MET AND NSCLC

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IASLC INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
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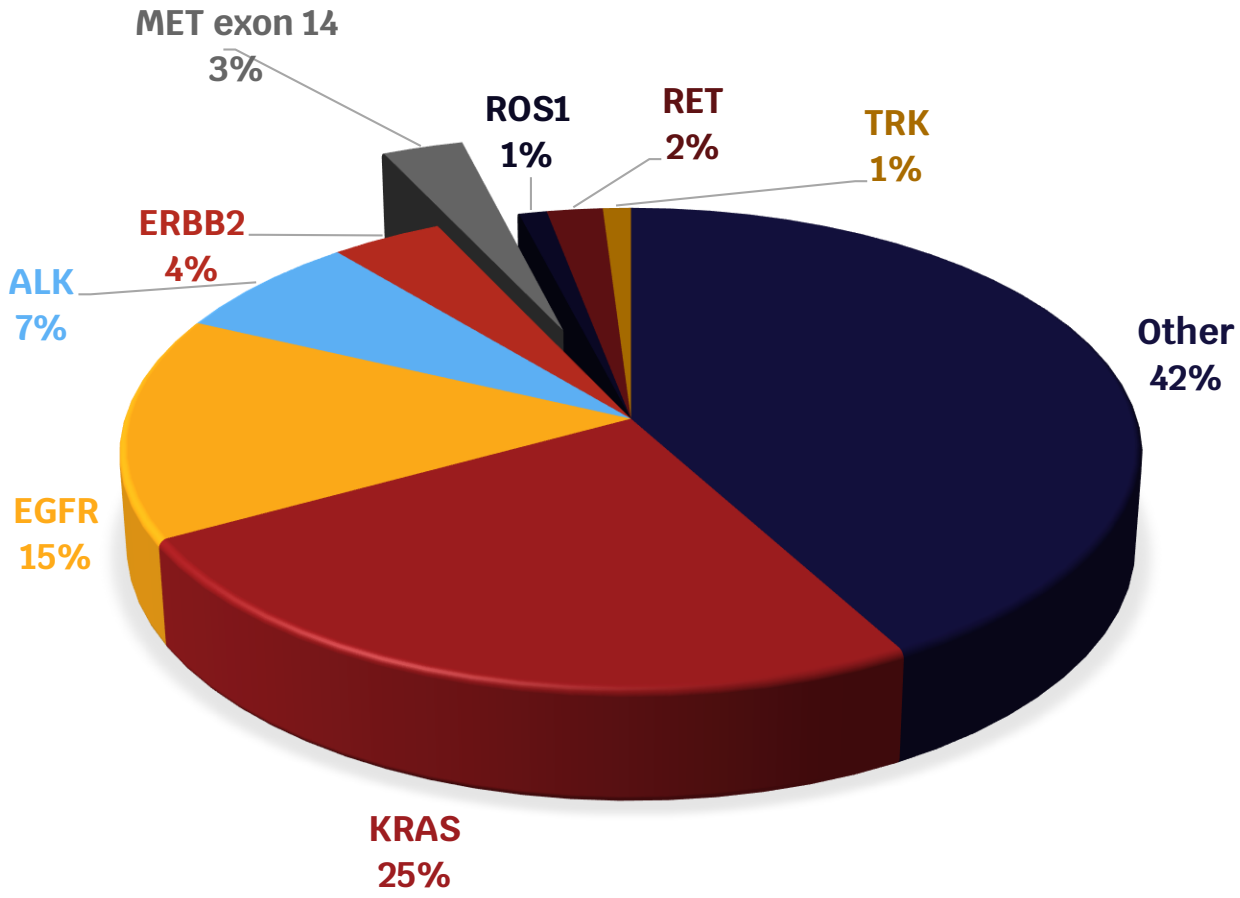
Overview

- MET exon 14 skipping
  - A bit of biology- what is it?
  - Unique population- who are these patients?
  - A bit of history- when did we start targeting it?
- MET inhibitors in patients with MET exon 14 skipping mutations
  - Efficacy and safety
  - Resistance mechanisms
  - LungMAP S1900K and other active efforts
- MET amplification as a primary driver
- What should the standard of care be for these patients?

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

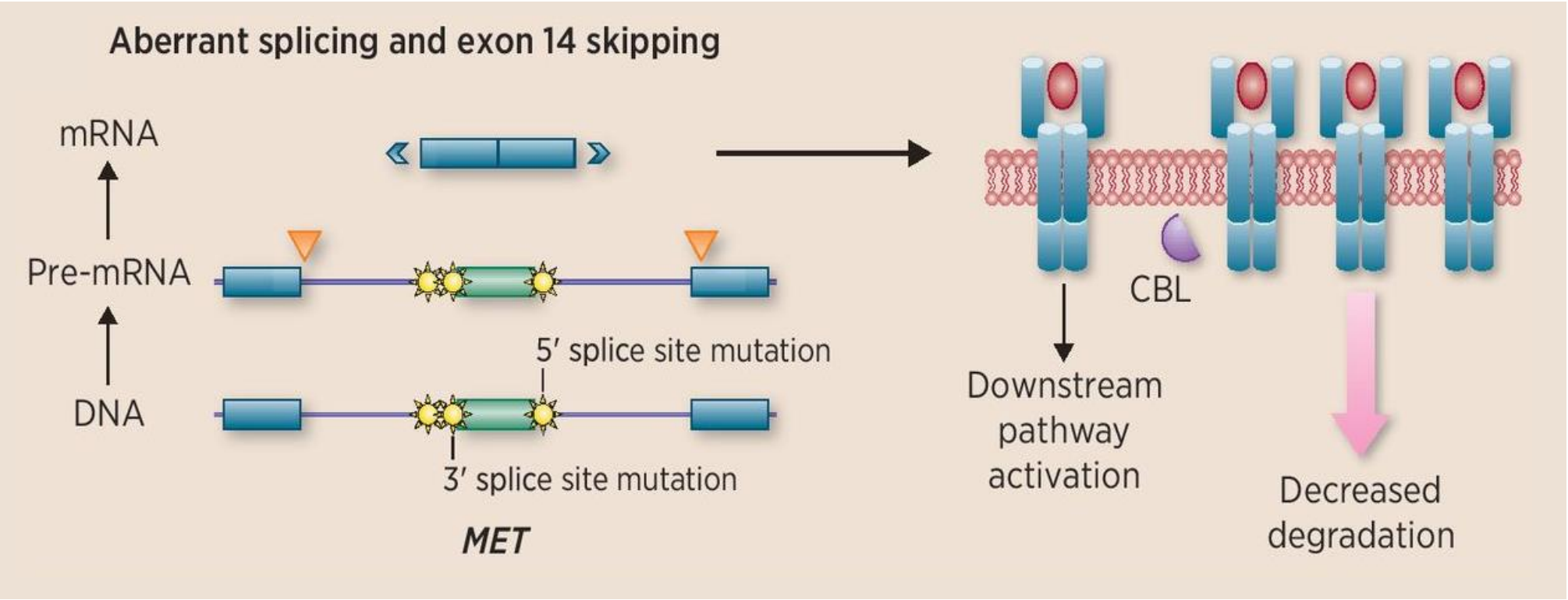


MET Background

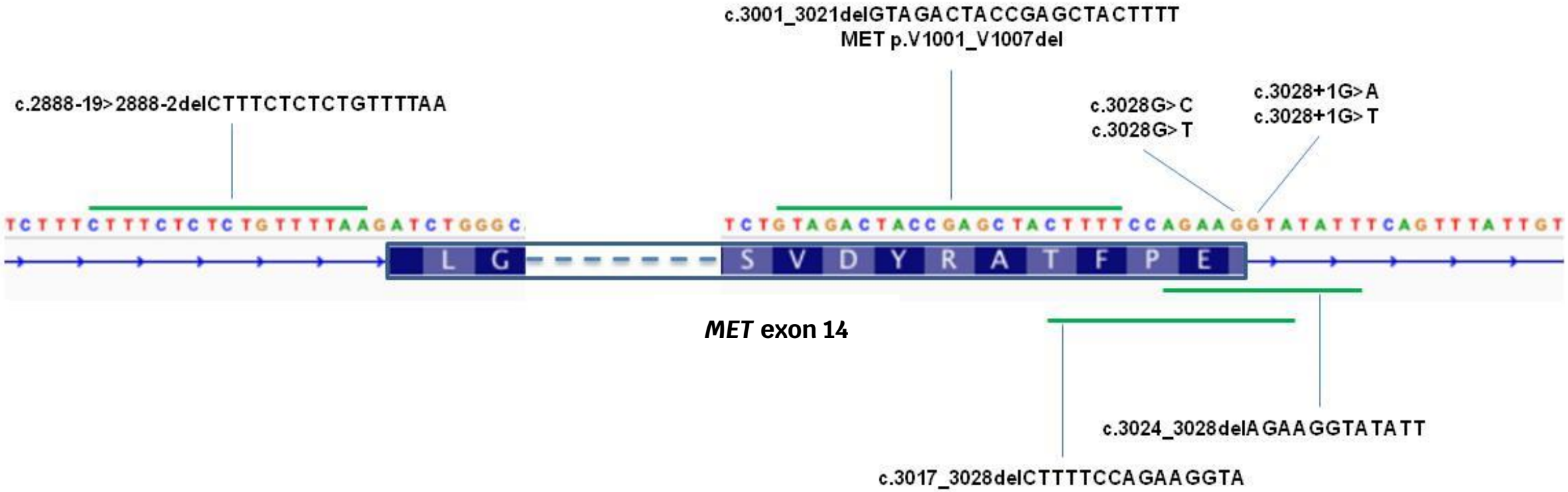
- MET receptor tyrosine kinase (RTK) is a proto-oncogene with roles in proliferation, apoptosis, and motility/invasion[1]
- Gain of function alterations include amplification and protein overexpression[2]
- These have been previous targets in lung cancer with no significant success (overexpression) or 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



