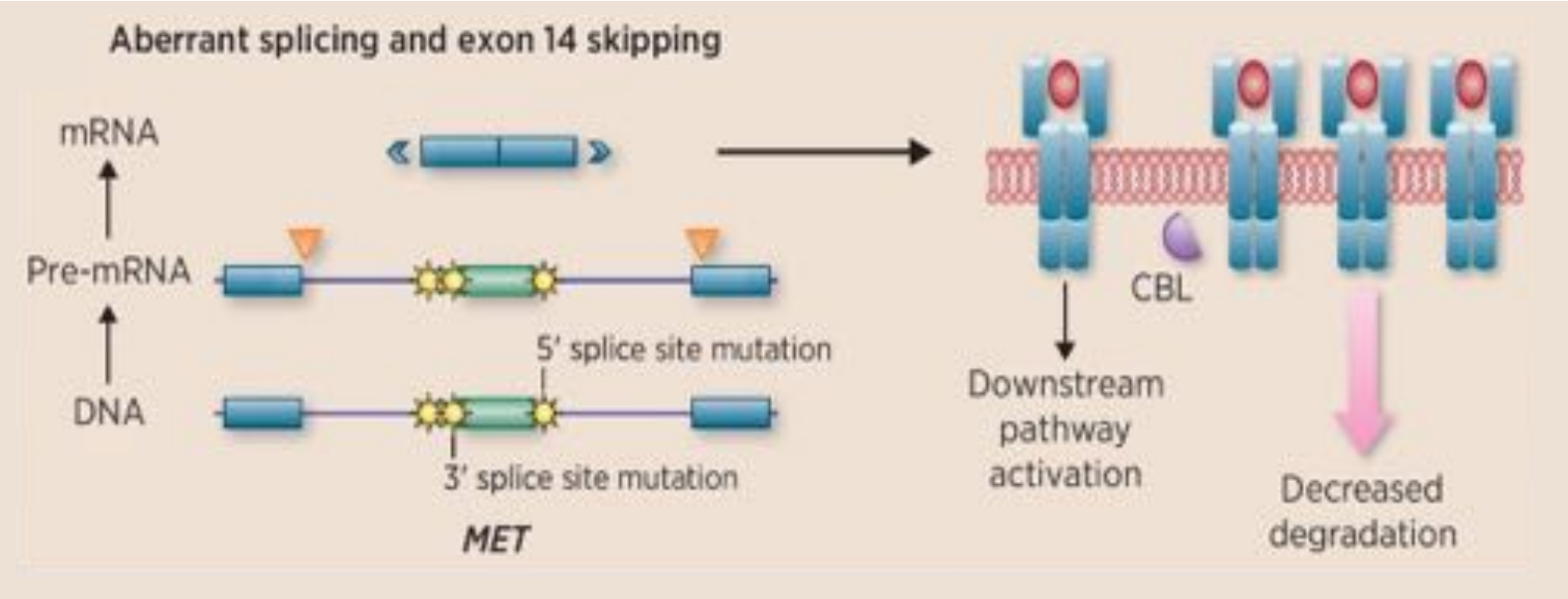


MET Background

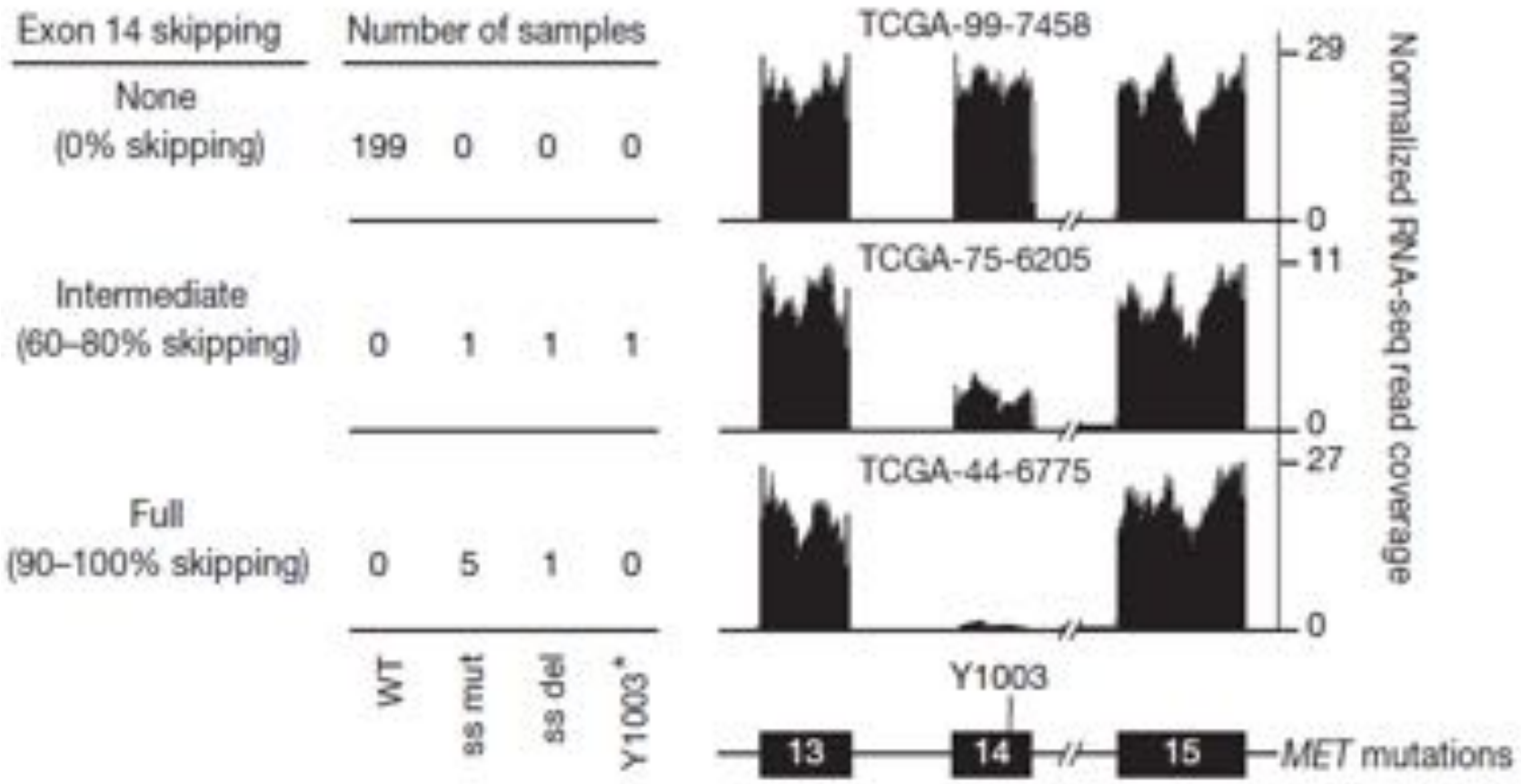
- MET receptor tyrosine kinase (RTK) is a proto-oncogene with roles in proliferation, apoptosis, and motility/invasion[1]
- Gain of function alterations include amplification and protein overexpression[2]
- These have been previous targets in lung cancer with no significant success (overexpression) or modest success (high amplification)[2,3]
- Mutations in the MET exon 14 RNA splice acceptor and donor sites lead to exon skipping, deletion of the juxtamembrane domain, and loss of Cbl E3-ligase binding to the resultant aberrant MET protein[1]
- MET exon 14 mutations are oncogenic in preclinical models of SCLC, NSCLC and gastric cancer, and are sensitive to MET inhibition[1,4]

1. Kong-Beltran M, et al. *Cancer Res*. 2006;66(1):283-289. 2. Spigel DR, et al. *J Clin Oncol*. 2017;35(4):412-420. 3. Camidge DR, et al. *ASCO* 2016; Abstract 9070. 4. Pilotto S, et al. *Ann Transl Med*. 2017;5(1):2.

MET exon 14 splice site mutations engender alternative splicing

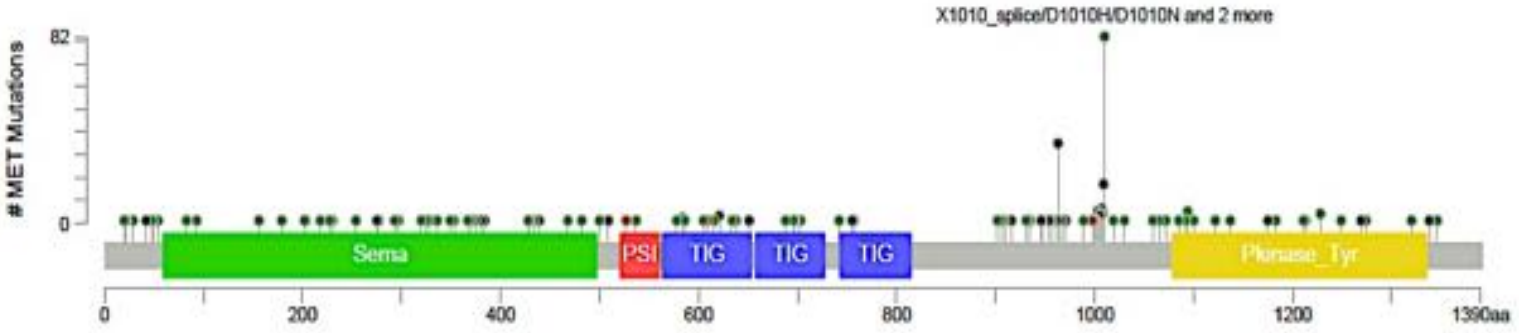


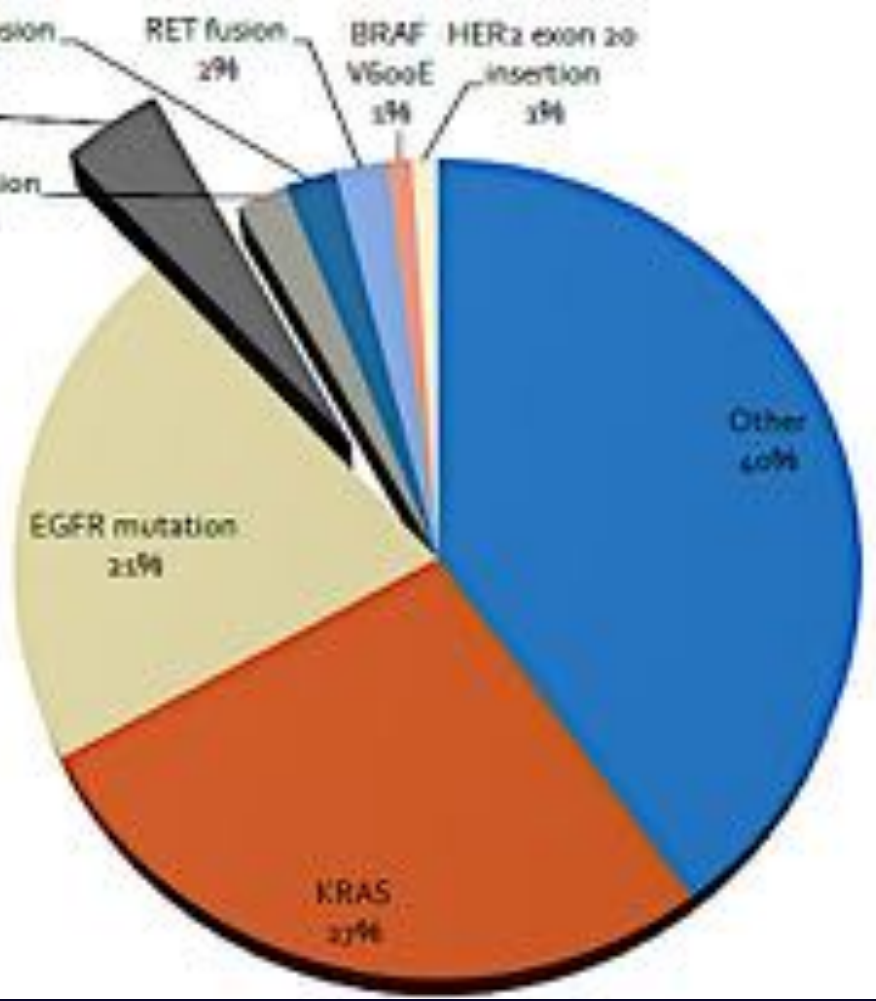
TCGA Identifies Aberrant Exon 14 Deleted MET RNA Transcripts



Cancer Genome Atlas Research Network. *Nature*. 2014;511(7511):543-550.

