Newly approved therapies for METex14 and METamp lung cancers

PRESENTED BY

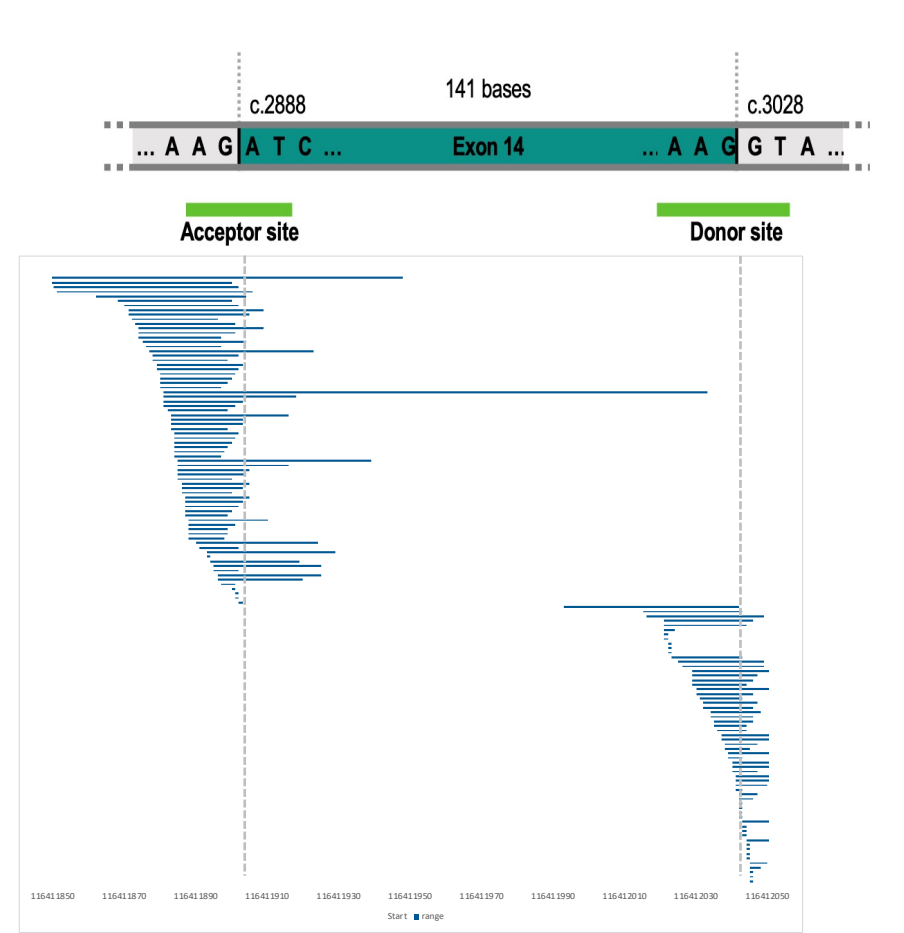
XIUNING LE MD PHD (MD ANDERSON CANCER CENTER)

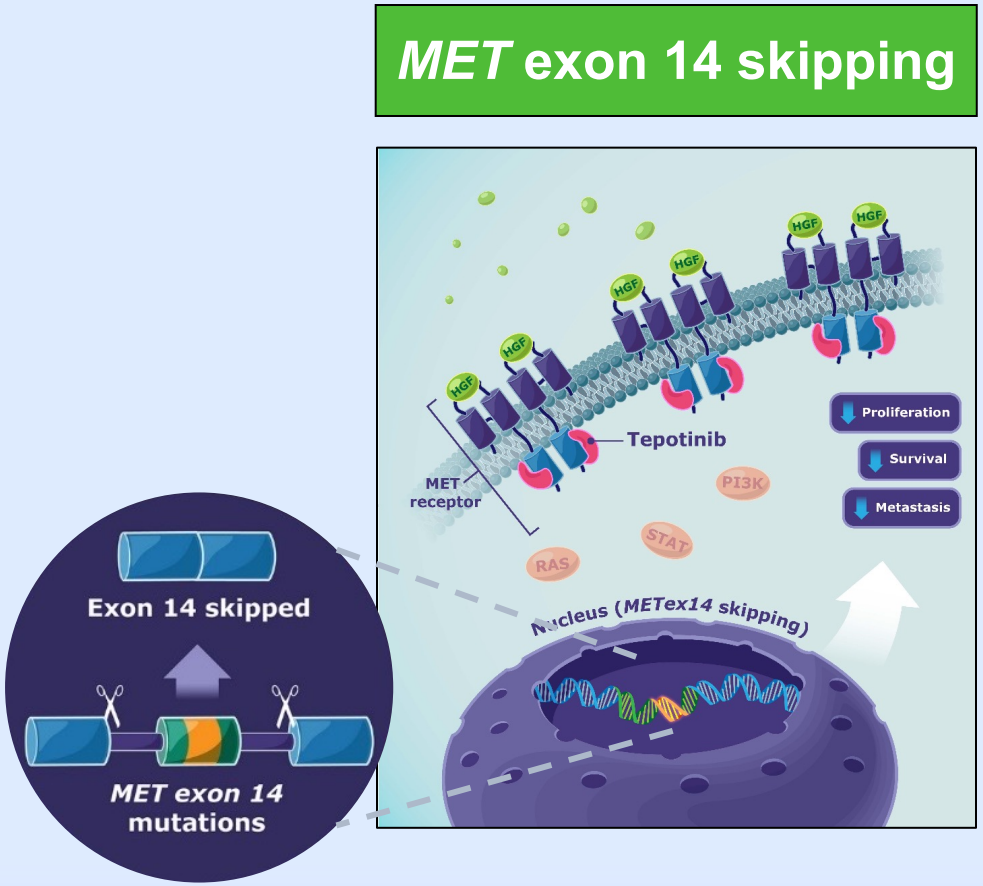
REBECCA HEIST MD MPH (MASS GENERAL HOSPITAL)