MET Exon 14 Splice Site Mutations Are Heterogeneous



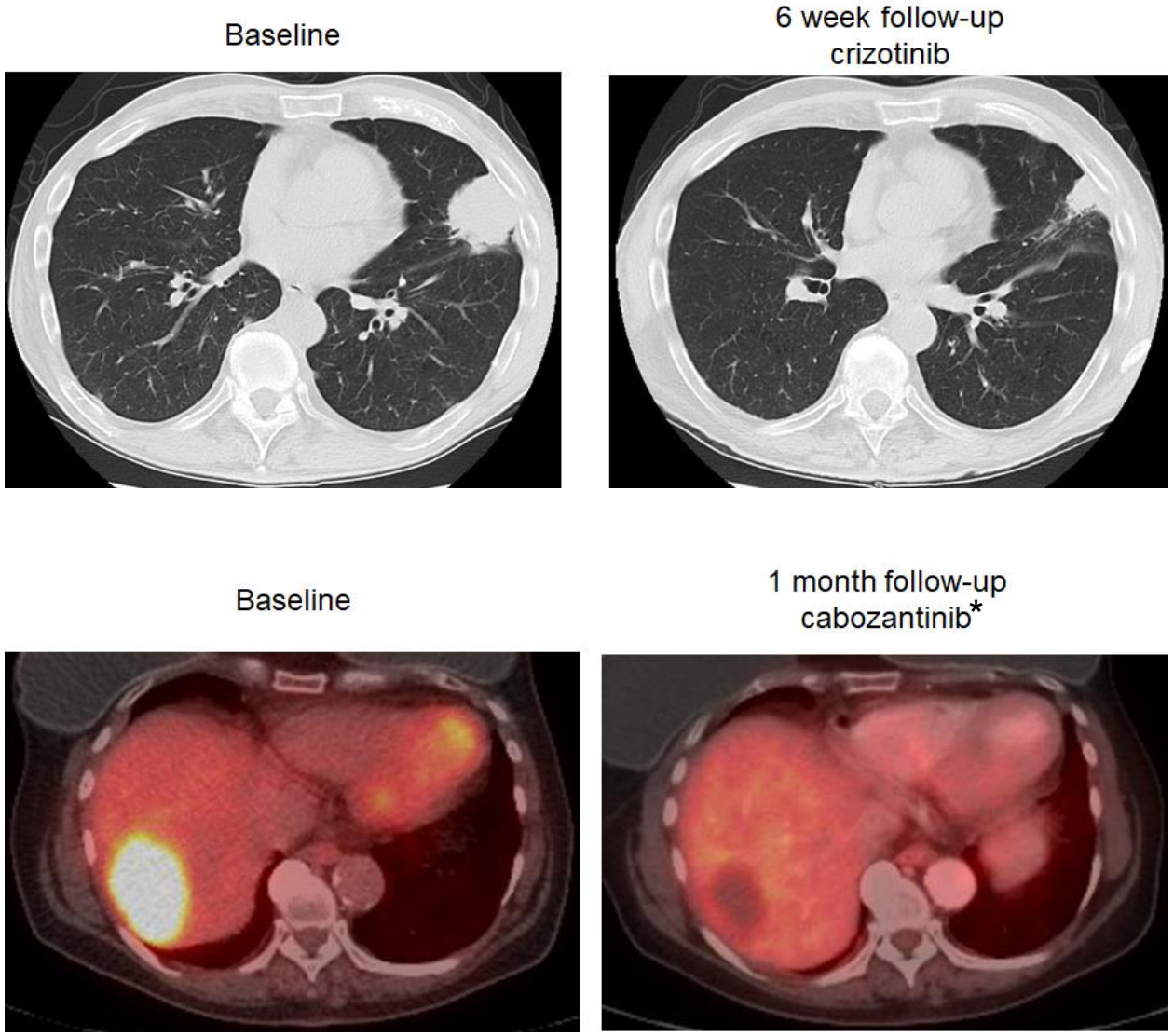
Paik PK, et al. *Cancer Discov*. 2015;5(8):842-849.

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]

Key inclusion criteria

- Advanced/metastatic NSCLC (all histologies)
- **Positive detection of *MET*ex14 skipping by liquid (ctDNA) and/or tissue biopsy (RNA)**
- ≤2 lines of prior therapy
- No prior treatment with therapies targeting the MET pathway

Cohort A*
*MET*ex14 skipping

Cohort C*
*MET*ex14 skipping
(confirmatory for Cohort A)

Tepotinib
500 mg
once daily†

Key endpoints

Primary endpoint:

- ORR by IRC

Secondary endpoints included:

- DCR, DOR, PFS, OS, HRQoL
- Safety and tolerability

GEOMETRY[3,4]

Figure 1. GEOMETRY mono-1 study design: *MET*ex14 cohorts

Selected eligibility criteria

- Age ≥18 years
- Stage IIIB/IV NSCLC
- *MET*ex14 irrespective of *MET* GCN by central RT-PCR
- *EGFR* wild-type (for L858R and delE19) and *ALK* rearrangement negative
- ECOG performance status 0-1
- ≥1 measurable lesion (RECIST 1.1)
- Neurologically stable or asymptomatic brain metastases allowed

Capmatinib
400 mg
Twice daily

Cohort 4
Pretreated 2/3L
N=69

Cohort 5b
Treatment-naive 1L
N=28

Cohort 6[a,b]
Pretreated 2L
N=31

Cohort 7[a]
Treatment-naive 1L
N=32

Primary endpoint

- Overall response rate (BIRC)

Key secondary endpoint

- Duration of response (BIRC)

Secondary endpoints

- Disease control rate (BIRC/investigator)
- Duration of response (investigator)
- Overall response rate (investigator)
- Time to response (BIRC/investigator)
- Progression-free survival (BIRC/investigator)
- Overall survival
- Safety
- Pharmacokinetics

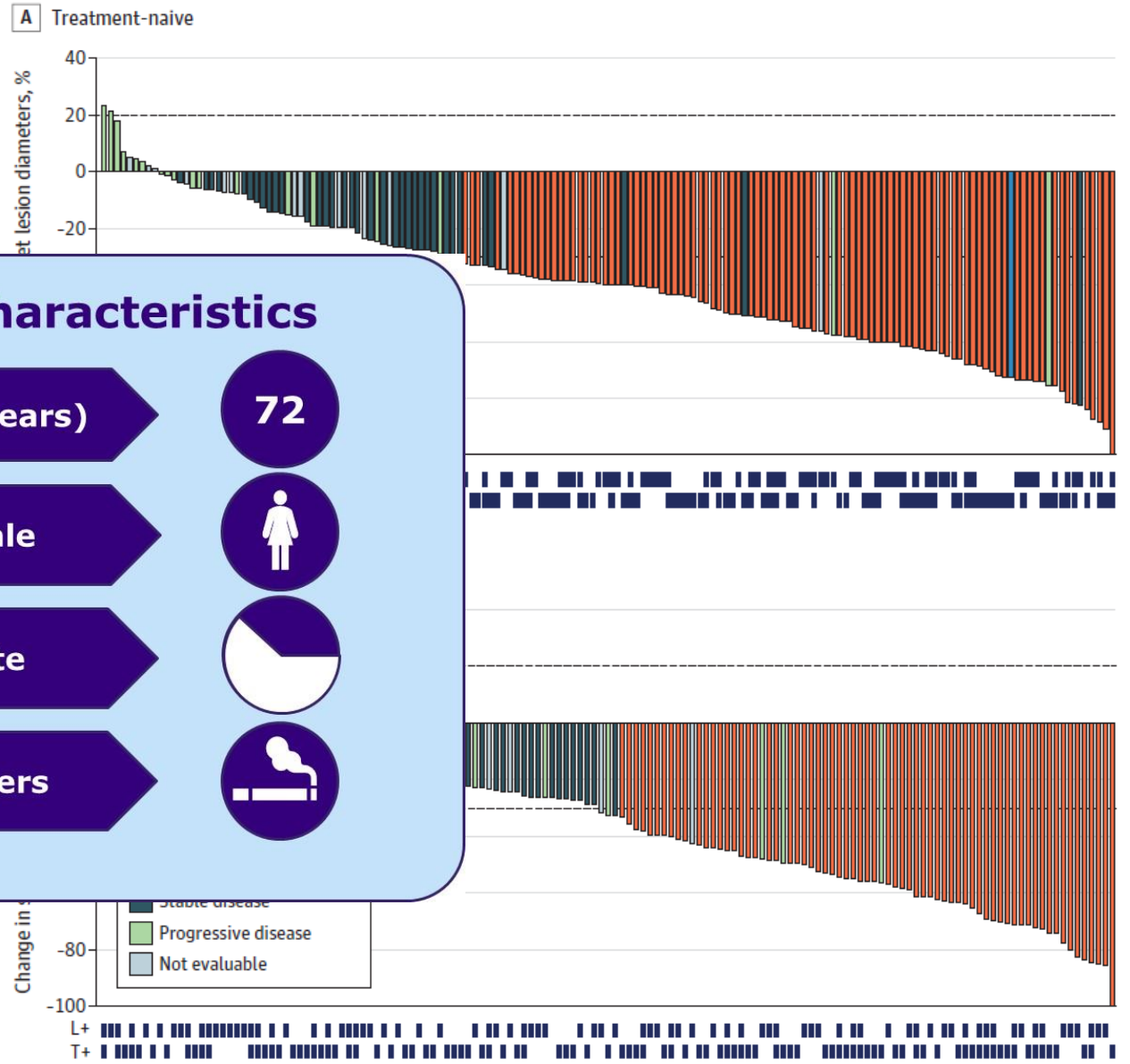
1. Felip E, et al. *WCLC* 2021. 2. Paik PK, et al. *N Engl J Med.* 2020;383(10):931-943. 3. Wolf J, et al. *ASCO* 2021; Abstract 9020. 4. Wolf J, et al. *N Engl J Med.* 2020;383:944–957.