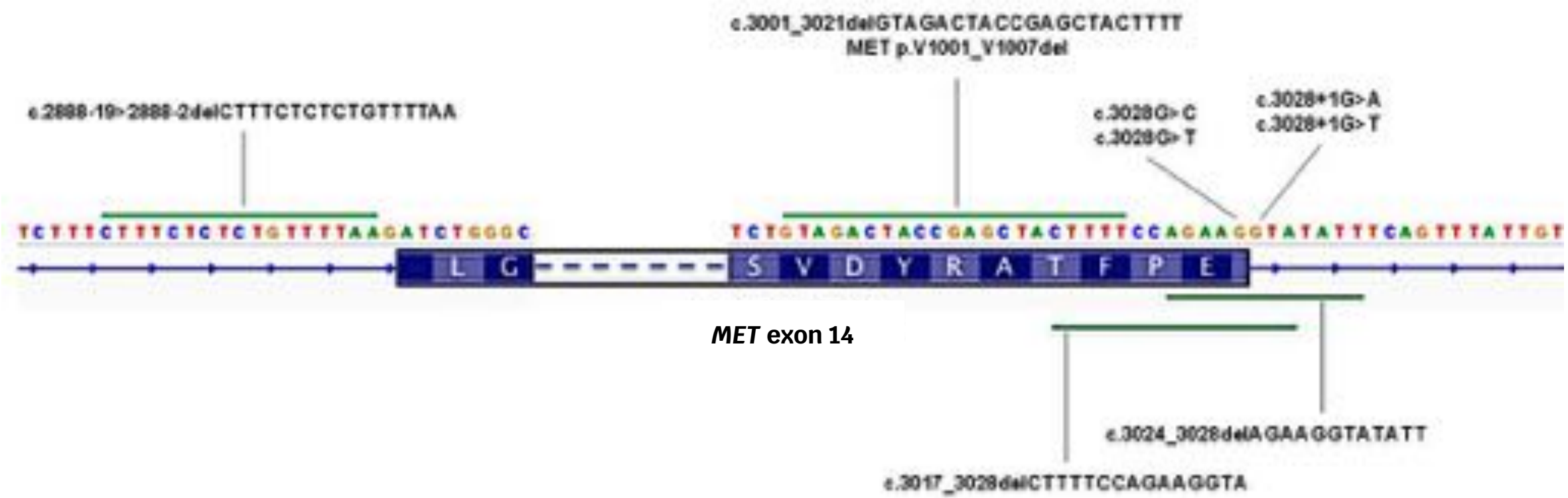
MSK IMPACT Detects Relative Abundance of MET Exon 14 Splice Site Mutations





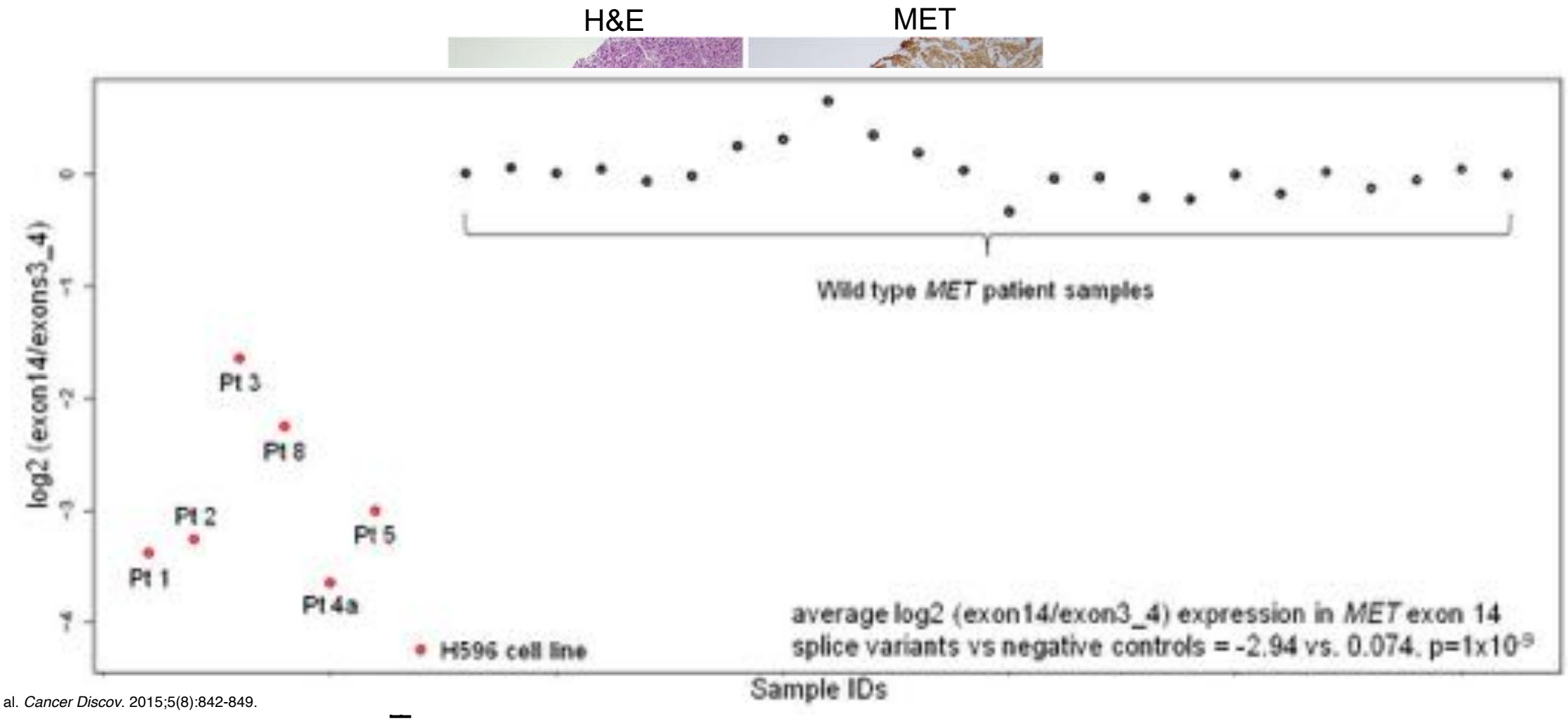
Memorial Sloan Kettering Cancer Cancer cBioPortal. Available at https://www.cbioportal.org/.

MET Exon 14 Splice Site Mutations Are Heterogeneous



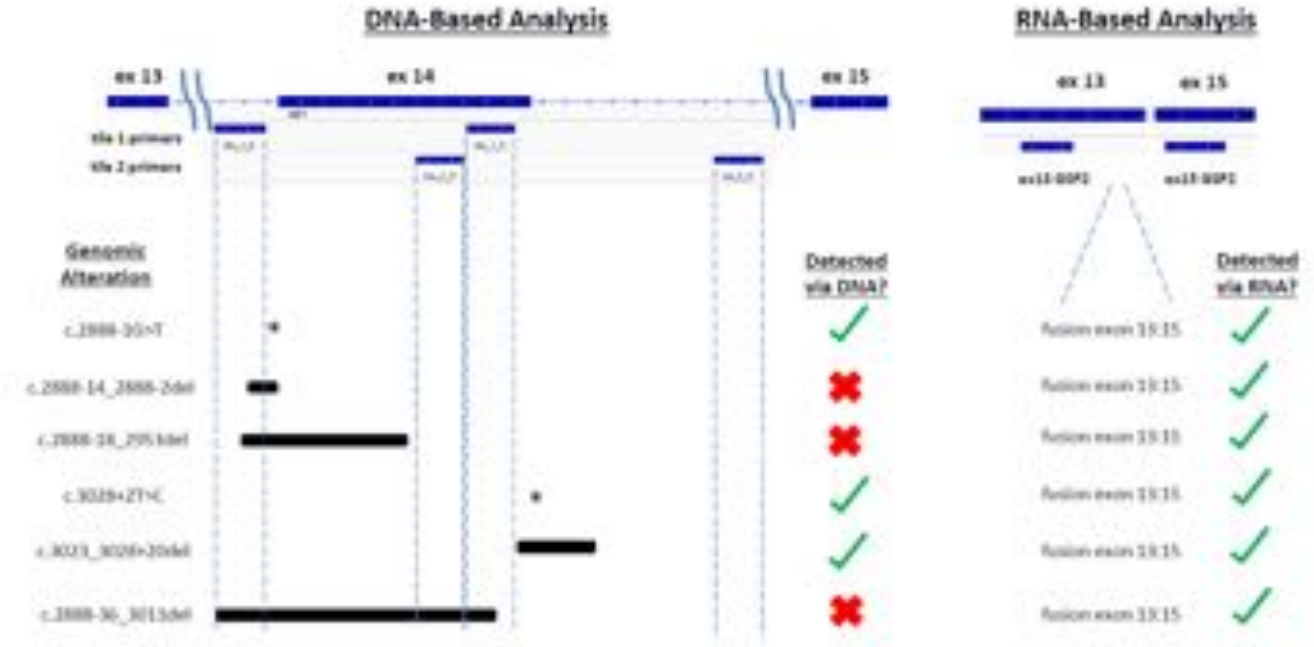
Paik PK, et al. *Cancer Discov*. 2015;5(8):842-849.

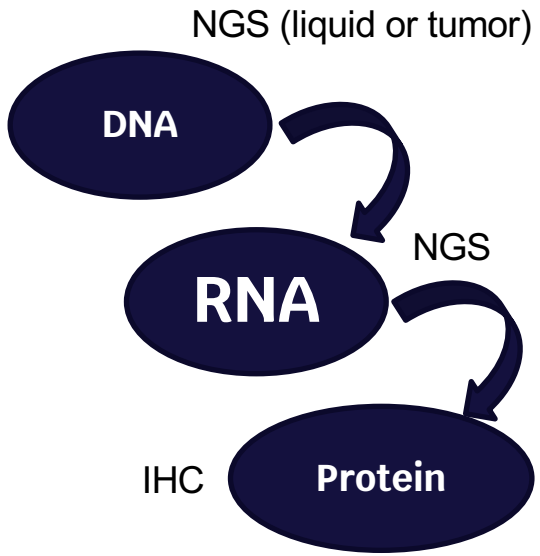
MET Exon 14 Splice Site Mutations Are Associated With High MET Protein and Low Exon 14 mRNA Expression



Paik PK, et al. *Cancer Discov*. 2015;5(8):842-849.

How Should We Look for *MET* Exon 14 Skipping Mutations? DNA vs. RNA NGS





- NGS absolutely required to cover the breadth of splice site alterations AND the many other actionable targets in NSCLC
- Test all NSCLC patients for every target

Davies KD, et al. *J Thorac Oncol.* 2019;14(4):737-741.