ANDREAS SALTOS MD (MOFFITT CANCER CENTER)

JOHN HALLICK (MET CRUSADERS)

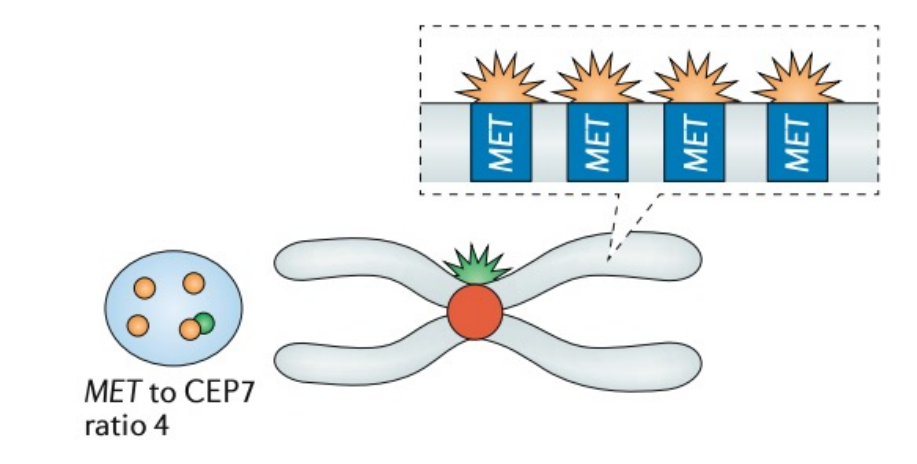
METex14 as an oncogene driver in lung cancer



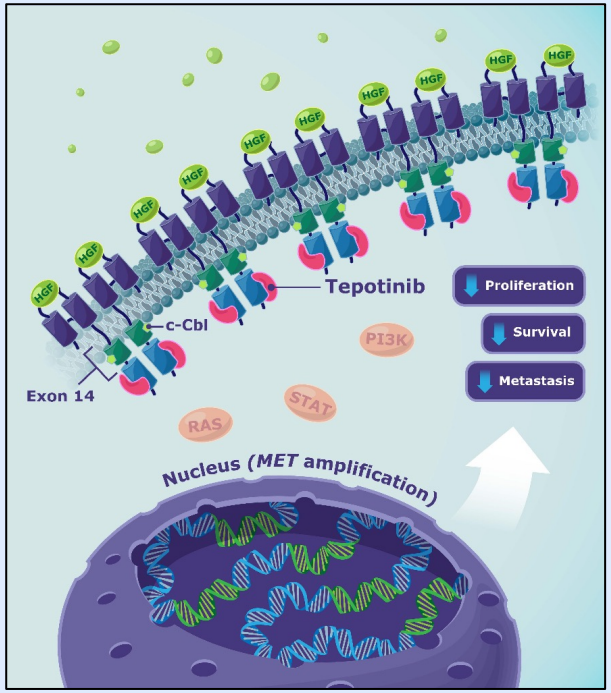


MET amplification in lung cancer

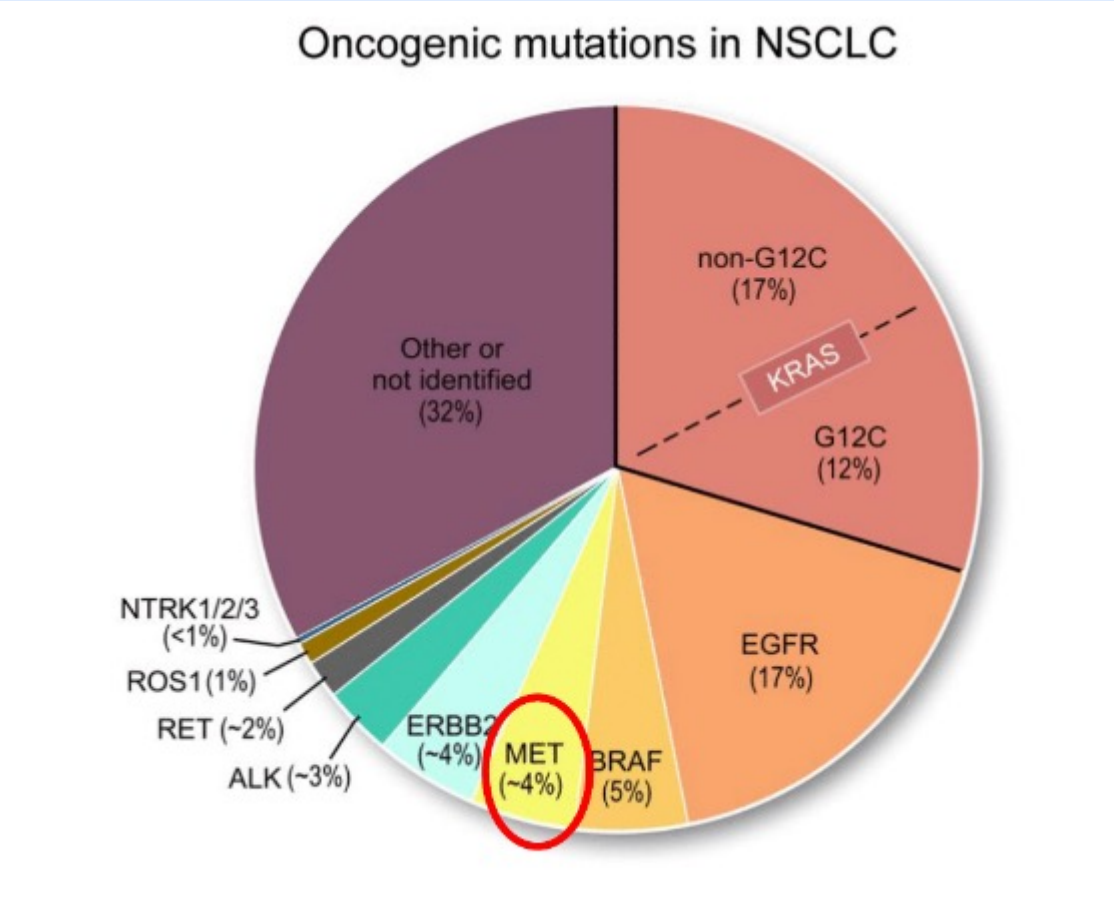
Focal amplification of MET can lead to MET pathway activation and oncogene dependency in lung cancer