VISION update 2023

	Cohort A+C (N=313)	Treatme Naïve (N=164
ORR, % (95% CI)	51.4 (45.8-57.1)	57.3 (49.4-65.
mDOR, months (95% CI)	18.0 (12.4, 46.4)	46.4 (13.8-NE
mPFS, months (95% CI)	11.2 (9.5, 13.8)	12.6 (9.7-17.
mOS, months (95% CI)	19.6 (16.2, 22.9)	21.3 (14.2-25.

Patient characteristics

- Average age (years): 72
- 50.8% female
- 62.3% white
- 47.6% smokers



Paik et al. ASCO 2023
Mazieres et al., JAMA Onc 2023

GEOMETRY efficacy update 2021: treatment-naive

	Treatment-naive			Pretreated		
	Cohort 5b N=28	Cohort 7 N=32	All patients N=60	Cohort 4 (2/3L) N=69	Cohort 6 (2L) N=31	All patients N=100
Best overall response, n (%)						
Complete response	1 (3.6)	0	1 (1.7)	0	0	0
Partial response	18 (64.3)	21 (65.6)	39 (65.0)	28 (40.6)	16 (51.6)	44 (44.0)
Stable disease	7 (25.0)	11 (34.4)	18 (30.0)	25 (36.2)	11 (35.5)	36 (36.0)
Non-complete response/ non-progressive disease	1 (3.6)	0	1 (1.7)	1 (1.4)	1 (3.2)	2 (2.0)
Progressive disease	1 (3.6)	0	1 (1.7)	6 (8.7)	0	6 (6.0)
Not evaluable[a]	0	0	0	9 (13.0)	3 (9.7)	12 (12.0)
ORR,[b] % (95% CI)	67.9 (47.6-84.1)	65.6 (46.8-81.4)	66.7 (53.3-78.3)	40.6 (28.9-53.1)	51.6 (33.1-69.8)	44.0 (34.1-54.3)
DCR,[c] % (95% CI)	96.4 (81.7-99.9)	100.0 (89.1-100.0)	98.3 (91.1-100.0)	78.3 (66.7-87.3)	90.3 (74.2-98.0)	82.0 (73.1-89.0)
DOR events,[d] n (%)	12 (63.2)	5 (23.8)	17 (42.5)	23 (82.1)	11 (68.8)	34 (77.3)
Median DOR, months (95% CI)	12.6 (5.6-NE)	NE (5.5-NE)	12.6 (8.4-NE)	9.7 (5.6-13.0)	8.4 (4.2-NE)	9.7 (5.6-13.0)
PFS events, n (%)	18 (64.3)	14 (43.8)	32 (53.3)	60 (87.0)	22 (71.0)	82 (82.0)
Median PFS, months (95% CI)	12.4 (8.2-23.4)	10.8 (6.9-NE)	12.3 (8.2-21.6)	5.4 (4.2-7.00)	6.9 (4.2-13.3)	5.5 (4.2-8.1)

Wolf et al. 9020 ASCO 2021

GEOMETRY efficacy update 2021: previously treated

	Treatment-naive			Pretreated		
	Cohort 5b N=28	Cohort 7 N=32	All patients N=60	Cohort 4 (2/3L) N=69	Cohort 6 (2L) N=31	All patients N=100
Best overall response, n (%)						
Complete response	1 (3.6)	0	1 (1.7)	0	0	0
Partial response	18 (64.3)	21 (65.6)	39 (65.0)	28 (40.6)	16 (51.6)	44 (44.0)
Stable disease	7 (25.0)	11 (34.4)	18 (30.0)	25 (36.2)	11 (35.5)	36 (36.0)
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Progressive disease	1 (3.6)	0	1 (1.7)	6 (8.7)	0	6 (6.0)
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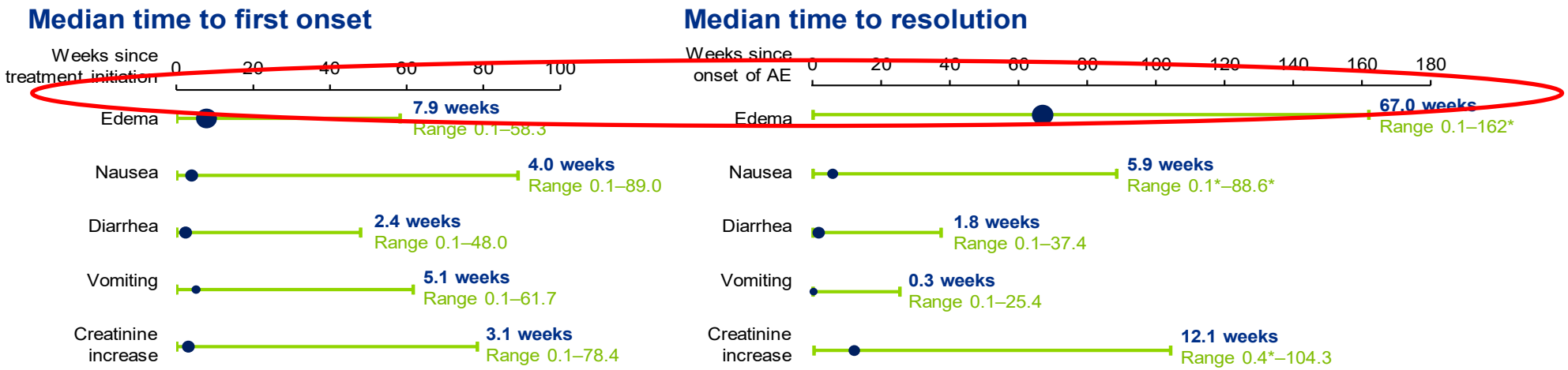
Wolf et al. 9020 ASCO 2021

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

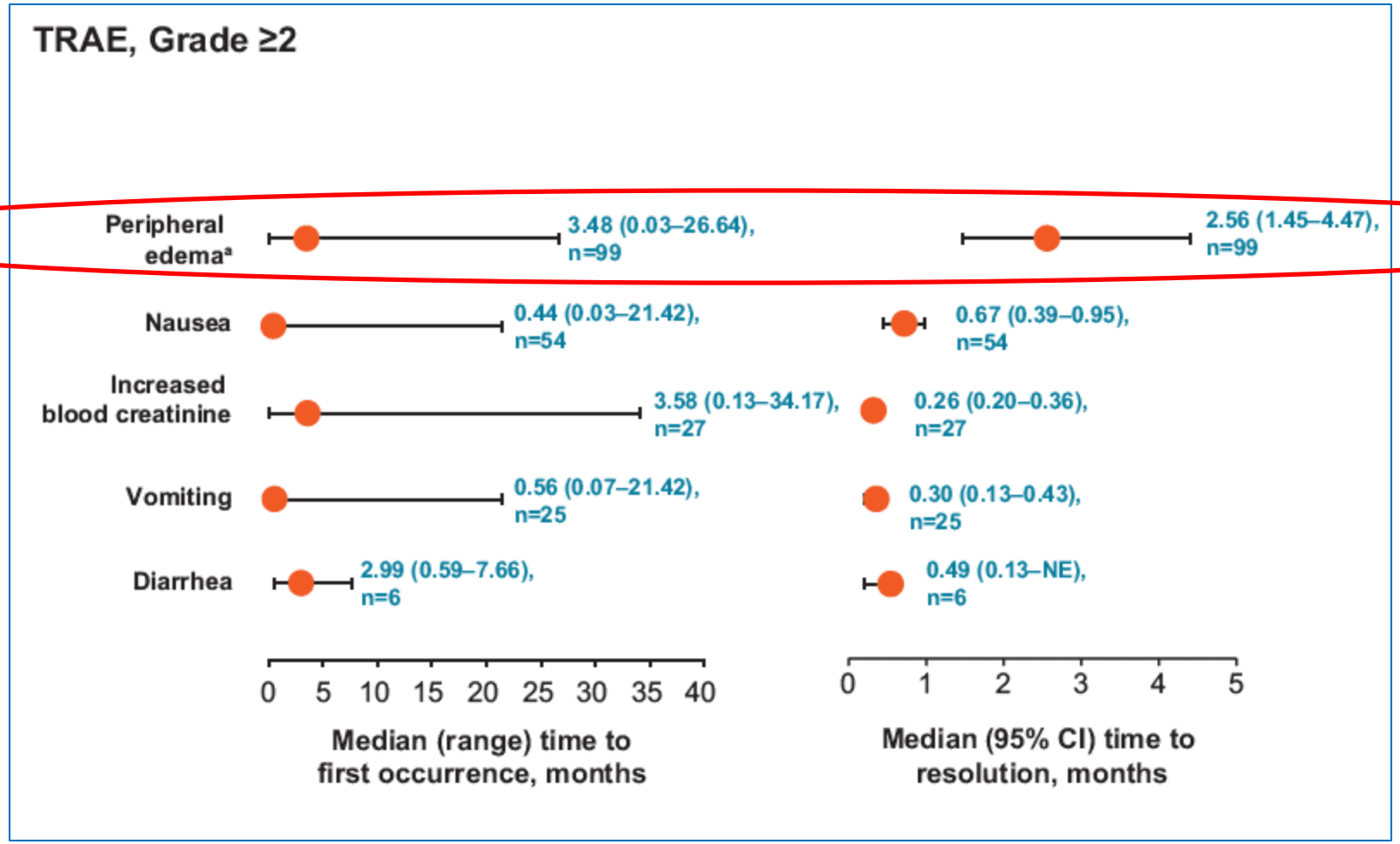


Events, n	Edema (n=178)	Nausea (n=68)	Diarrhea (n=67)	Vomiting (n=33)	Creatinine increase (n=66)
Total	337	87	112	47	96
Resolved at time of analysis	115	67	102	44	67