How Should We Look for *MET* Exon 14 Skipping Mutations? Tissue vs. Liquid biopsies

Tissue biopsy

- Standard of care
- Provides histological data
- Invasive; potential for adverse events
- Difficulty obtaining adequate samples
  - Can require multiple passes
- Not all patients suitable for biopsy
- Single-site tissue biopsies may miss genetic heterogeneity

Liquid biopsy (plasma ctDNA)

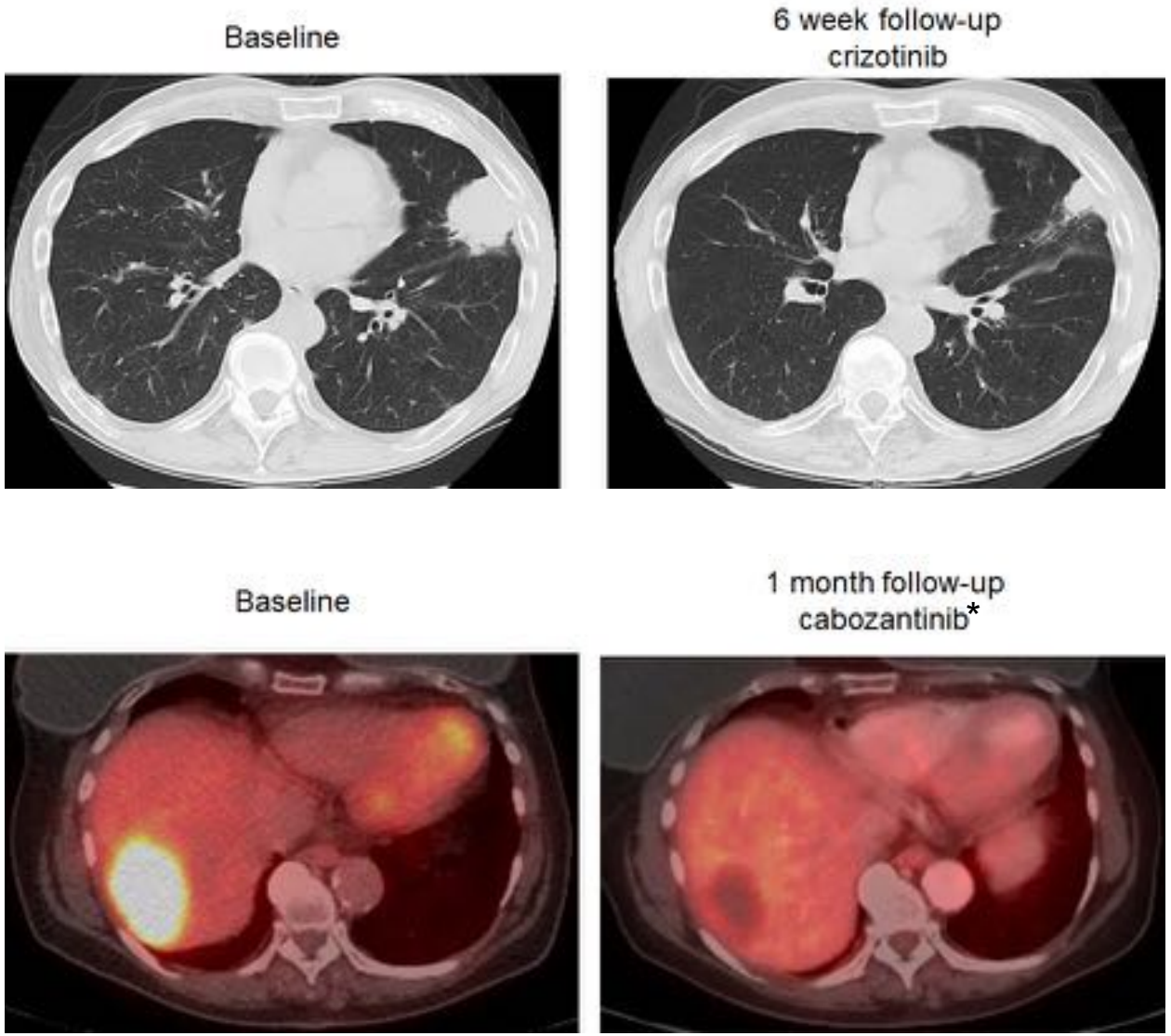
- Non-invasive; safe
- Potential for reduced cost and risk of complications
- Assesses DNA from all tumor sites (good and bad)
- Can obtain serial samples at diagnosis and at acquired resistance
- Issues with sensitivity, specificity and standardization

Clinical Characteristics of MET-Altered Lung Cancers Are Heterogeneous and Different from Other Lung Cancers

Patients With MET Exon 14-Altered Lung Cancers (N = 69)		
Age, years	Median (range)	72 (34–91)
Sex, n (%)	Female	40 (58)
	Male	29 (42)
Race, n (%)	White	50 (72)
	Asian	11 (16)
	Black	2 (3)
	Other	6 (9)
Smoking history, n (%)	Former smoker	42 (61)
	Never smoker	26 (38)
	Smoker	1 (1)
Tumor histology, n (%)	Adenocarcinoma	58 (84)
	Sarcomatoid carcinoma	6 (9)
	Squamous cell carcinoma	3 (4)
	Adenosquamous carcinoma	2 (3)
ECOG performance status, n (%)	0	19 (28)
	1	49 (71)
	2	1 (1)
Prior treatments for advanced disease, n (%)	0	26 (38)
	≥1	43 (62)

Drilon A, et al. *Nat Med*.2020;26:47–51.

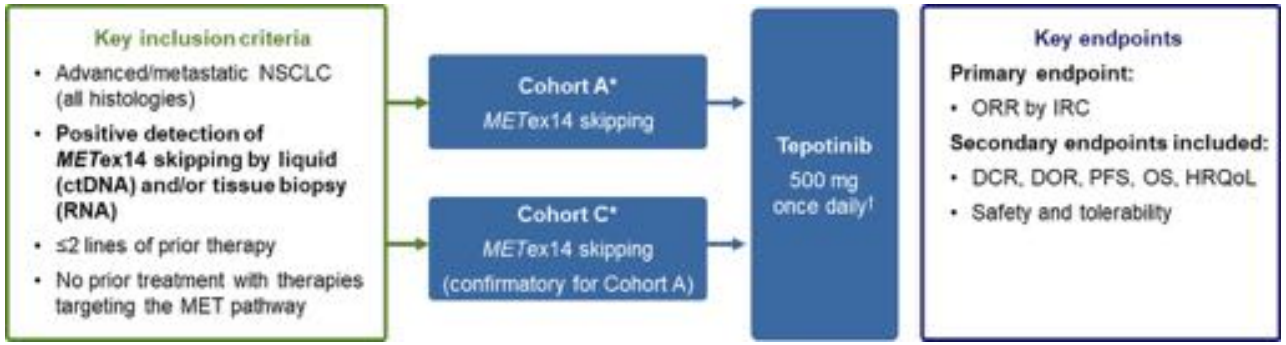
MET Exon 14-Altered NSCLC Patients Respond to MET Inhibitors



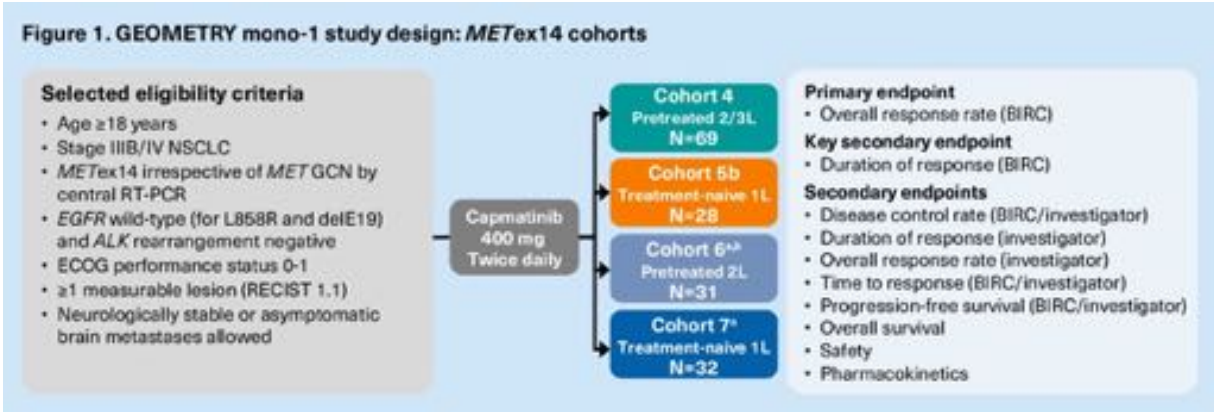
Paik PK, et al. *Cancer Discov.* 2015;5(8):842-849.

VISION and GEOMETRY Trial Designs: Single Arm Phase 2 Trials

VISION[1,2]



GEOMETRY[3,4]



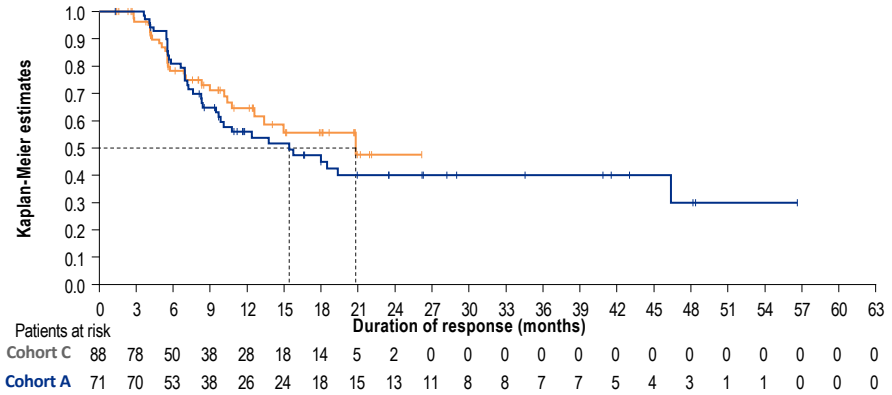
1. Felip E, et al. *WCLC* 2021. 2. Paik PK, et al. *N Engl J Med.* 2020;383(10):931-943. 3. Wolf J, et al. *ASCO* 2021; Abstract 9020. 4. Wolf J, et al. *N Engl J Med.* 2020;383:944–957.

VISION update 2022

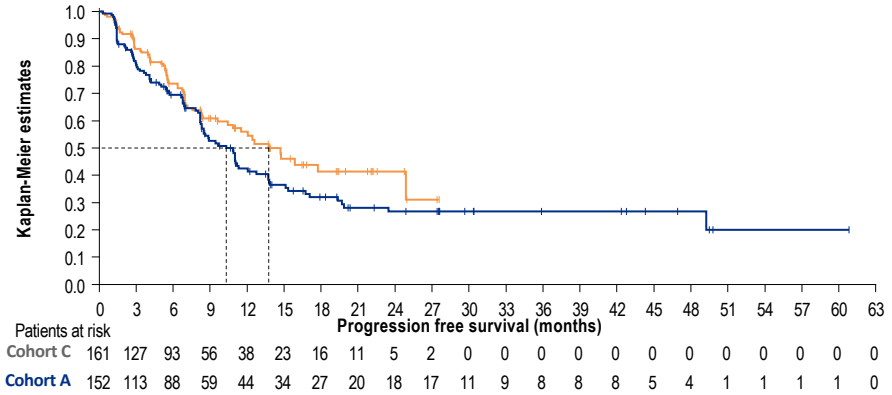
Cohort C primary analysis provided independent confirmation for robust and durable efficacy of tepotinib

	Cohort C (N=161)	Cohort A (N=152)	Cohort A+C (N=313)
ORR, % (95% CI)	54.7 (46.6, 62.5)	46.7 (38.6, 55.0)	50.8 (45.1, 56.5)
DCR, % (95% CI)	80.1 (73.1, 86.0)	72.4 (64.5, 79.3)	76.4 (71.3, 81.0)
mDOR, months (95% CI)	20.8 (12.6, ne)	15.4 (9.7, 46.4)	18.0 (12.4, ne)
mPFS, months (95% CI)	13.8 (10.4, ne)	10.3 (8.2, 12.7)	11.2 (9.5, 13.8)
mOS, months (95% CI)	18.8 (14.4, 25.5)	19.8 (15.2, 22.9)	19.3 (15.8, 22.3)

DOR



PFS



Thomas et al. WCLC 2022

Efficacy was particularly meaningful in treatment-naïve patients enrolled by tissue biopsy

- 74.5% of patients were enrolled in Cohort C based on *MET*ex14 skipping detection by tissue biopsy

1L T+	Cohort C (n=69)	Cohort A (n=42)	Cohort A+C (n=111)
BOR, n (%) CR PR SD PD NE	 0 43 (62.3) 17 (24.6) 7 (10.1) 2 (2.9)	 1 (2.4) 19 (45.2) 13 (31.0) 3 (7.1) 6 (14.3)	 1 (0.9) 62 (55.9) 30 (27.0) 10 (9.0) 8 (7.2)
ORR, % (95% CI)	62.3 (49.8, 73.7)	47.6 (32.0, 63.6)	56.8 (47.0, 66.1)
DCR, % (95% CI)	87.0 (76.7, 93.9)	78.6 (63.2, 89.7)	83.8 (75.6, 90.1)
mDOR, months (95% CI)	ne (10.4, ne)	46.4 (7.6, ne)	46.4 (13.4, ne)
mPFS, months (95% CI)	15.9 (10.8, ne)	15.3 (8.2, ne)	15.3 (11.3, ne)
mOS, months (95% CI)	22.7 (12.7, ne)	29.7 (13.5, ne)	25.9 (17.5, 36.6)