MET amplification



METex14 and METamp in lung cancer



METex14 in about 3% of NSCLC

High copy-number gain of MET in about 1% of NSCLC

Both tissue-based and blood-based next-generation sequencing can detect MET changes.

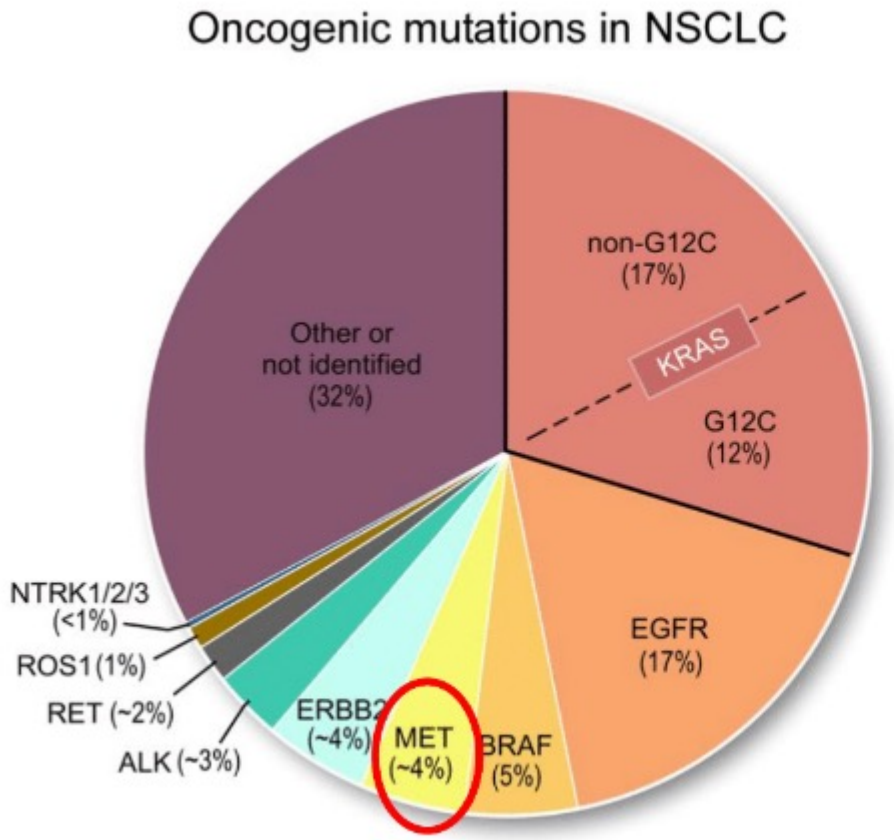
The patents and needs

	EGFR-mutant	ALK- rearranged	General NSCLC	METex14
Median age	~60 (57-64)	~ 53 (50-57)	70 (USA)	~71 (69-74)
Female	62-80%	60%	40%	50% (45-50%)
Smoking Hx	7-37%	35%	75%	42-62%
PDL1 high	Rare	Rare	25-40%	41%
Non-adeno path	Rare	Rare	30-40%	Up to 26%

Challenges:

- Testing in this population who has similar features to general NSCLC
- How to select treatments for this elderly population
- How to mitigate side effects from therapies and best serve those patients

FDA approved MET therapies



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

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

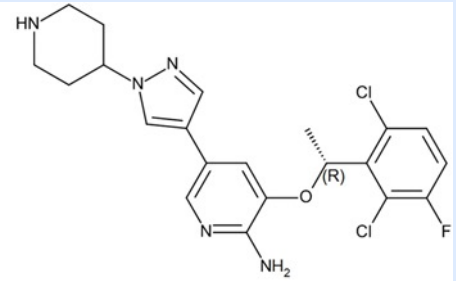
Crizotinib PROFILE 1001 Study Design

- Multicenter phase 1 trial (NCT00585195) – *MET* exon 14-altered NSCLC subgroup
- Key Objective: investigate the safety and antitumor activity of crizotinib in *MET* exon 14-altered NSCLC

Eligibility	Advanced NSCLC *MET* exon 14 alteration No prior MET-directed targeted therapy Treated brain metastases allowed if stable for ≥2 weeks
Diagnosis of *MET* exon 14 alteration	Local molecular profiling
Treatment	Crizotinib at 250 mg twice daily
Response Assessment	Response Evaluation Criteria in Solid Tumors (RECIST) v1.0 Imaging at baseline and every 8 weeks
Adverse Events	Common Terminology Criteria for Adverse Events (CTCAE) v3.0
Biomarker Analysis	Retrospective analysis for *MET* exon 14 status was performed by: • Central testing of available tumor tissue (FoundationOne CDx, FMI) • Circulating cell free DNA analysis (PlasmaSELECT-R 64, PGDx)