Analyses of time to first onset and time to resolution were carried out for AEs of clinical interest, including composite categories comprising preferred terms, and were analyzed irrespective of causal relation to study treatment. Time to first onset was described by median and range for observed AEs, not accounting for competing events. Time to resolution was analyzed using Kaplan–Meier method in a descriptive manner, not accounting for the fact that one patient could contribute by more than one event of the respective AE. *Denotes a censored value.
AE, adverse event.

Veillon et al. WCLC 2020

Capmatinib AE kinetics similar to tepotinib



Heist et al. ESMO 2021

Drug selectivity as a window into therapeutic approach: cabozantinib has notably low rates of edema

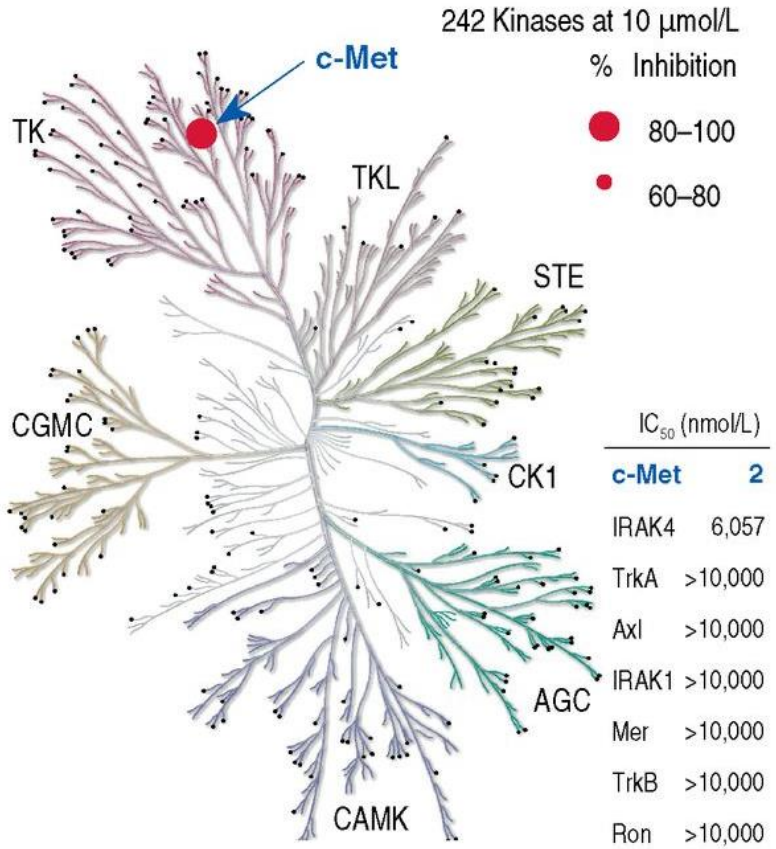
Study	Drug	Disease	Peripheral edema, % all grade
Abou-alfa et al. NEJM 2018	Cabozantinib	Hepatocellular carcinoma	13%
Choueiri et al. NEJM 2015	Cabozantinib	Renal cell carcinoma	9%
Smith et al. J Clin Oncol 2016	Cabozantinib	Prostate cancer	15%
Drilon et al. Lancet Oncol 2017	Cabozantinib	RET+ lung cancer	<5%
Paik et al. NEJM 2020	Tepotinib	MET exon 14+ lung cancer	58%
Wolf et al. NEJM 2020	Capmatinib	MET exon 14+ lung cancer	54%

Cabozantinib kinase profile: exquisite VEGFR2 inhibition, similar MET potency as MET TKIs

Kinase	$IC_{50} \pm SD$,[a] nmol/L	Enzyme concentration, nmol/L	ATP concentration, μmol/L	Assay
VEGFR2	0.035 ± 0.01	0.05	3	A
MET	1.3 ± 1.2	10	1	C
MET (Y1248H)	3.8	13	1	C
MET (D1246N)	11.8	12	1	C
MET (K1262R)	14.6	12	1	C
RET	5.2 ± 4.3	15	2	C
TIE2	14.3 ± 1.1	15	5	R
AXL	7	TBD	TBD	TBD
FLT3	11.3 ± 1.8	0.5	1	C
KIT	4.6 ± 0.5	1	3	A
RON	124 ± 1.2	60	1	C

Abbreviations: A, AlphaScreen; C, Coupled luciferase; R, radiometric; TBD, to be determined.
[a]Mean ± SD of at least 3 independent determinations.

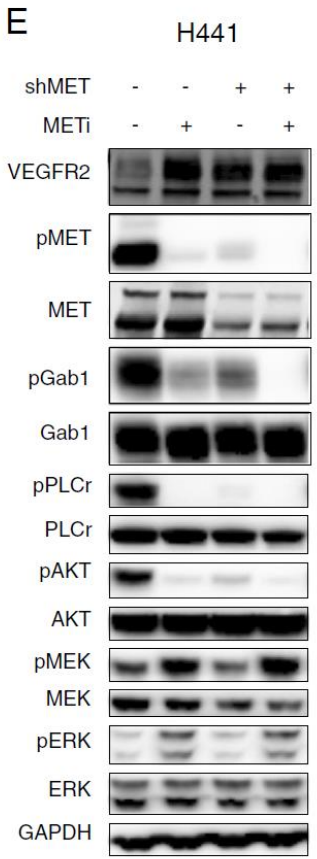
Cabozantinib

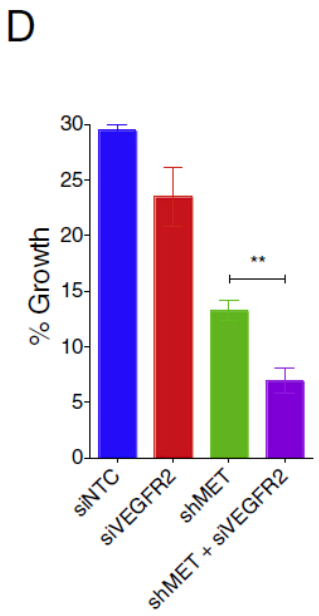


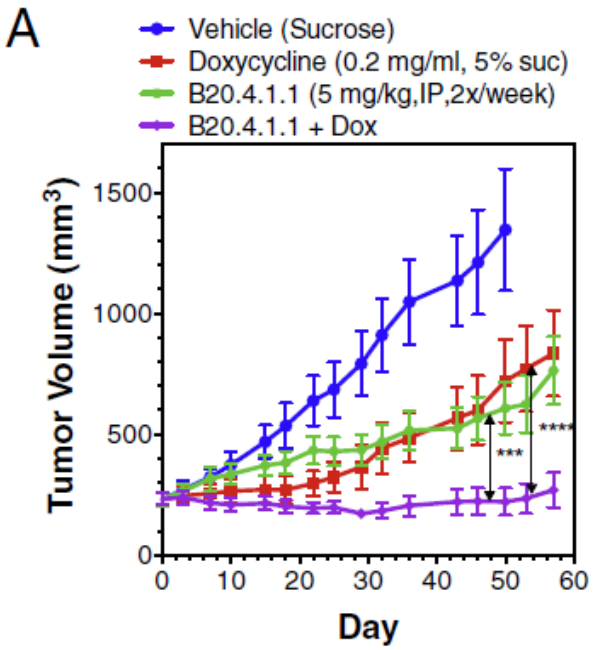
Tepotinib

Bladt et al. Clin Cancer Res 2013; Yakes et al. Mol Cancer Ther 2011

MET and VEGF signaling: MET inhibition causes VEGFR2 upregulation, can be co-targeted to engender further anti-tumor activity