Thomas et al. WCLC 2022

VISION update 2022

Efficacy was also robust and durable in previously treated patients enrolled by tissue biopsy

2L+ T+	Cohort C (n=51)	Cohort A (n=46)	Cohort A+C (n=97)
BOR, n (%) CR PR SD PD NE	 0 26 (51.0) 16 (31.4) 4 (7.8) 5 (9.8)	 0 22 (47.8) 12 (26.1) 9 (19.6) 3 (6.5)	 0 (0.0) 48 (49.5) 28 (28.9) 13 (13.4) 8 (8.2)
ORR, % (95% CI)	51.0 (36.6, 65.2)	47.8 (32.9, 63.1)	49.5 (39.2, 59.8)
DCR, % (95% CI)	82.4 (69.1, 91.6)	73.9 (58.9, 85.7)	78.4 (68.8, 86.1)
mDOR, months (95% CI)	12.6 (4.3, ne)	12.4 (7.0, 18.0)	10.2 (8.3, 18.0)
mPFS, months (95% CI)	13.8 (6.9, ne)	11.0 (8.2, 16.8)	11.5 (8.2, 16.8)
mOS, months (95% CI)	19.6 (14.6, ne)	20.8 (14.3, 27.2)	20.4 (17.0, 26.8)

Thomas et al. WCLC 2022

GEOMETRY efficacy update 2021: treatment-naive

Wolf et al. 9020 ASCO 2021

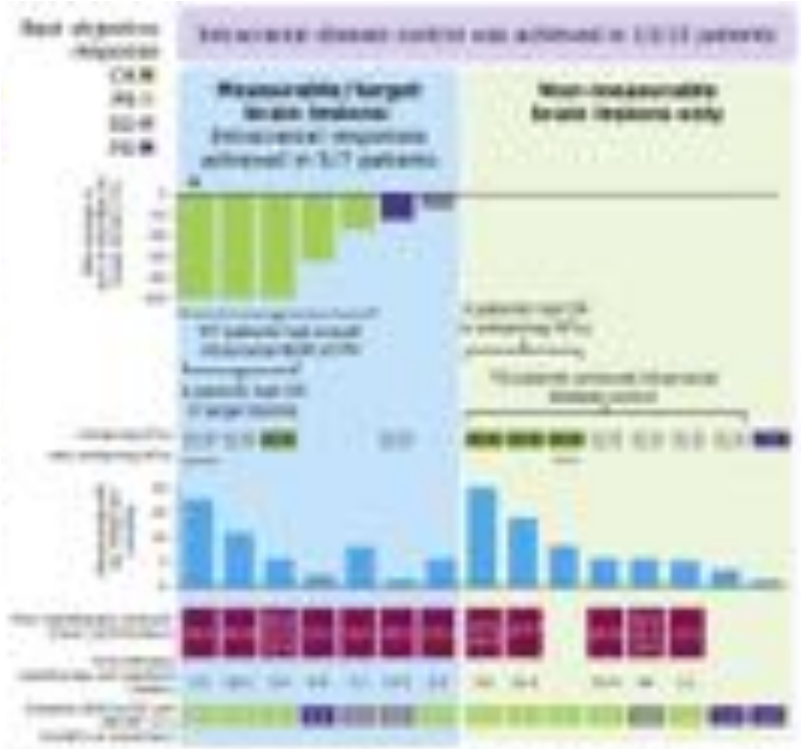
GEOMETRY efficacy update 2021: previously treated

Wolf et al. 9020 ASCO 2021

MET Inhibitor CNS Activity is Likely Present but Requires Prospective Assessment

Phase II VISION Trial: Tepotinib

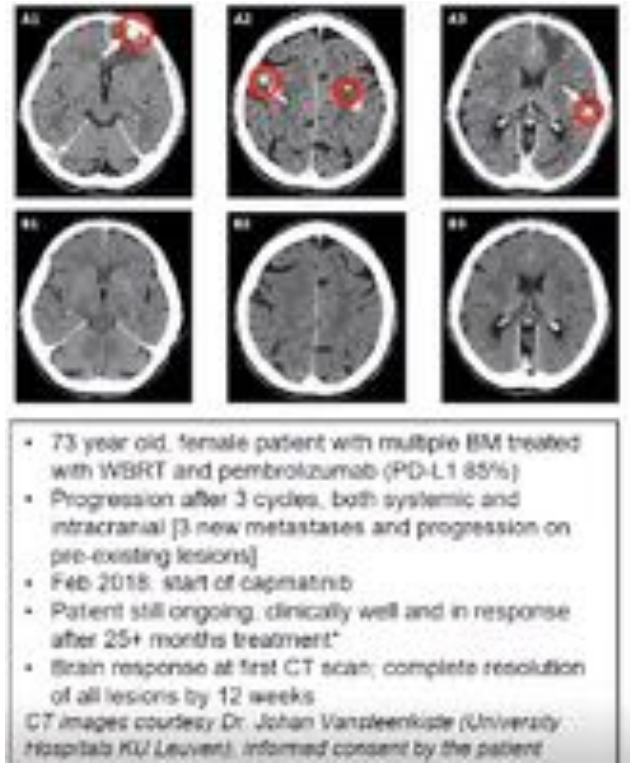
- 7 pts with baseline BM
  - **ORR=71%**



Patel et al. *ASCO* 2021; Abstract 9084.

Phase II GEOMETRY Trial: Capmatinib

- 13 pts with baseline BM
  - **ORR=54%**



Garon E, et al. presented at *AACR*. 2020: Abstract CT082.

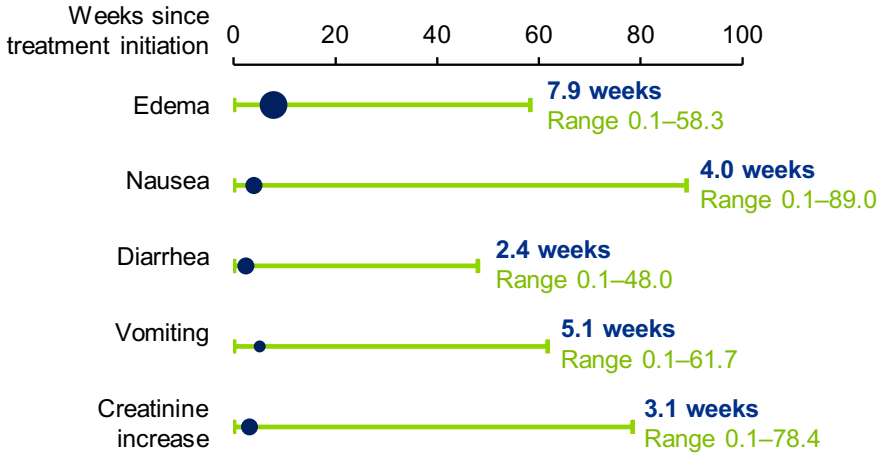
Safety profile: MET inhibition has a unique signature

TEAEs (Overall Rate ≥10%)	Related TEAE Crizotinib		Related TEAE Capmatinib		Related TEAE Tepotinib		Related TEAE Savolitinib	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Peripheral Edema	51%	1%	42%	8%	63%	7%	54%	7%
AST increase	17%		NR	NR	7%	2%	37%	13%
ALT increase	4%		NR	NR	7%	3%	37%	10%
Hypoalbuminemia	NR	NR	NR	NR	16%	2%	23%	0%
Creatinine increase	NR	NR	20%	0%	18%	1%	NR	NR
Fatigue	NR	NR	14%	3%	7%	1%	NR	NR
Nausea	41%	0%	33%	2%	26%	1%	44%	0%
Vision disorder	45%	1%	NR	NR	NR	NR	NR	NR

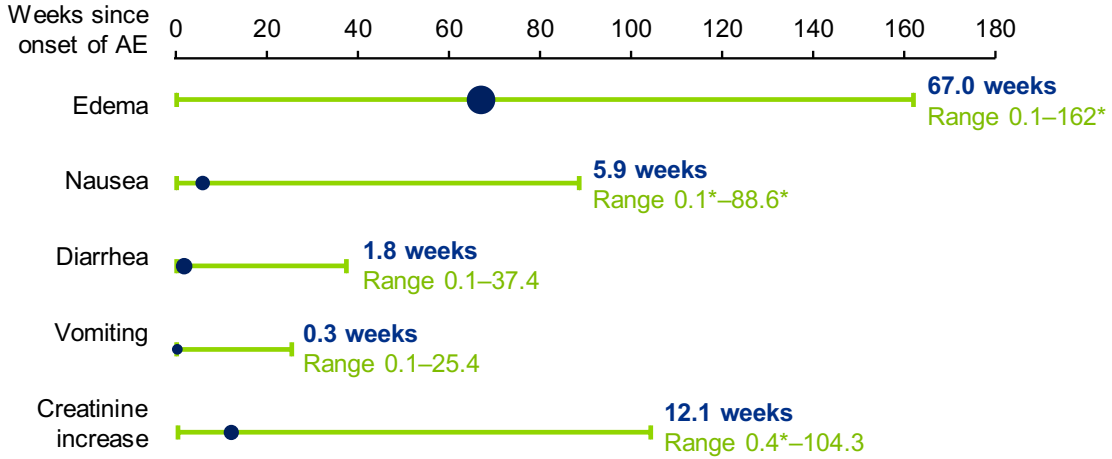
1. Drilon A, et al. *Nature Med* 2020. 2. Wolf et al. ASCO Annual Meeting 2019. 3. Paik et al. NEJM 2020. 4. Lu et al. ASCO Annual Meeting 2020