Drilon et al WCLC 2018

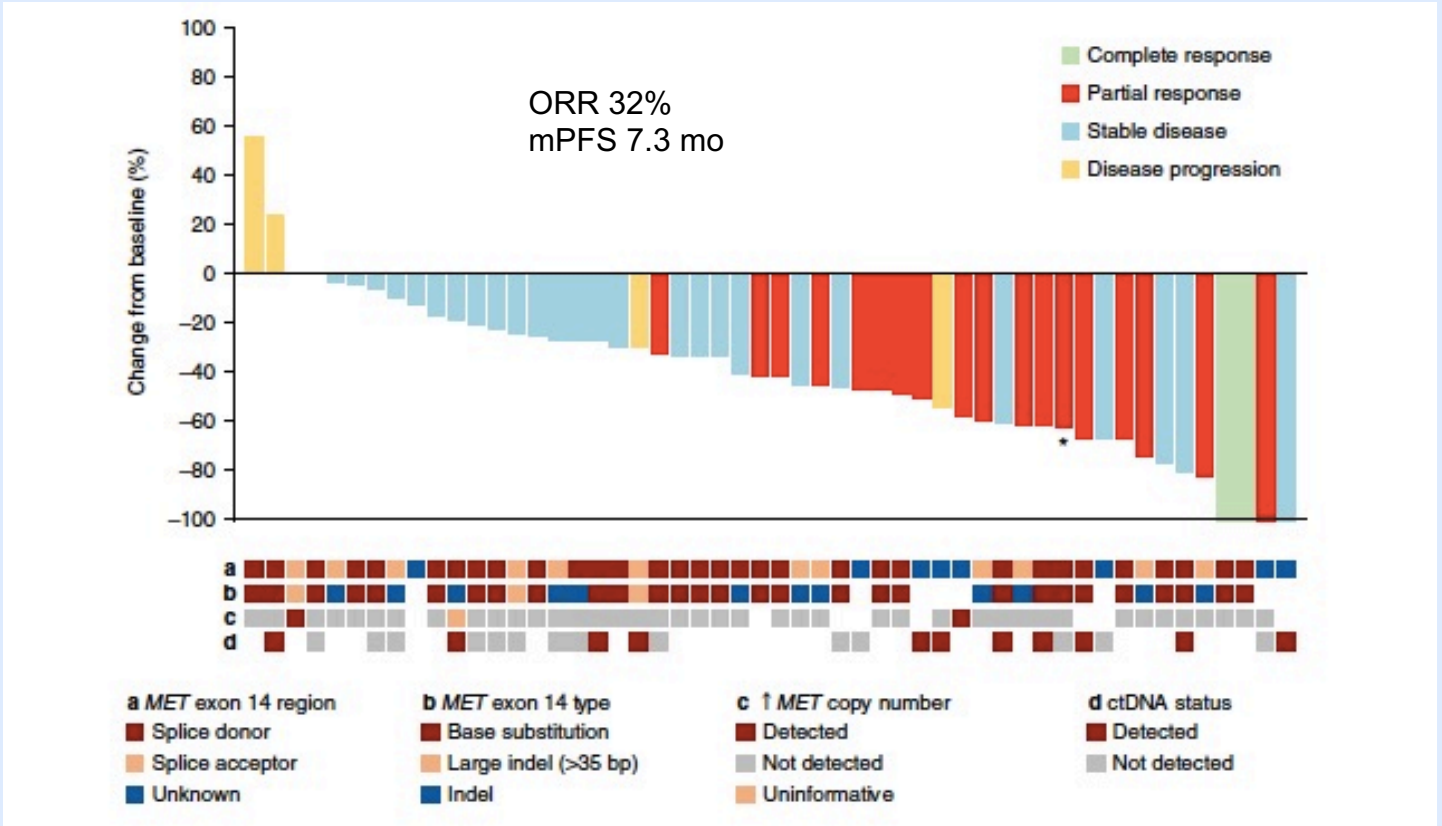
Crizotinib activity in METex14



Cellular selectivity on 10 of 13 relevant hits

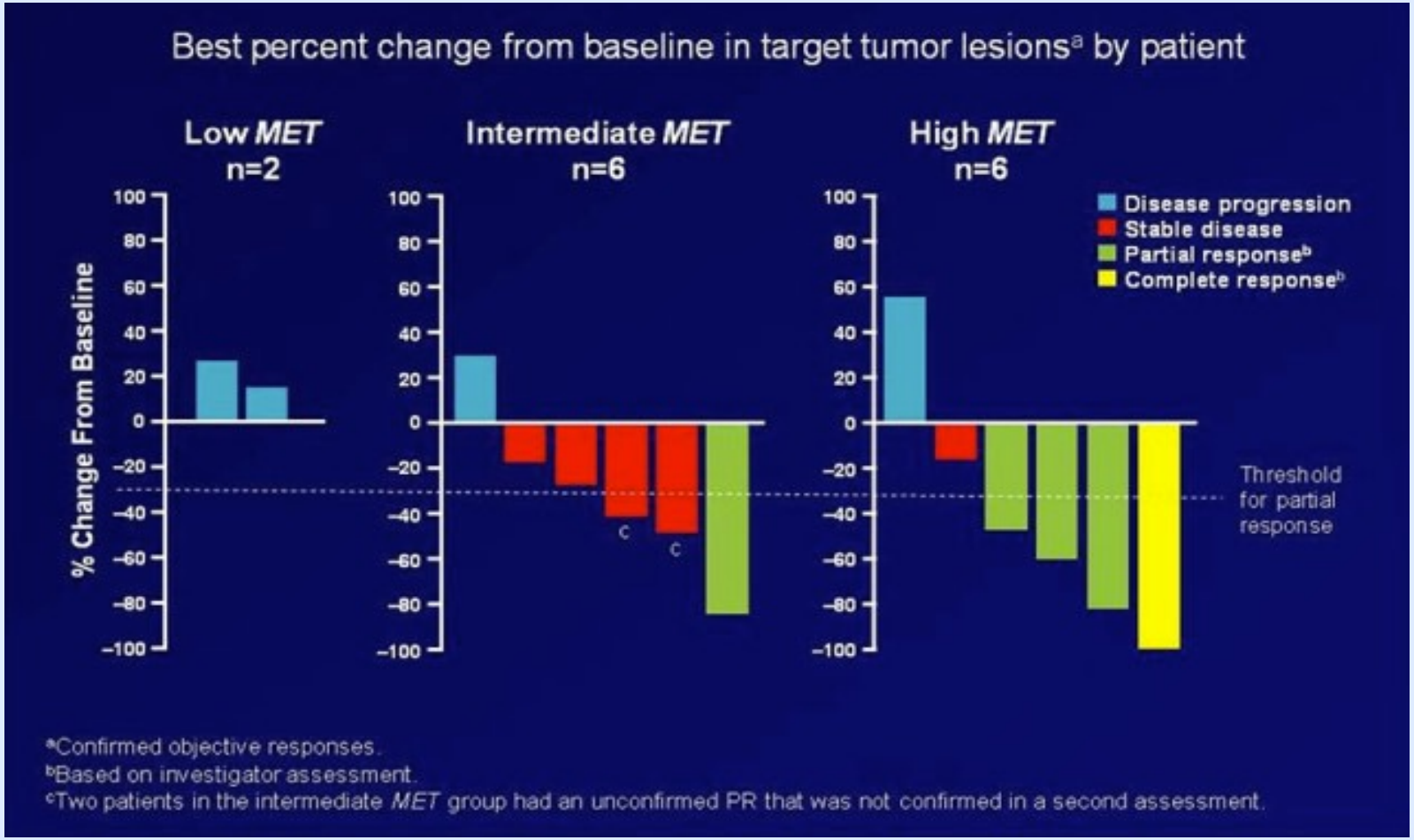
Kinase	IC_{50} (nM) mean*	Selectivity ratio
c-MET	8	–
ALK	20	2X
RON	298	34X
	189	22X
Axl	294	34X
	322	37X
Tie-2	448	52X