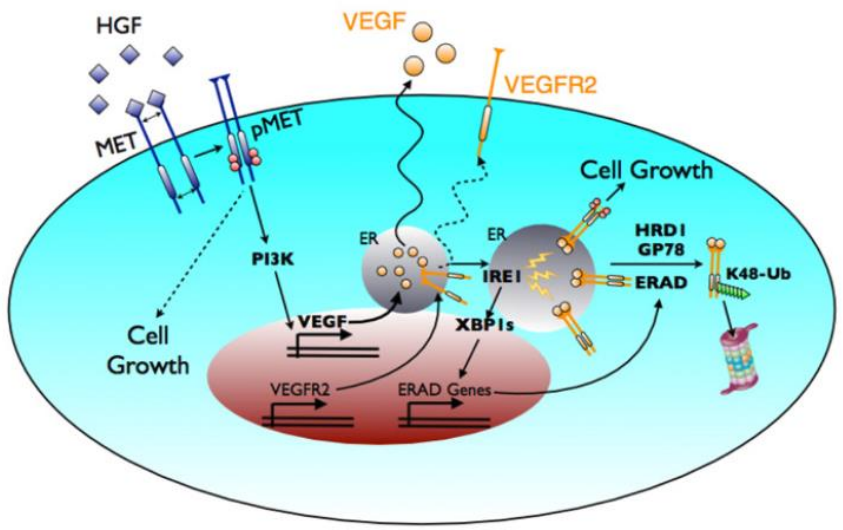


H411 adenoca xenograft,
shMET (doxy inducible)
B20.4.1.1 = anti-VEGF ab

Chen et al. EBioMedicine 2015

Model: MET inhibition relieves VEGFR2 degradation, engenders compensatory switch to VEGFR2 signaling

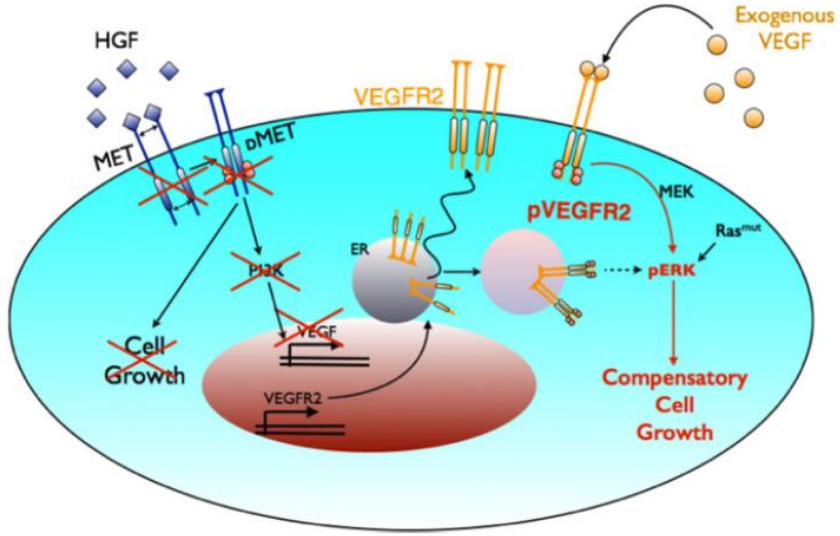
H



HGF/MET On

MET induced VEGF via PI3K, folded in ER with VEGFR2 -> ubiquitination and degradation

I

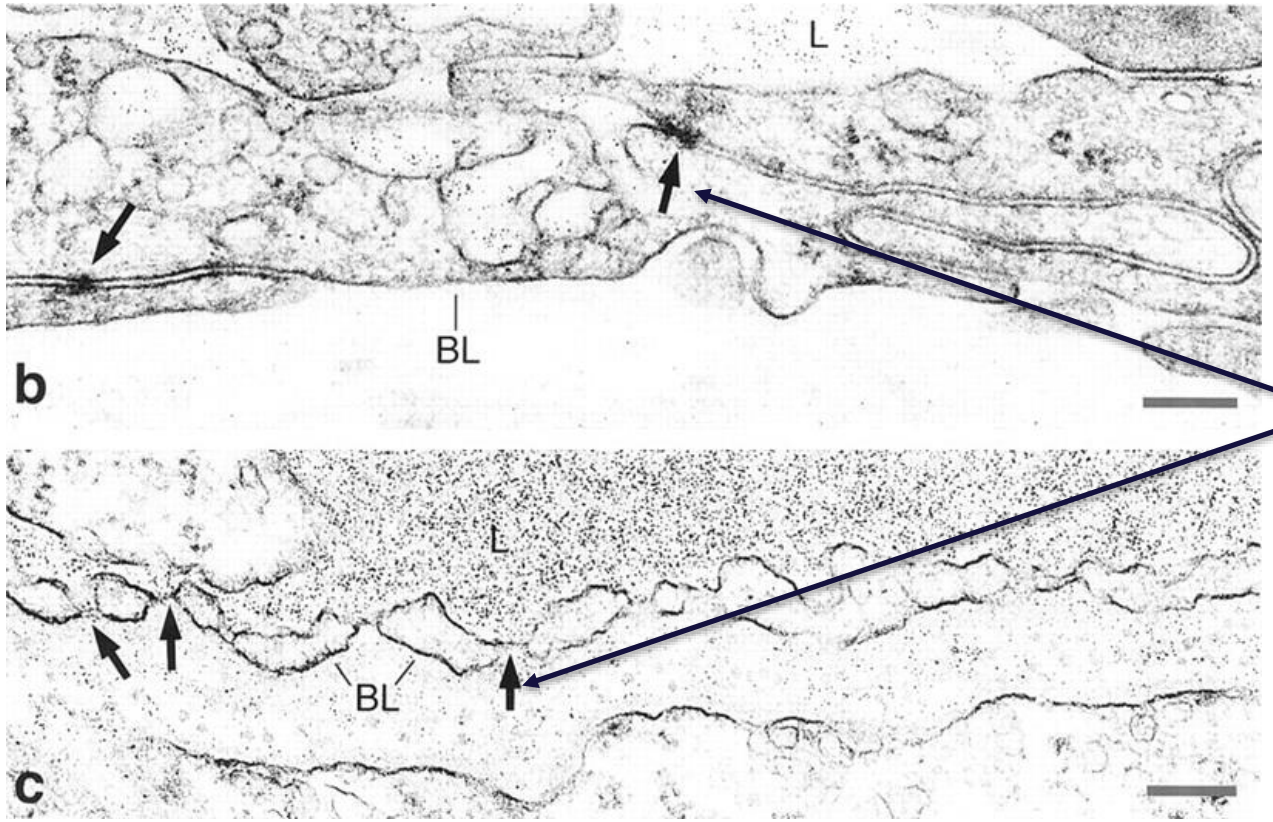


HGF/MET Off

MET inhibition shuts off VEGF induction, prevents VEGFR2 degradation, potentiates VEGFR2 signaling

Chen et al. EBioMedicine 2015

VEGF signaling and edema: VEGF-A disrupts endothelial junction



Endothelial cell junctions pre/post VEGF-A

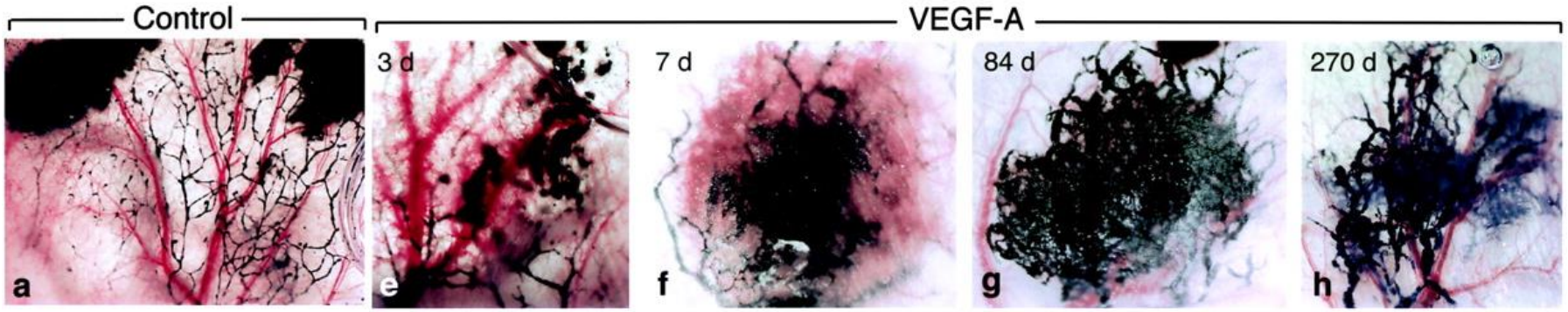
Dvorak et al. JCO 2002

VEGF-A perturbs lymphangiogenesis: giant lymphatics and incompetence

VEGF-A induces a strong lymphangiogenesis response

BUT New lymphatics are abnormal

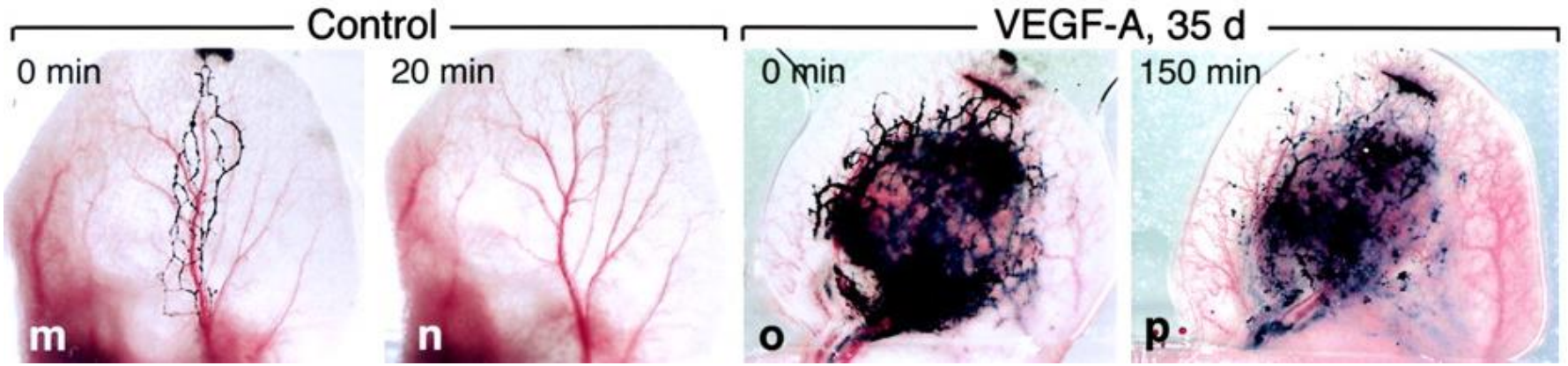
- Very large
- Incompetent valves
- Sluggish flow
- Delayed lymph clearance



Murine ear lymphatics after intravital infusion of colloidal carbon, injected w/ Ad-VEGF-A.
Marked by giant lymphatics, bulbous valves

Nagy et al. J Exp Med 2002

VEGF-A perturbs lymphangiogenesis: delayed lymphatic clearance



Murine ear lymphatics after intravital infusion of colloidal carbon, injected w/ Ad-VEGF-A.