AEs of clinical interest: Time to first onset and time to resolution

Median time to first onset



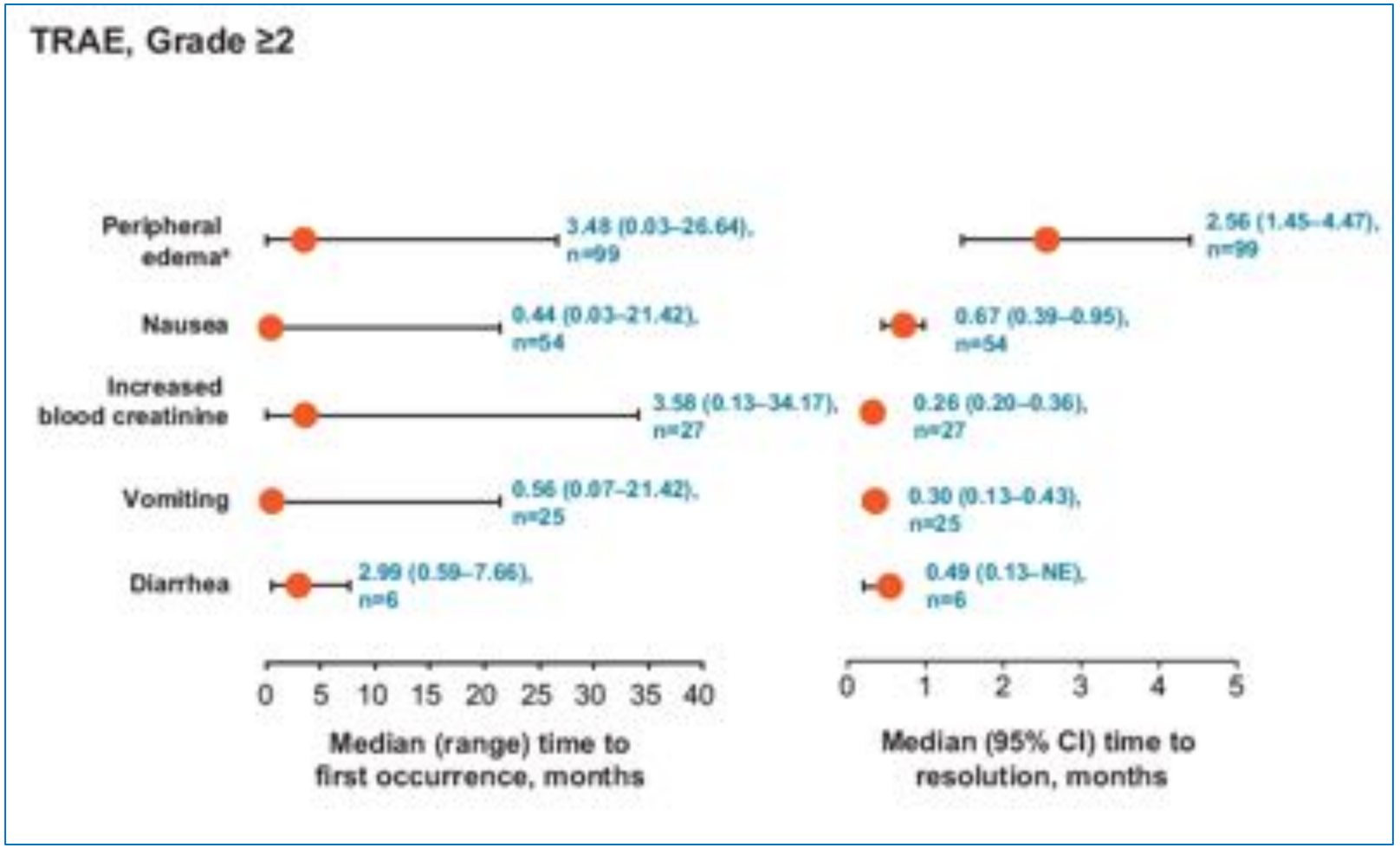
Median time to resolution



Events, n	Edema (n=178)	Nausea (n=68)	Diarrhea (n=67)	Vomiting (n=33)	Creatinine increase (n=66)
Total	337	87	112	47	96
Resolved at time of analysis	115	67	102	44	67