Trk A	580	67X
Trk B	399	46X
Abl	1,159	166X
IRK	2,887	334X
Lck	2,741	283X
Sky	>10,000	>1,000X
VEGFR2	>10,000	>1,000X
PDGFRβ	>10,000	>1,000X

*The cellular kinase activities were measured using ELISA capture method



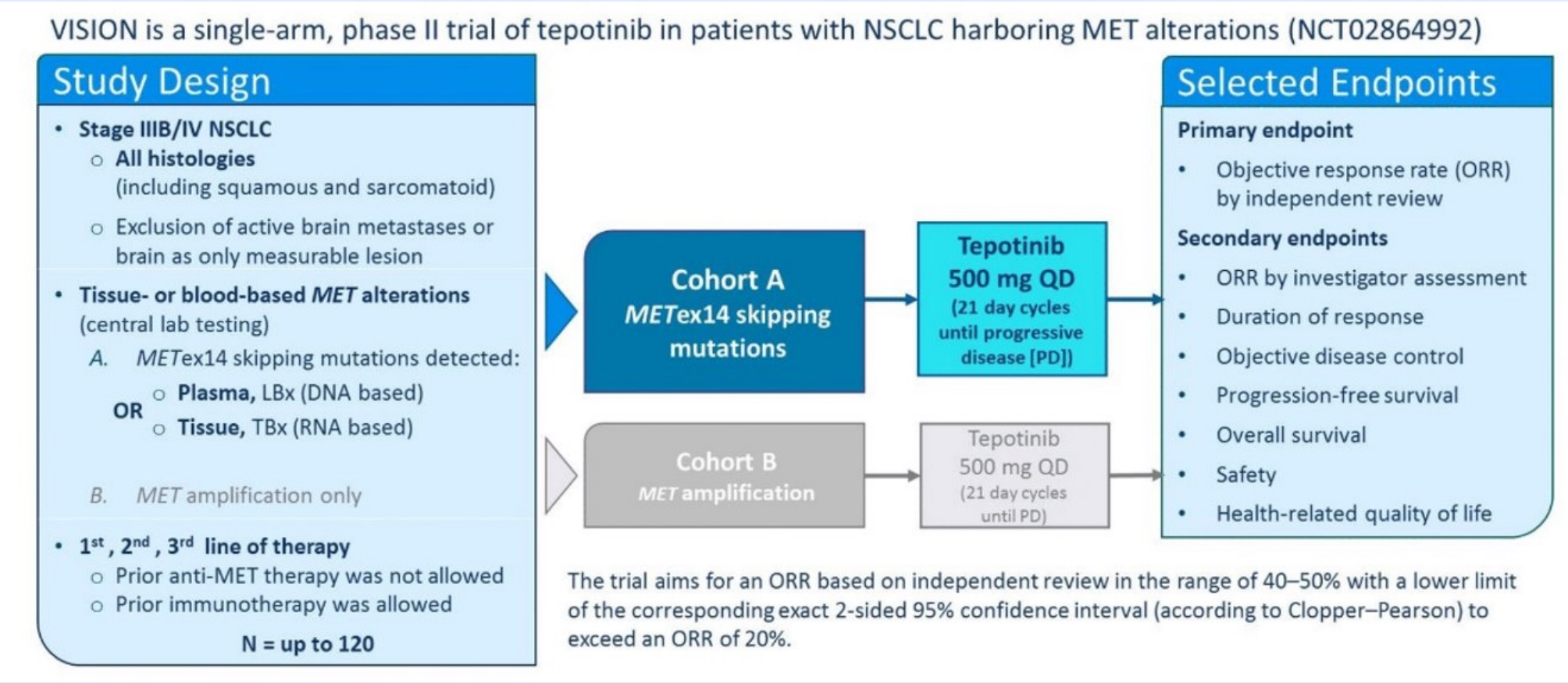
Bang et al ASCO 2010; Drilon et al, Nat Medicine 2019