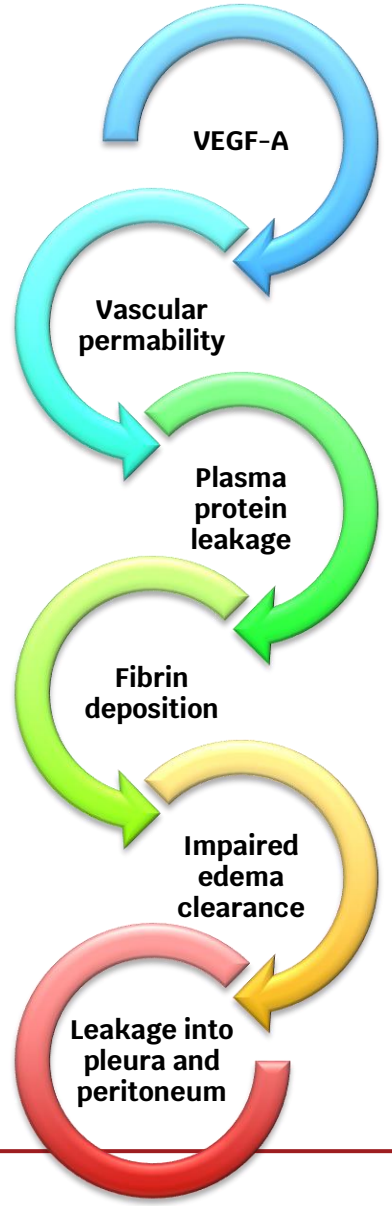
Kinetics of lymphatics clearance in Control (m,n) and Ad-VEGF-A (o,p) mice. Clearance occurs within 20 minutes in control mice, but persists for at least 150min in Ad-VEGF-A mice.

Nagy et al. J Exp Med 2002

Hypothesis: dual VEGFR2 and MET inhibition will increase efficacy while decreasing toxicity

MET inhibition leads to increased VEGF production, causing 1) bypass resistance through VEGFR2 and 2) changes in the microvasculature that instigate many of the MET inh class-associated side (i.e. edema)

Administration of ramucirumab with tepotinib will effectively abrogate the inducible intratumoral switch to VEGFR2 signaling as a bypass pathway while also blunting the effect of VEGF/VEGFR2 interaction in the periphery, decreasing the frequency and magnitude of peripheral edema, effusions, and hypoalbuminemia caused by tepotinib



S1900K: A Randomized Phase II Study of Tepotinib with or without Ramucirumab in Participants with MET Exon 14 Skipping Positive Stage IV or Recurrent Non-Small Cell Lung Cancer

CHAIR: PAUL K. PAIK, MD (MSKCC)
CO-CHAIR: XIUNING LE (MD ANDERSON)

S1900K schema: please consider activation!

Key Eligibility

- Stage IIIB/IV/recurrent NSCLC
- *MET* exon 14 skipping + (LungMAP screening, tumor or liquid, consider local testing by FDA approved assay)
- CNS mets allowed if not active/symptomatic, <1cm
- No contraindications to angiogenesis inhibition
- MET inhibitor naïve
- Received prior first-line therapy
- No prior angiogenesis inhibition

Treatment

Tepotinib 450mg po qd
+
Ramucirumab 10mg/kg q3wk
(21 day cycles)

N=25

Tepotinib 450mg po qd
(21 day cycles)

N=25

Endpoints

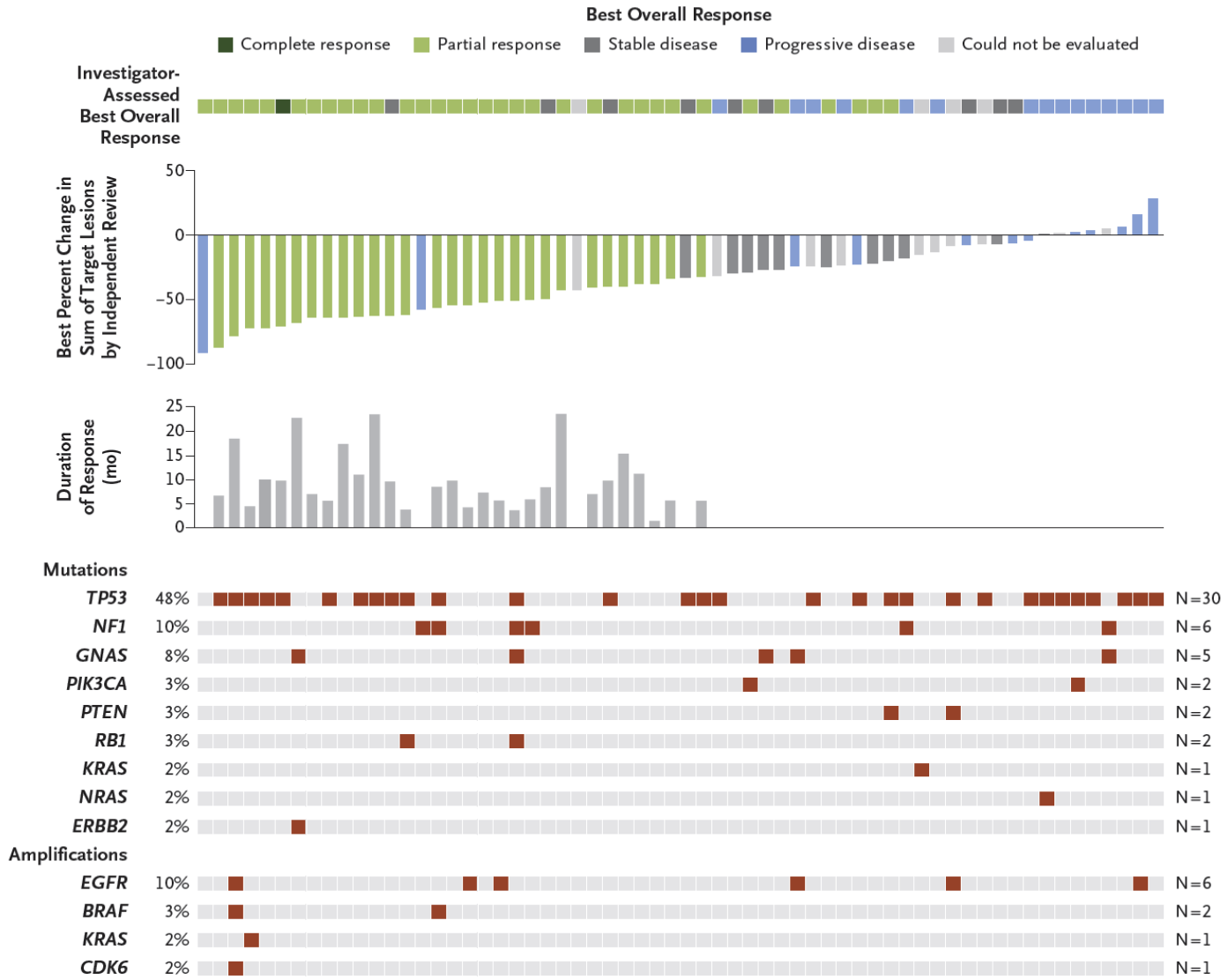
Primary:

- ORR

Secondary:

- PFS
- Frequency of all grade edema
- Lymphoscintigraphy scan changes

MET inhibition: resistance mechanisms are generally not known



Paik PK, et al. NEJM 2020

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

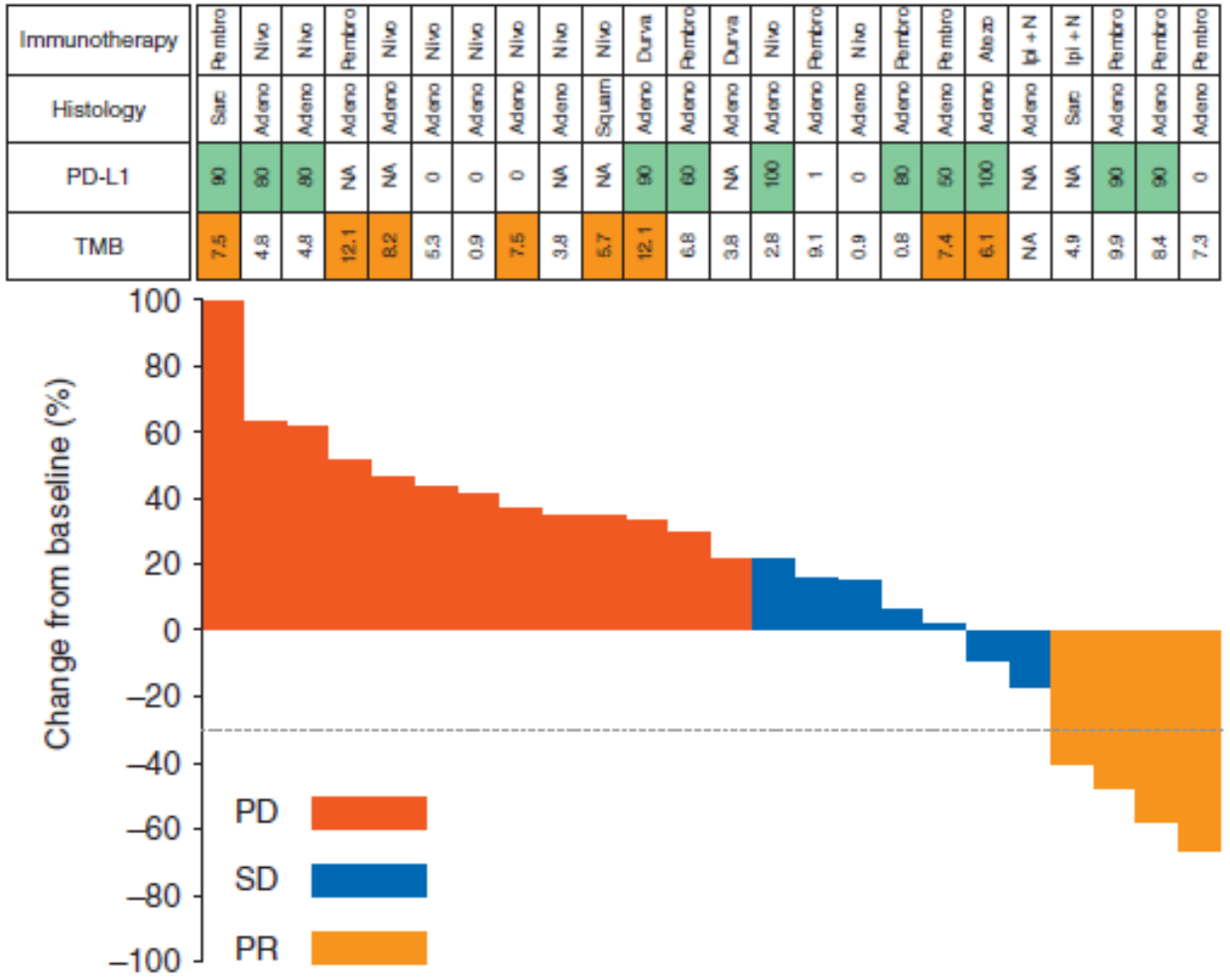
N=52

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

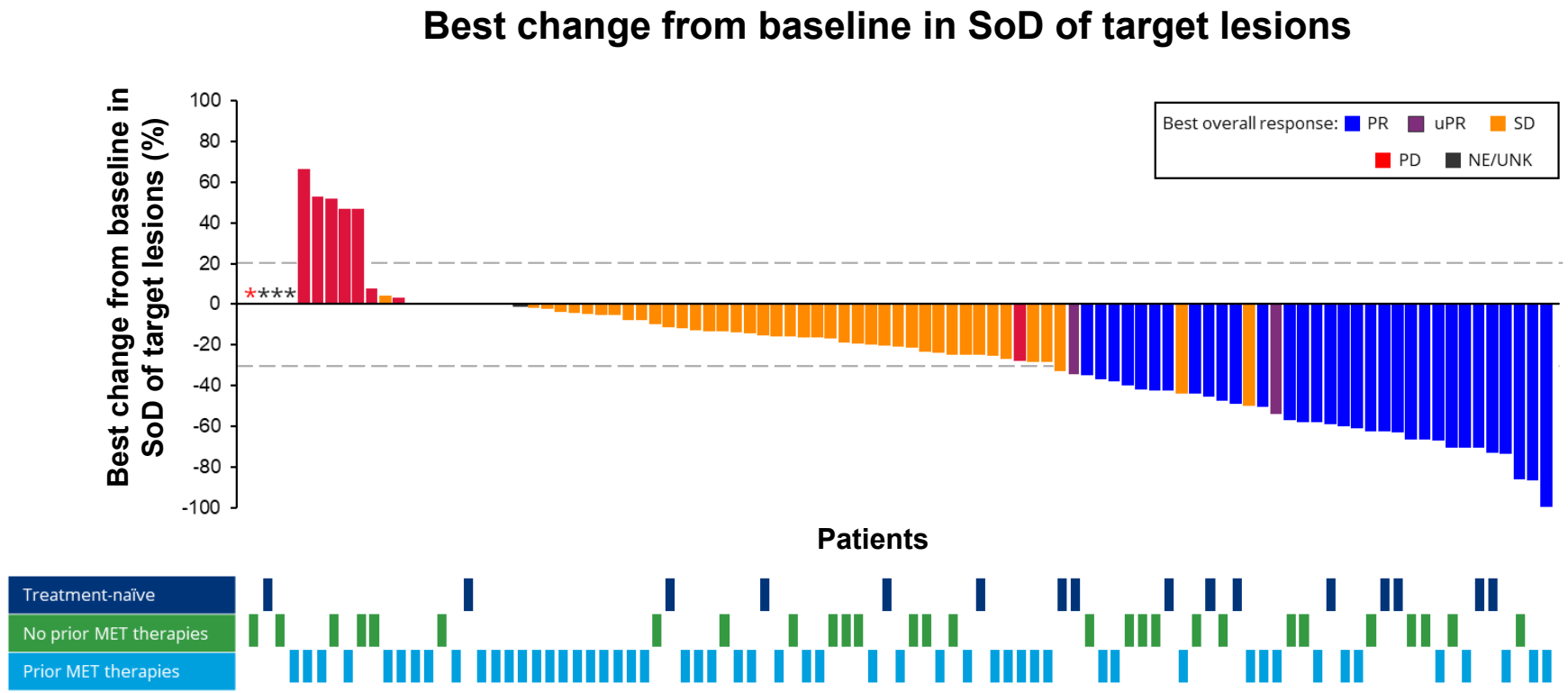
Immunotherapy in MET+ lung cancer: concern for potential resistance



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

Objective and Best Overall Response to Amivantamab

- The **ORR[a] was 33%,** with a total of 32 PRs observed
- Responses to amivantamab were observed in both treatment-naïve and prior treatment settings
  - Treatment-naïve: 8 PRs / 16; **ORR[a] = 50%**
  - No prior MET therapies: 13 PRs / 28; **ORR[a] = 46%**
  - Prior MET therapies: 11 PRs / 53; **ORR[a] = 21%**



MET, mesenchymal-epithelial transition factor; NE/UNK, not evaluable/unknown; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; SoD, sum of diameters; uPR, unconfirmed partial response.
Four patients (marked with *) did not have postbaseline disease assessment.
[a]Two patients with uPR were not included in the ORR estimates.