Veillon et al. WCLC 2020

Capmatinib AE kinetics similar to tepotinib

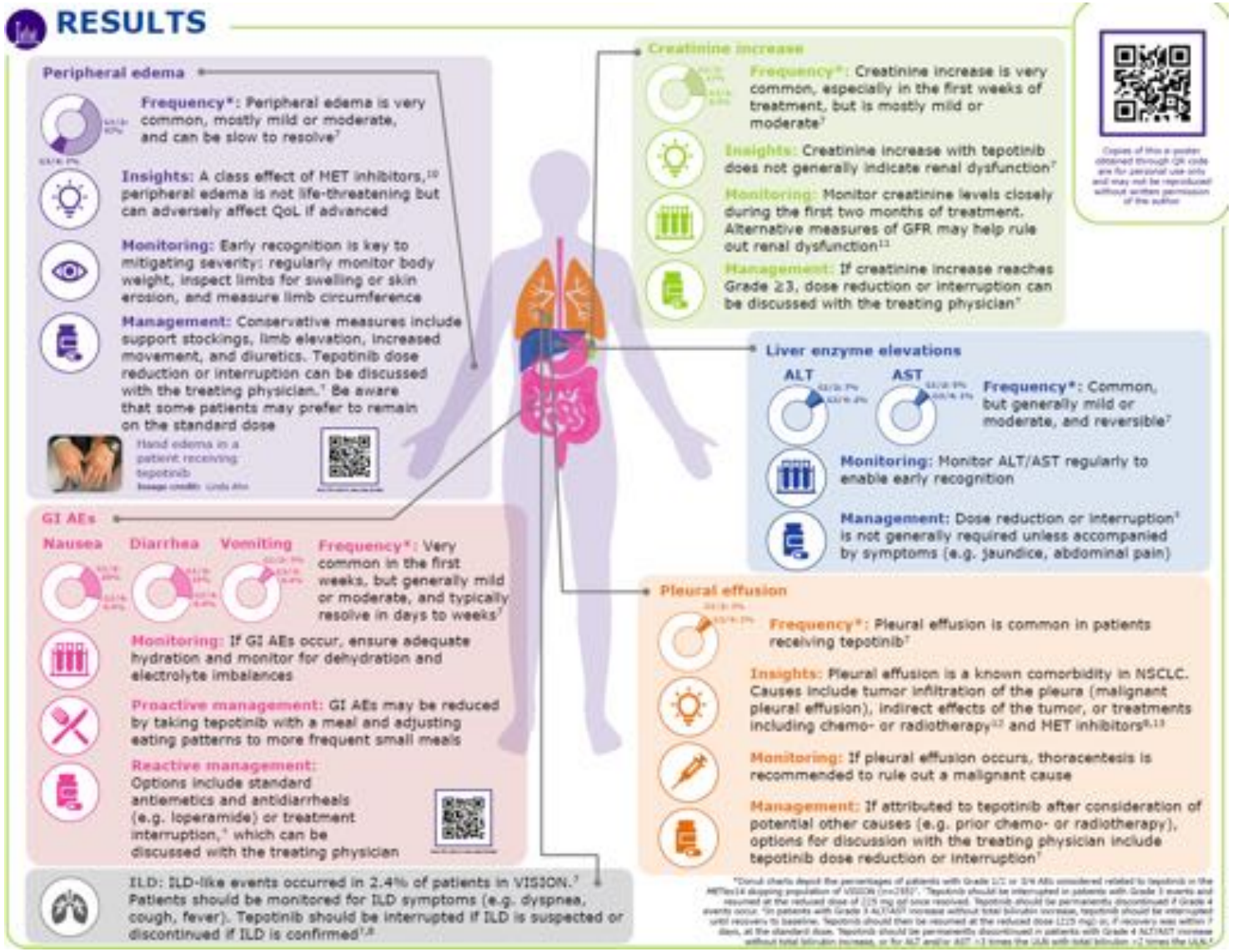


Heist et al. ESMO 2021

Management of tepotinib-related peripheral edema

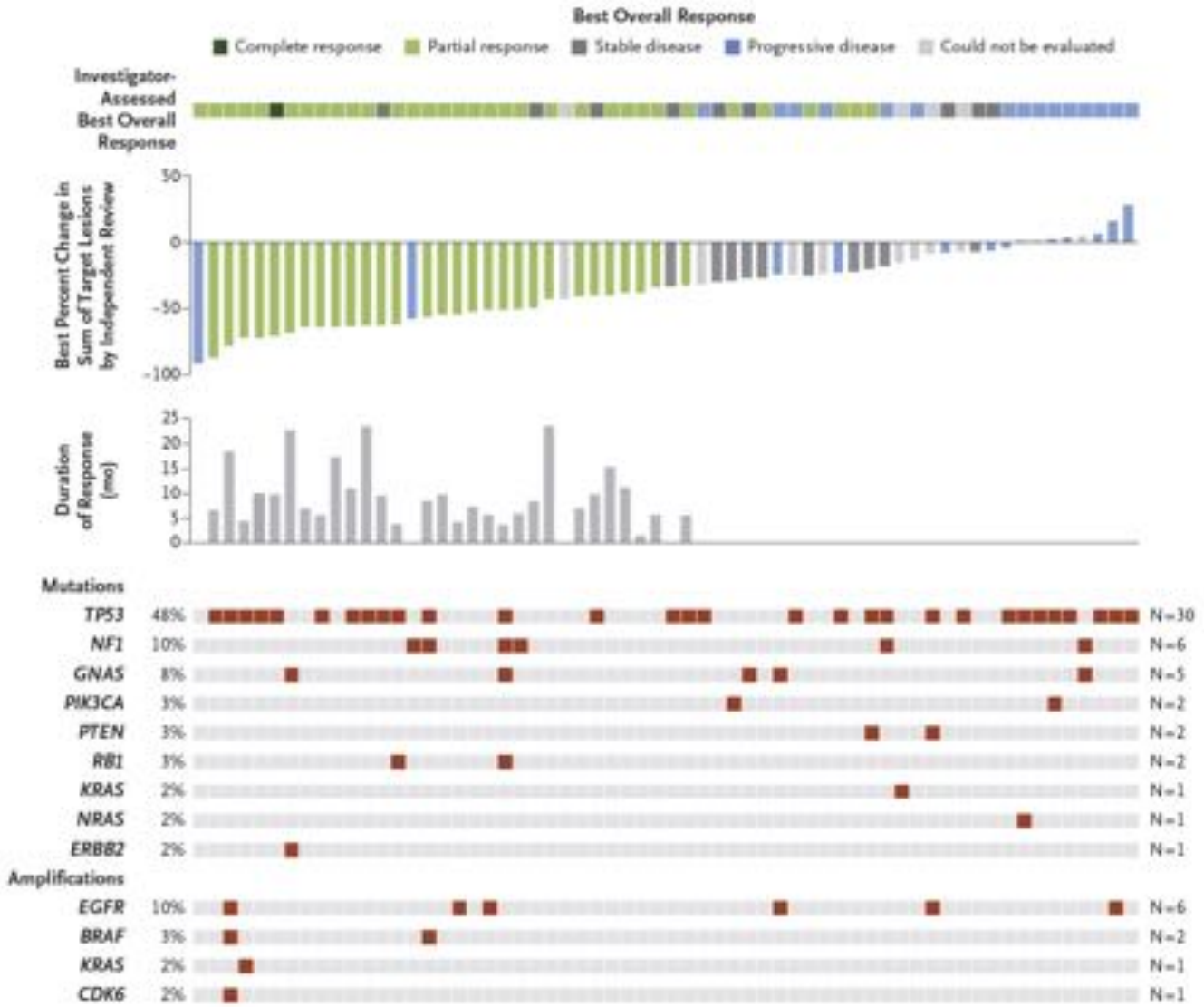
Alexander T. et al. ONS 2021

Managing MET inhibitor common side effects



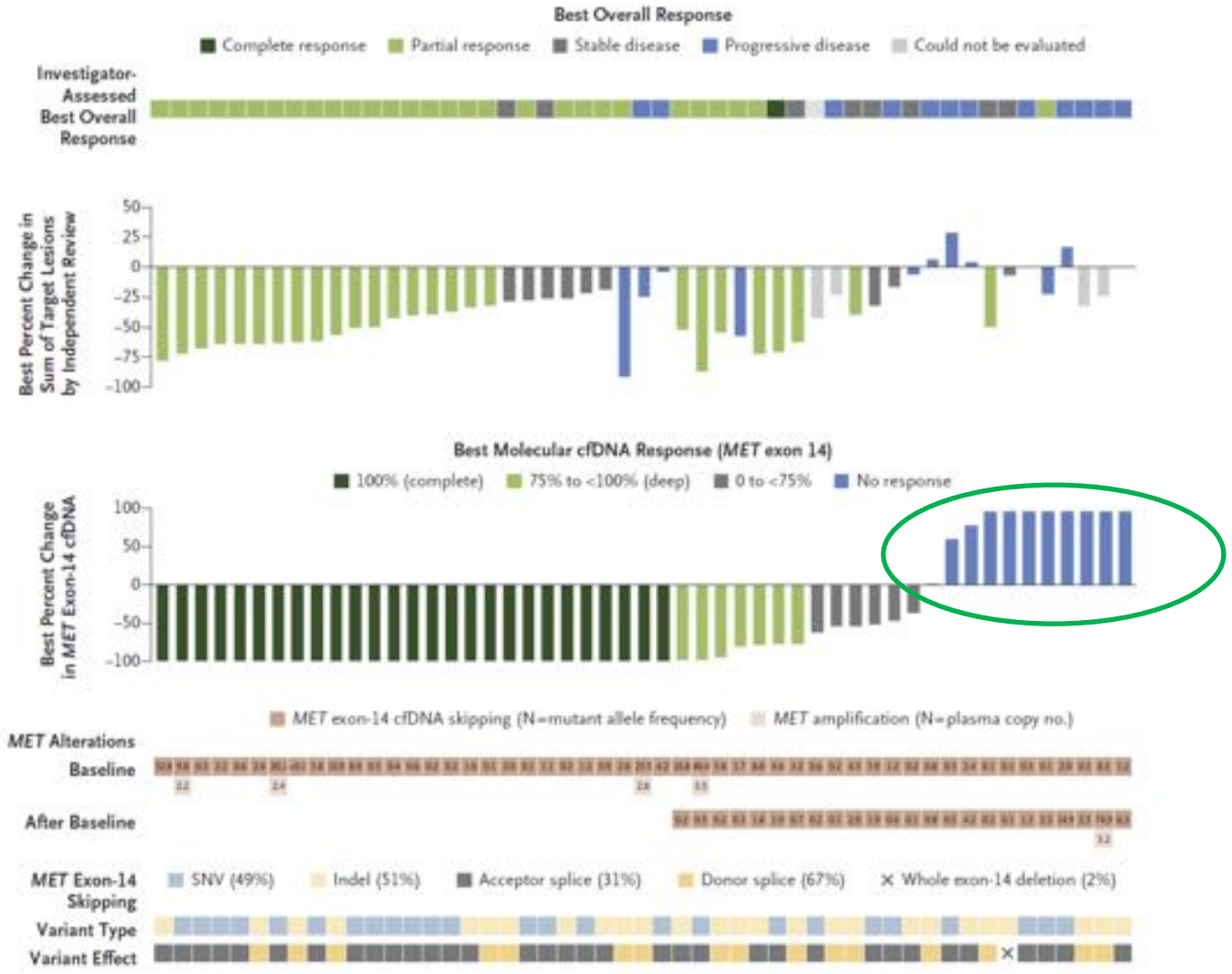
Alexander T. et al. ONS 2021

MET inhibition: resistance mechanisms



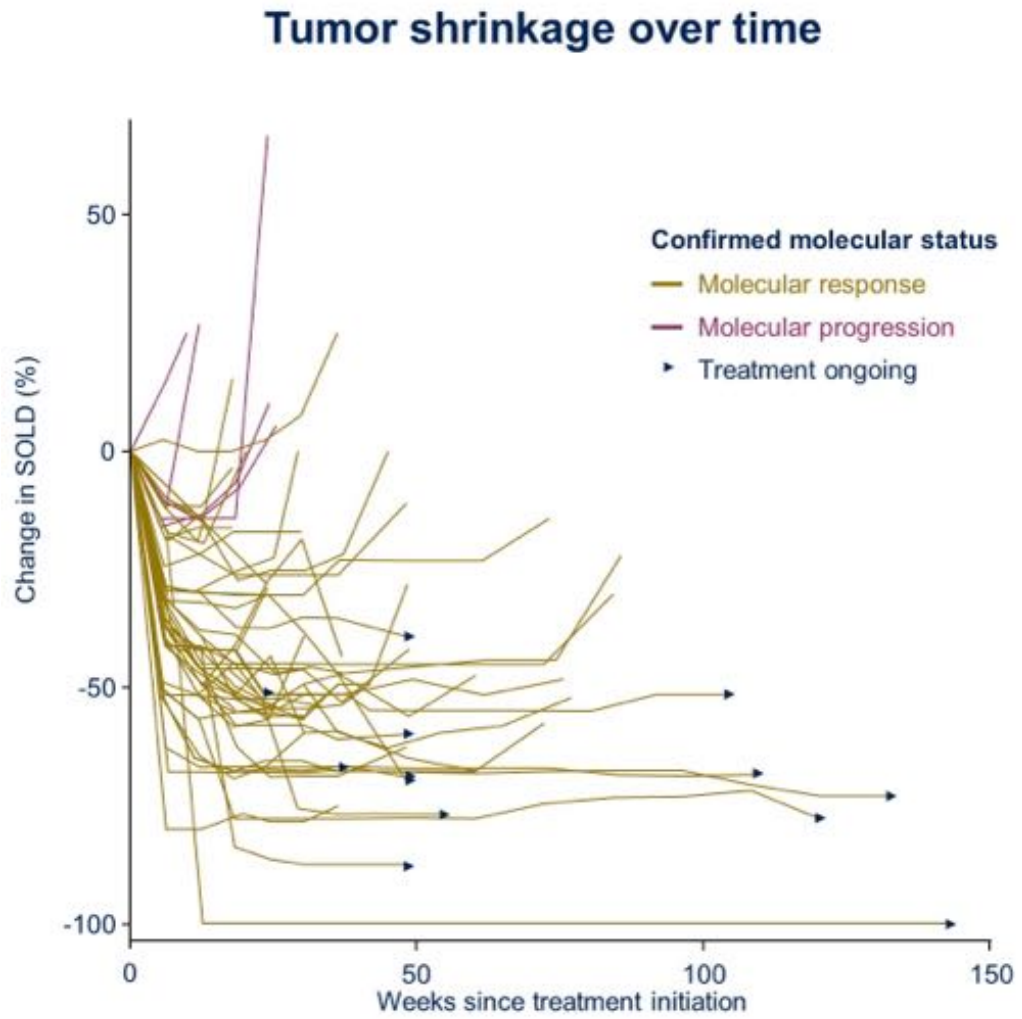
Paik PK, et al. NEJM 2020

MET inhibition: resistance mechanisms



Paik PK, et al. NEJM 2020

Molecular responses associated with clinical responses



Paik PK, ASCO 2021

Emerging resistance mechanisms were detected in samples taken at the time of disease progression

End-of-treatment

Emerging *MET* resistance mechanisms

Includes all patients with matched baseline + EOT biomarker profiles that discontinued due to disease progression; this includes patients with baseline liquid biopsy negative for *MET* exon 14 skipping who were enrolled based on *MET* exon 14 skipping detection in tissue biopsy

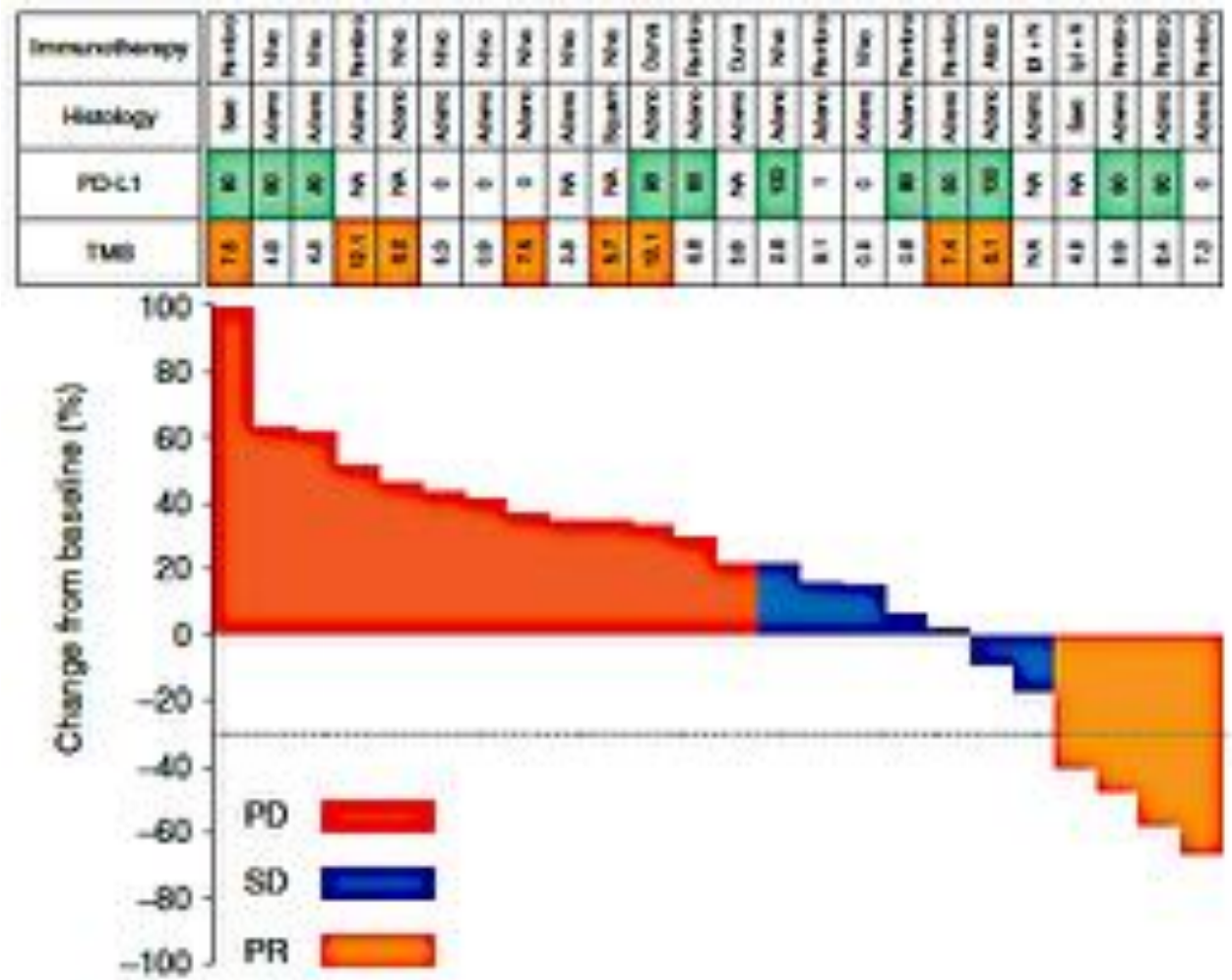
N=52

MET kinase domain mutations	Other *MET* mutations	Best objective response	PFS, months
D1228N	–	Partial response	11.2
D1228H	–	Partial response	11.1
Y1230H	G685E	Complete response	11.0
D1228N	–	Partial response	11.0
D1228G	–	Partial response	10.6
Y1230H/C	–	Partial response	6.9
–	G344R	Stable disease	5.6
Y1230H/C		Partial response	4.2
–	S156L	Stable disease	4.2

- *MET* kinase domain mutations, which were not present at Week 6 or 12, were detected at EOT in 7/52 patients (13%)
  - All patients with emerging Y1230 and D1228 mutations were responders and 5/7 had PFS >10 months
  - Other *MET* mutations (of unknown functional significance) were detected in three patients

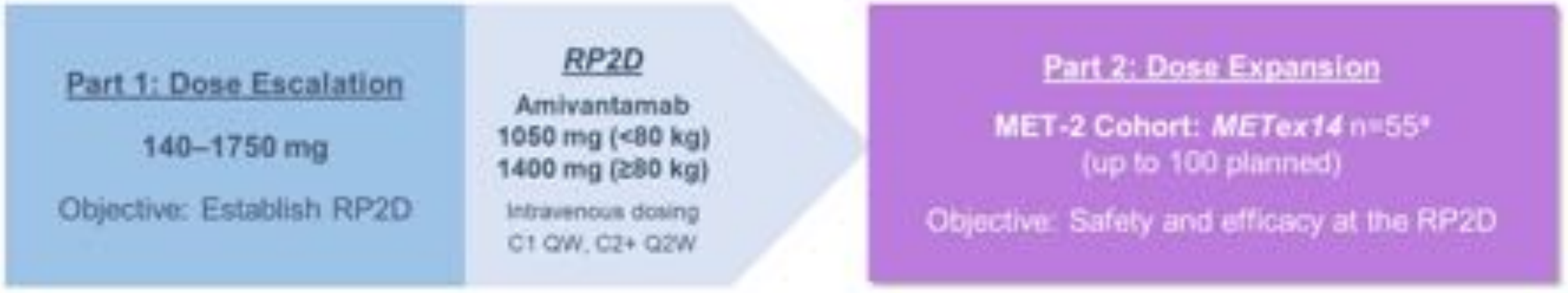
Paik PK, ASCO 2021

Immunotherapy in MET+ lung cancer: concern for potential resistance



Sabari JK, et al. *Ann Oncol.* 2018;29(10):2085-2091.