Crizotinib activity in MET amplified NSCLC



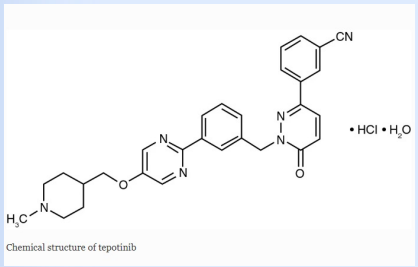
Camidge et al, ASCO 2014

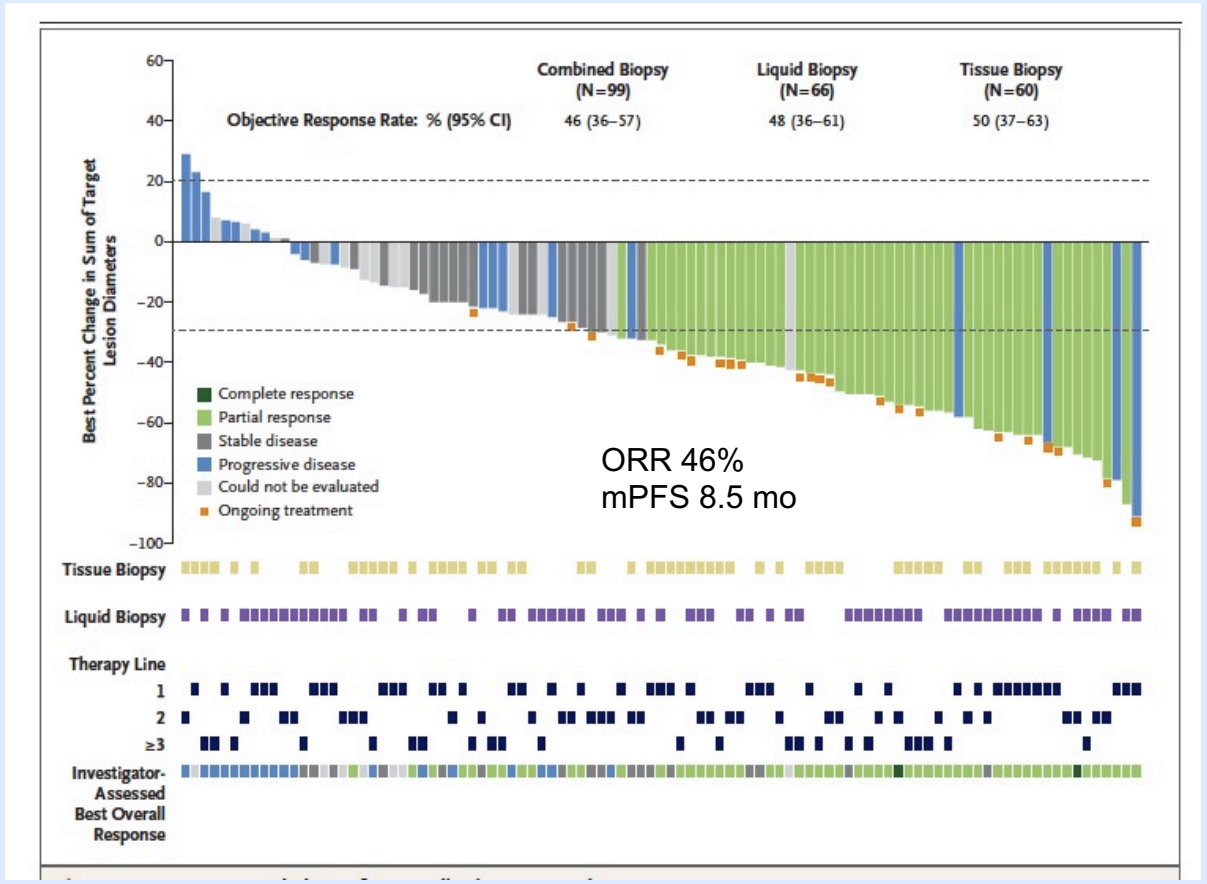
Tepotinib VISION study design



Paik et al ASCO 2019

Tepotinib activity in METex14



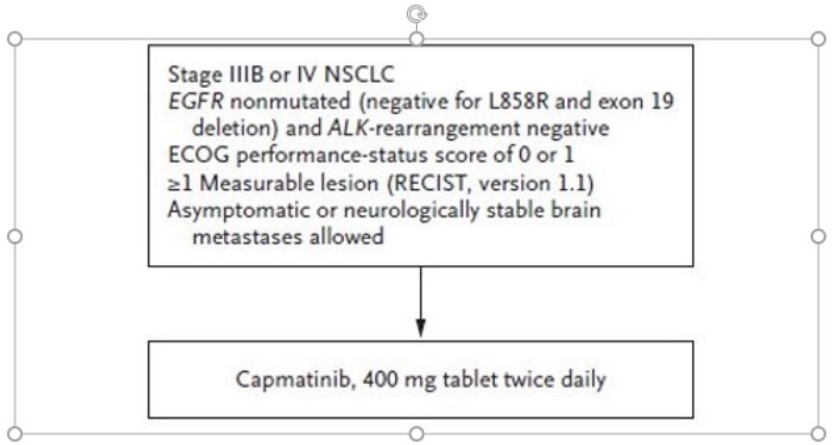


Efficacy according to IRC	Treatment-naïve (n=69)	Previously treated (n=83)	Overall (N=152)
ORR, % (95% CI)	**44.9** (32.9, 57.4)	**44.6** (33.7, 55.9)	**44.7** (36.7, 53.0)
BOR, n (%)			
CR	0	0	0
PR	31 (44.9)	37 (44.6)	68 (44.7)
SD	16 (23.2)	23 (27.7)	39 (25.7)
PD	13 (18.8)	13 (15.7)	26 (17.1)
NE	9 (13.0)	10 (12.0)	19 (12.5)
Median DOR, months (95% CI)	10.8 (6.9, ne)	11.1 (9.5, 18.5)	11.1 (8.4, 18.5)
Median PFS, months (95% CI)	8.5 (6.8, 11.3)	10.9 (8.2, 12.7)	8.9 (8.2, 11.2)

Data cut-off: July 1, 2020.

- Bladt et al CCR 2013; Paik et al NEJM 2020; Paik et al WCLC 2020