Leighl et al. WCLC 2023

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

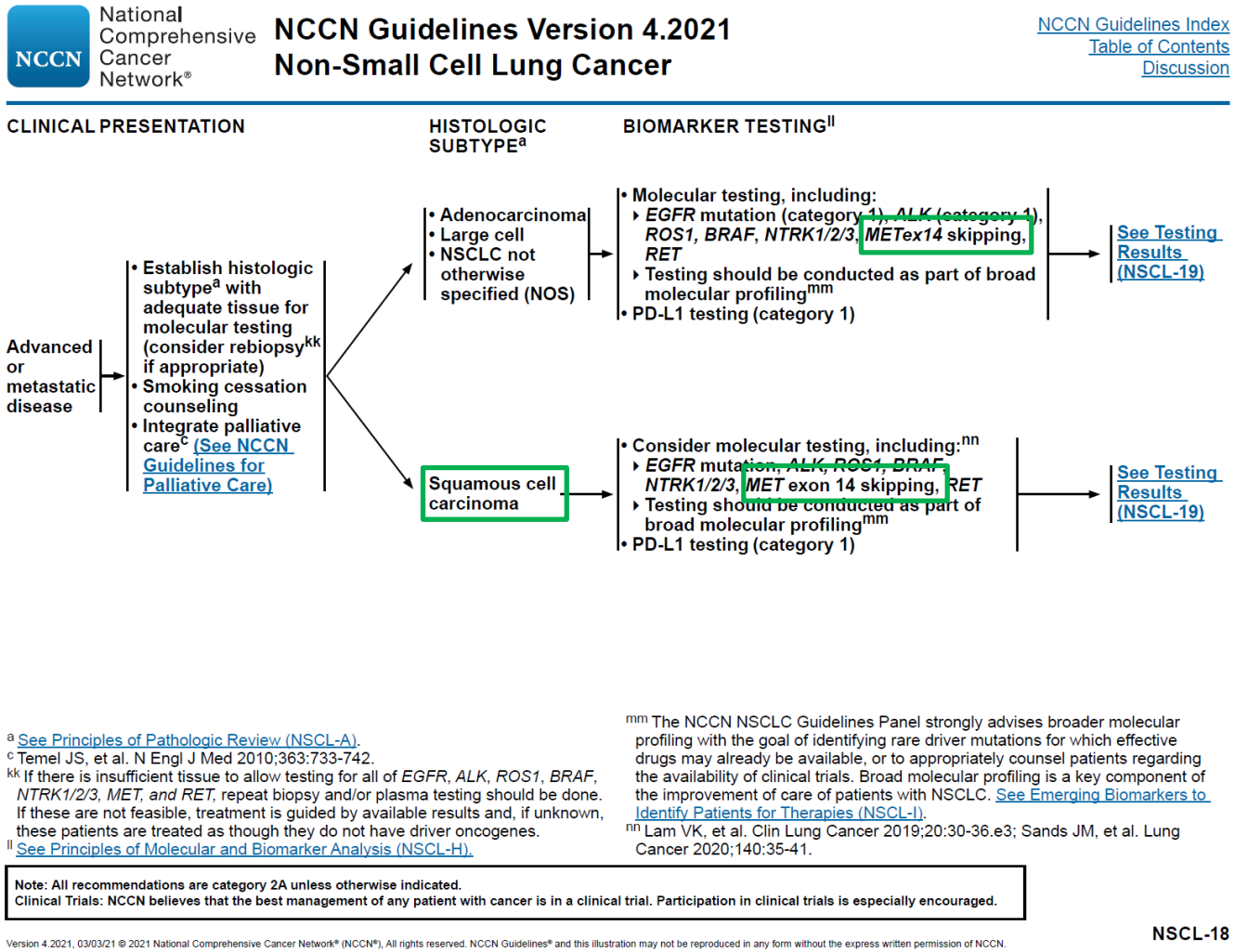
TABLE 2. Adverse Events

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)

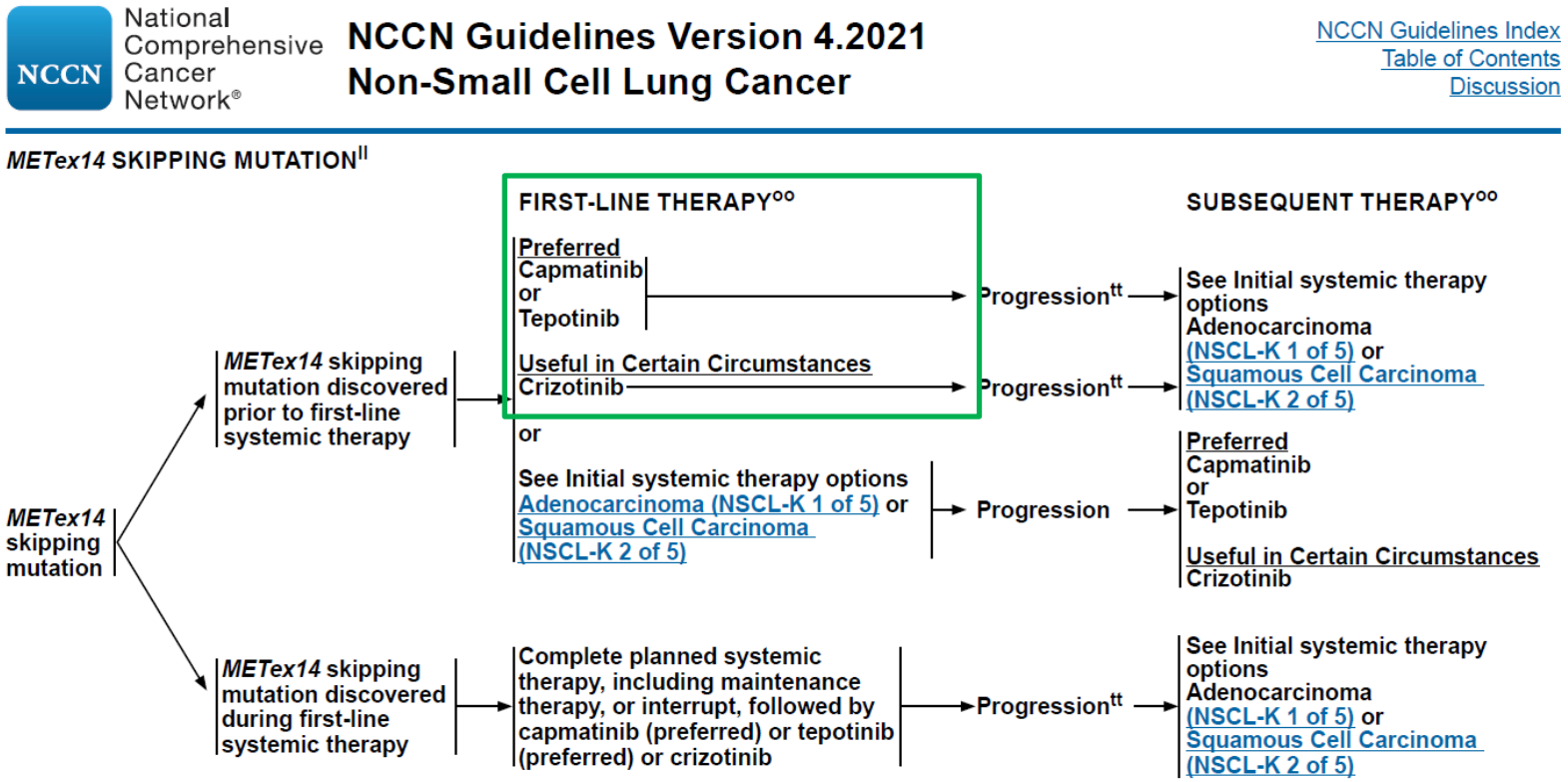
Response	Teliso-V Plus Erlotinib			
	c-Met+ *EGFR*-M+ (n = 28), No./n (%)	c-Met+ *EGFR*-WT (n = 5), No./n (%)	c-Met+ *EGFR*-Rare/Unknown (n = 3), No./n (%)	Total (N = 36), No./N (%)
Best overall response[a]				
Complete response	1/28 (4)	0/5	0/3	1/36 (3)
Partial response	8/28 (29)	2/5 (40)	0/3	10/36 (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

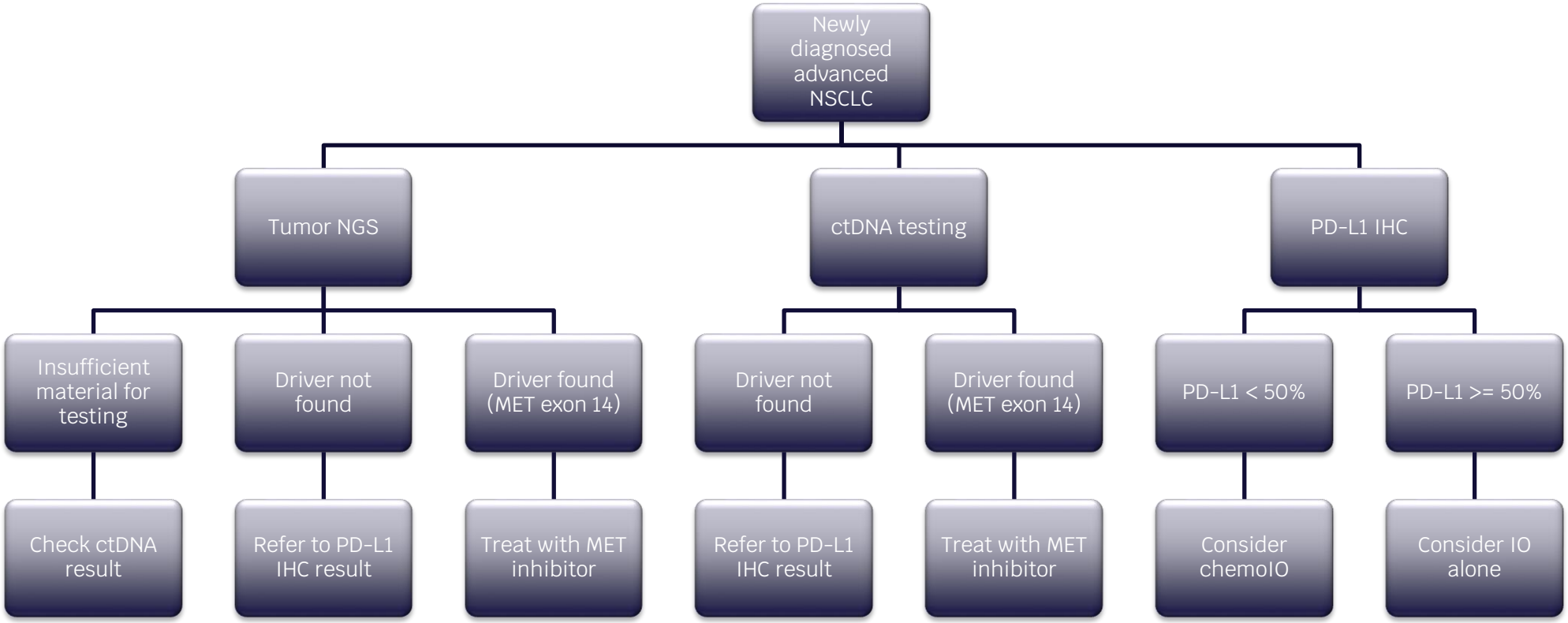
MET exon 14 testing is now standard of care



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



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



Thank you!

Endorsed by

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