CHRYSALIS Phase 1: METex14 Population



Eligibility

- Metastatic or unresectable/advanced NSCLC
- Failed or ineligible for standard of care therapy

Eligibility for METex14 Cohort

- Measurable disease
- Primary METex14 mutation by NGS of tumor or ctDNA

[a]As of April 11, 2022 (clinical cutoff).
C, cycle; ctDNA, circulating tumor DNA; NGS, next generation sequencing; NSCLC, non-small cell lung cancer; QW, once weekly; Q2W, every two weeks; RP2D, recommended phase-2 dose; SOC, standard of care

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METex14 Cohort Demographics and Baseline Characteristics

- As of April 11, 2022, 55 patients had been enrolled in the METex14 cohort, 28 of whom had prior MET inhibitor therapy

Characteristic, n (%)	Treatment-naive, n=9	Previously-treated		Total, n=55
		No Prior MET Inhibitor,[a] n=18	Prior MET Inhibitor, n=28	
Median age, years (range)	70 (57–75)	69.5 (49–80)	70 (43–88)	70 (43–88)
Female / Male	5 (56) / 4 (44)	11 (61) / 7 (39)	16 (57) / 12 (43)	32 (58) / 23 (42)
Race				
Asian	5 (56)	9 (50)	14 (50)	28 (51)
White	4 (44)	7 (39)	10 (36)	21 (38)
Black	0	0	1 (4)	1 (2)
Not reported	0	2 (11)	3 (11)	5 (9)
History of brain metastases	1 (11)	2 (11)	**7 (25)**	10 (18)
Smoking history				
Non-smoker	4 (44)	9 (50)	16 (57)	29 (53)
Smoker	5 (56)	9 (50)	12 (43)	26 (47)
Median number of prior lines (range)	0	1.5 (1–4)	**3 (1–10)**	2 (0–10)

[a]Previously-treated, MET inhibitor-naive patients. METex14, MET exon 14 skipping mutations.

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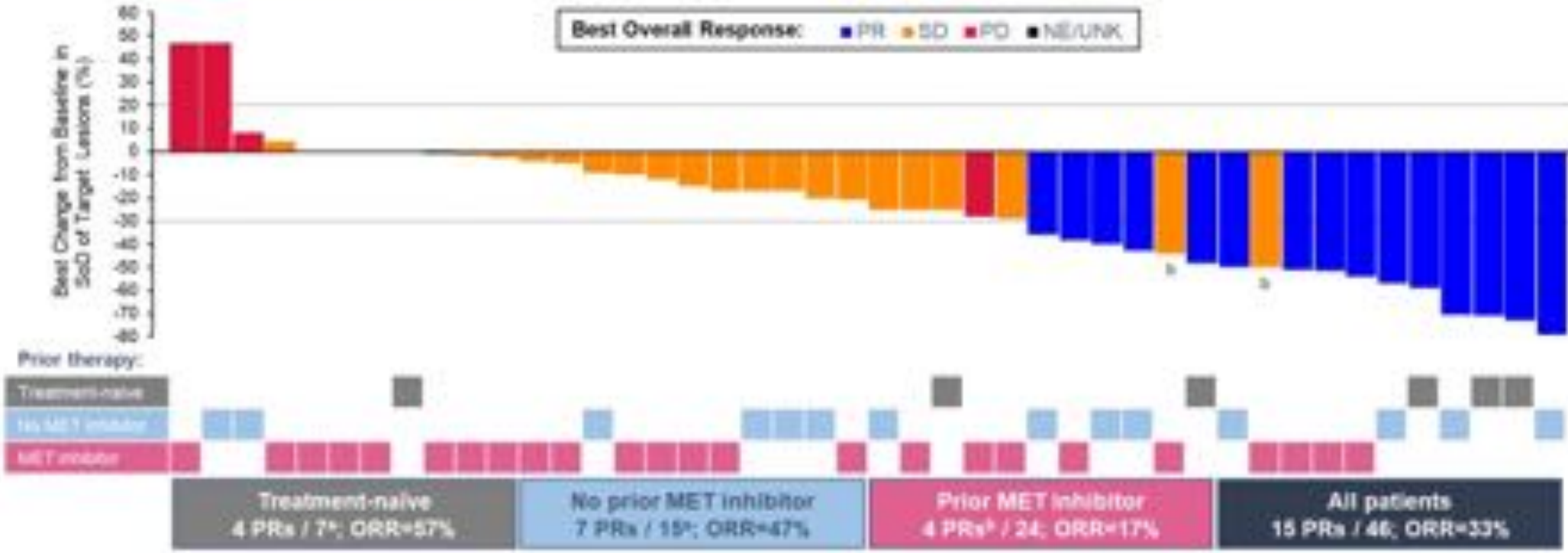
ASCO KNOWLEDGE CONQUERS CANCER

Antitumor Activity of Amivantimab Monotherapy

- A total of 46 patients were efficacy evaluable



*Two patients discontinued prior to completing their second postbaseline disease assessment (1 in treatment naive group and 1 in no prior MET inhibitor group). [b]Two additional patients had a best timepoint response of PR but did not confirm. NE/UNK, not evaluable/unknown; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; SoD, sum of diameters; TKI, tyrosine kinase inhibitor.

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Safety Profile

TEAE (≥15%) by Preferred Term, n (%)	RP2D (n=425) Median follow-up 11.8 months		METex14 Subset (n=55) Median follow up 5.1 months	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Infusion related reaction	283 (67)	11 (3)	38 (69)	3 (5)
Rash	155 (36)	8 (2)	17 (31)	1 (2)
Dermatitis acneiform	155 (36)	4 (1)	22 (40)	0
Paronychia	193 (45)	7 (2)	21 (38)	0
Fatigue	93 (22)	8 (2)	17 (31)	2 (4)
Hypoalbuminemia	135 (32)	10 (2)	15 (27)	1 (2)
Stomatitis	91 (21)	2 (0.5)	15 (27)	0
Decreased appetite	76 (18)	2 (0.5)	12 (22)	0
Dyspnea	96 (23)	21 (5)	12 (22)	4 (7)
Peripheral edema	104 (24)	4 (1)	11 (20)	0
Pruritus	79 (19)	0	12 (22)	0
Nausea	104 (24)	2 (0.5)	11 (20)	0
Constipation	105 (25)	0	10 (18)	0
Hypomagnesemia	41 (10)	0	9 (16)	0
Aspartate aminotransferase increased	64 (15)	5 (1)	9 (16)	1 (2)
Alanine aminotransferase increased	72 (17)	10 (2)	8 (15)	1 (2)
Cough	78 (18)	0	3 (5)	0

- Treatment modifications due to toxicity (n=425): interruptions in 21%, reductions in 12%, and discontinuations in 5% of patients
  - Rates of pneumonitis/ILD was 4%
  - Cumulative grouped rash-related AEs[a] occurred in 322 (76%) patients, with 16 grade ≥3 (4%)
- Safety profile for METex14 subset is consistent with the larger CHRYSALIS safety population, with majority of events grade 1-2
- No new safety signals found

[a]Rash-related terms include rash, dermatitis acneiform, acne, blister, dermatitis, dermatitis atopic, dermatitis exfoliative generalized, dermatitis infected, eczema asteatotic, erythema, erythema multiforme, folliculitis, hand dermatitis, macule, palmar-plantar erythrodysaesthesia syndrome, perineal rash, perioral dermatitis, pustule, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin lesion, and toxic epidermal necrolysis. cumulative grouped rash-related AEs occurred 39 (69%; grade ≥3, 2 [4%]) patients for the METex14 subset. AE, adverse event; ILD, interstitial lung disease; METex14, MET exon 14 skipping mutations; RP2D, recommended phase-2 dose; TEAE, treatment-emergent AE.

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Teliso-V (MET ADC) + erlotinib (H-score ≥ 150)

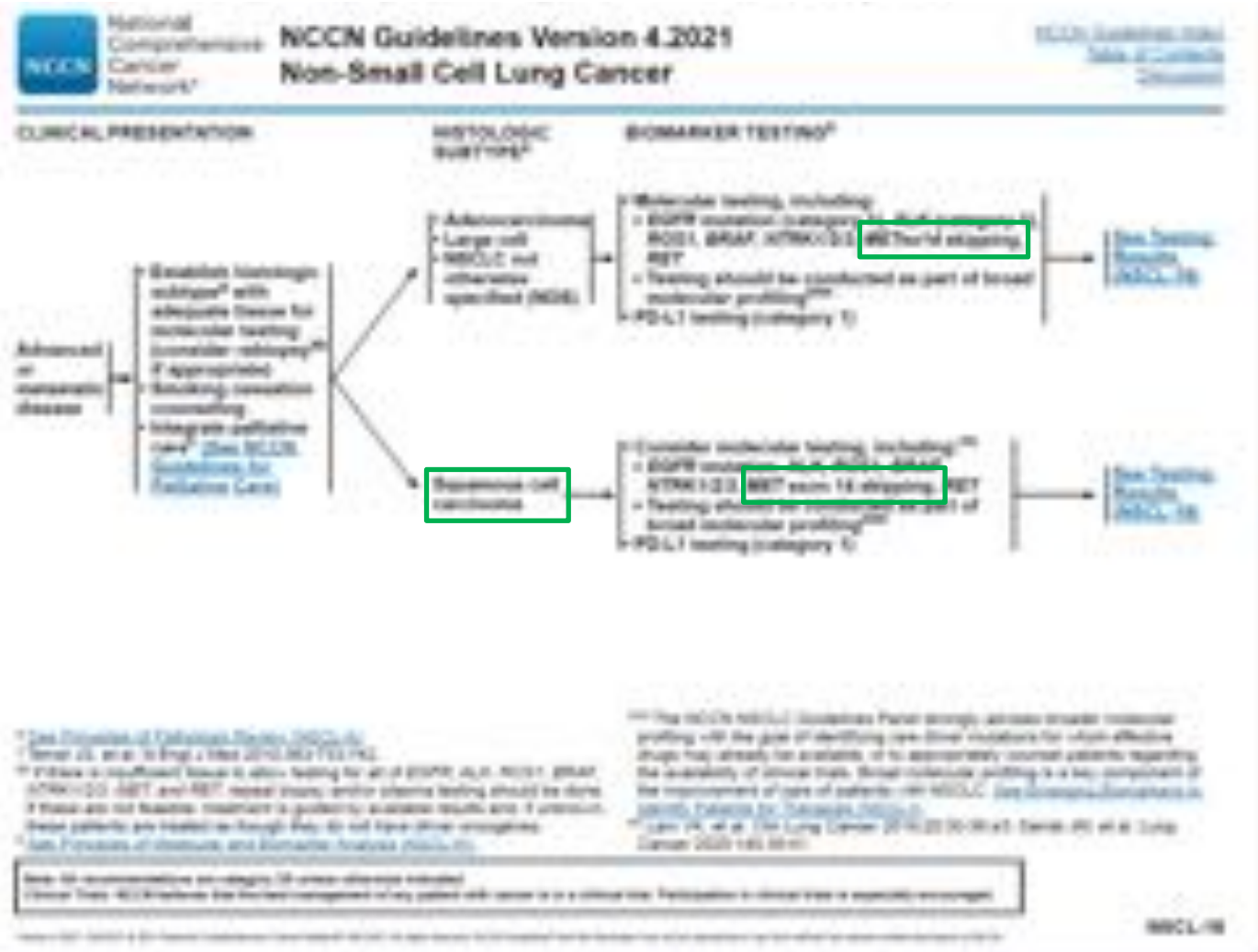
TABLE 2. Adverse Events

Adverse Event	Teliso-V Plus Erlotinib (N = 42), No. (%)	
	Any Grade (≥ 10% of Patients)	Grade ≥ 3 (≥ 5% of Patients)
Any adverse event	42 (100)	27 (64)
Peripheral sensory neuropathy	18 (43)	3 (7)
Dermatitis acneiform	16 (38)	2 (5)
Diarrhea	14 (33)	3 (7)
Hypoalbuminemia	14 (33)	0
Fatigue	13 (31)	2 (5)
Dyspnea	12 (29)	2 (5)
Decreased appetite	10 (24)	1 (2)
Nausea	10 (24)	0
Asthenia	9 (21)	2 (5)
Vomiting	9 (21)	0
Cough	8 (19)	0
Peripheral neuropathy	8 (19)	1 (2)