Capmatinib Geometry mono-1 Study design

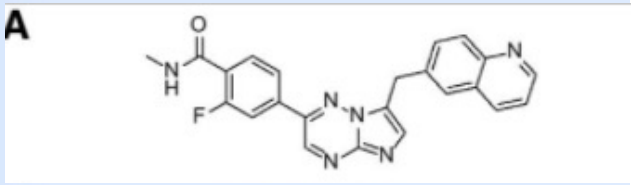


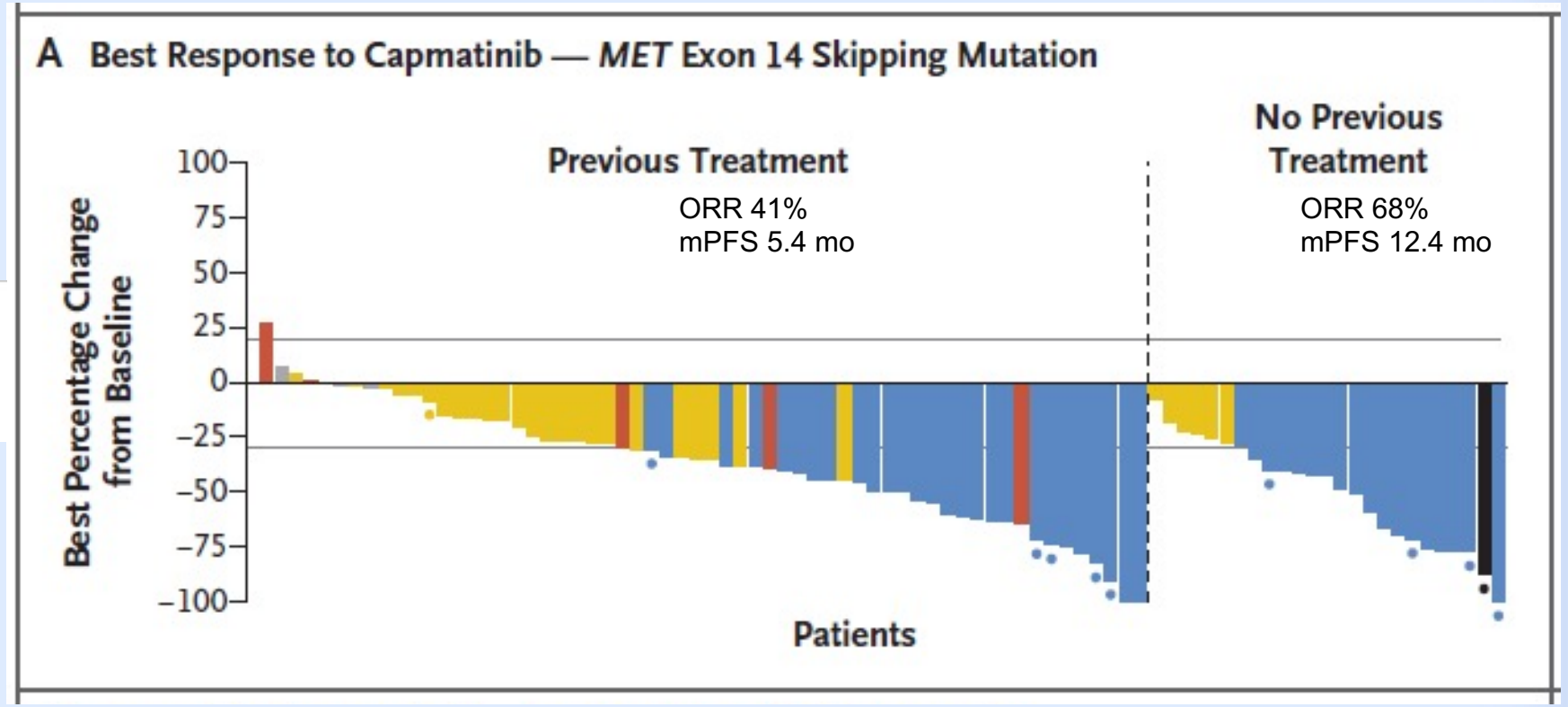
Wolf et al NEJM 2020

Cohorts	Expansion Cohorts
Previous Treatment	
1 or 2 Lines of therapy	1 Line of therapy
Cohort 1a: *MET* amplification, GCN ≥10 (N=69)	Cohort 6: *MET* amplification, GCN ≥10; or *MET* exon 14 skipping mutation, any GCN (N=34)
Cohort 1b: *MET* amplification, GCN 6 to 9 — closed for futility (N=42)	
Cohort 2: *MET* amplification, GCN 4 or 5 — closed for futility (N=54)	
Cohort 3: *MET* amplification, GCN <4 — closed for futility (N=30)	
Cohort 4: *MET* exon 14 skipping mutation, any GCN (N=69)	
No Previous Treatment	
Cohort 5a: *MET* amplification, GCN ≥10 (N=15)	Cohort 7: *MET* exon 14 skipping mutation, any GCN (N=23)
Cohort 5b: *MET* exon 14 skipping mutation, any GCN (N=28)	