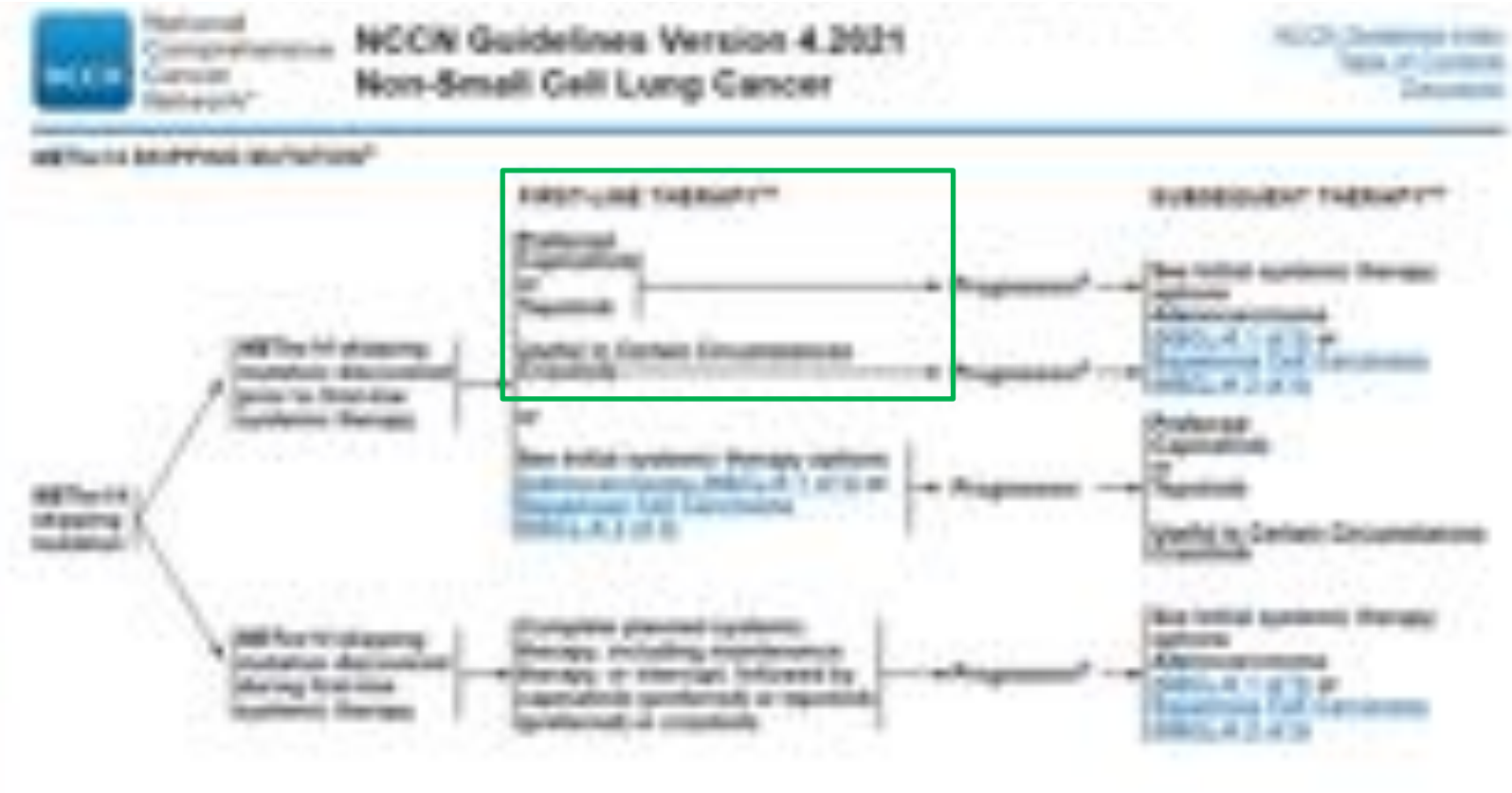
Response	Teliso-V Plus Erlotinib			
	c-Met+ *EGFR*-M+ (n = 28), No./n (%)	c-Met+ *EGFR*-WT (n = 5), No./n (%)	c-Met+ *EGFR*-Rare/Unknown (n = 3), No./n (%)	Total (N = 36), No./N (%)
Best overall response[a]				
Complete response	1/28 (4)	0/5	0/3	1/36 (3)
Partial response	8/28 (29)	2/5 (40)	0/3	10/36 (28)
Stable disease	15/28 (54)	2/5 (40)	3/3 (100)	20/36 (56)
Progressive disease	4/28 (14)	1/5 (20)	0/3	5/36 (14)
Objective response rate[b] [95% CI]	9/28 (32.1) [15.9 to 52.4]	2/5 (40.0) [5.3 to 85.3]	0 [0.0 to 70.8]	11/36 (30.6) [16.3 to 48.1]
Disease control rate[c] [95% CI]	24/28 (85.7) [67.3 to 96.0]	4/5 (80.0) [28.4 to 99.5]	3/3 (100) [29.2 to 100]	31/36 (86.1) [70.5 to 95.3]
Progression-free survival				
Median, months [95% CI]	5.9 [2.8 to NR]	6.0 [1.2 to NR]	4.0 [1.6 to NR]	5.9 [2.8 to NR]

Camidge et al. JCO 2022

MET exon 14 testing is now standard of care



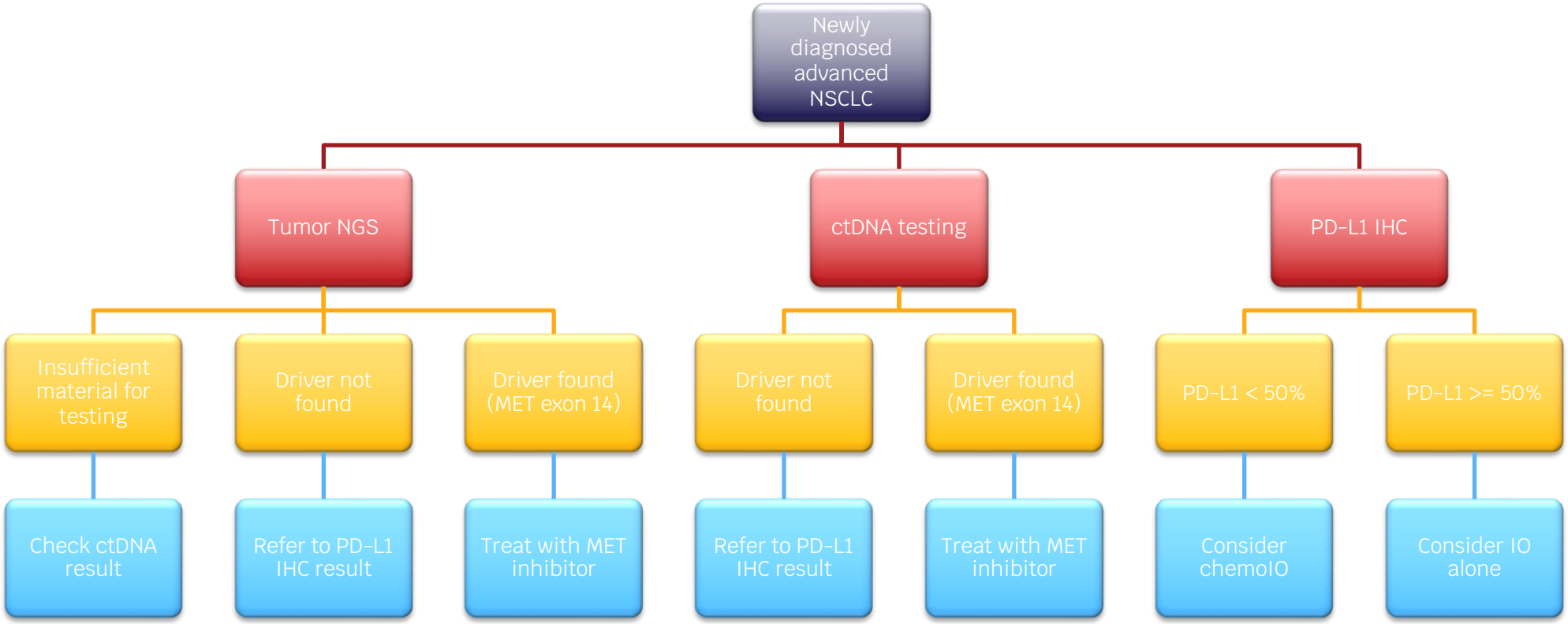
NCCN recommends first-line MET therapy for MET exon 14 skipping + patients



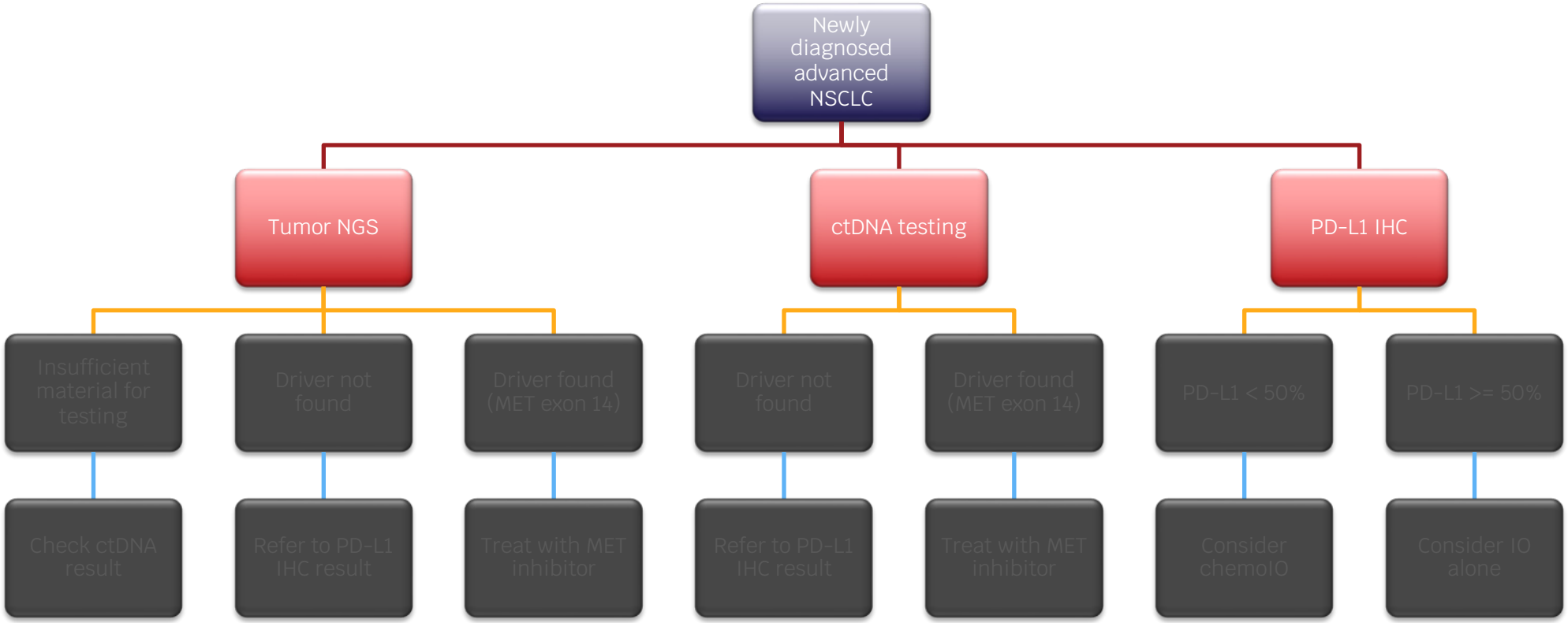
How to apply MET exon 14 testing as standard of care

- Next-generation sequencing (NGS) is standard of care for all newly diagnosed NSCLC patients
  - Will identify many potential actionable drivers such as EGFR, ALK fusions, MET exon 14, HER2, BRAF V600E, KRAS G12C, RET fusions, ROS1 fusions, NTRK fusions
- NGS should be performed on both tumor and blood simultaneously
- Tumor testing is gold standard (sensitivity/specificity) but:
  - Has issues with tissue availability/quantity
  - Is slower in turnaround
- ctDNA testing is increasingly being adopted up-front because:
  - Not invasive/easy to obtain
  - Faster turnaround time
- ctDNA testing is subject to false negatives based largely on tumor bulk and potential coverage limitations depending on country

How to apply MET exon 14 testing as standard of care: my algorithm



How to apply MET exon 14 testing as standard of care: my algorithm



Thank you!

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