Wolf et al NEJM 2020

Capmatinib activity in METex14



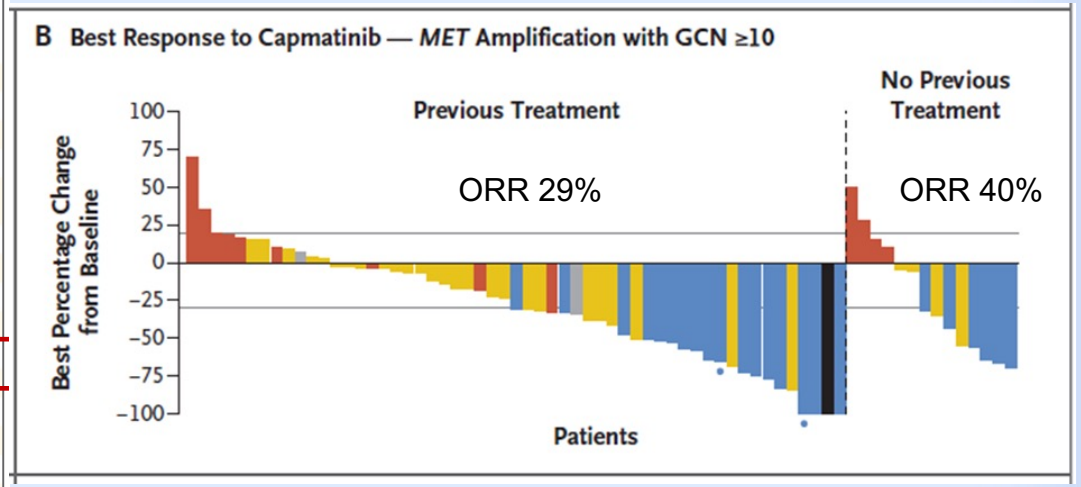


Baltschukat et al CCR 2019; Wolf et al NEJM 2020

Capmatinib in MET GCN cohorts

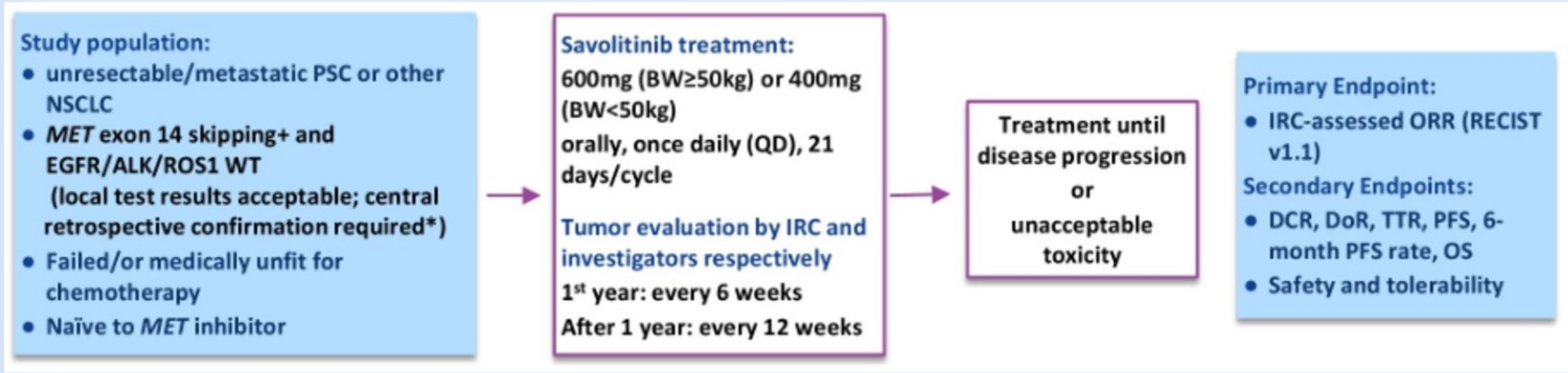
Table 2. Responses to Capmatinib Treatment, as Assessed by the Independent Review Committee.*

Response	NSCLC with *MET* Exon 14 Skipping Mutation		NSCLC with *MET* Amplification				
	Cohort 4 (N=69)	Cohort 5b (N=28)	Cohort 1a (N=69)	Cohort 5a (N=15)	Cohort 1b (N=42)	Cohort 2 (N=54)	Cohort 3 (N=30)
Best response — no. (%)							
Complete response	0	1 (4)	1 (1)	0	0	0	0
Partial response	28 (41)	18 (64)	19 (28)	6 (40)	5 (12)	5 (9)	2 (7)
Stable disease	25 (36)	7 (25)	28 (41)	4 (27)	17 (40)	20 (37)	14 (47)
Noncomplete response or nonprogressive disease	1 (1)	1 (4)	1 (1)	0	1 (2)	0	0
Progressive disease	6 (9)	1 (4)	12 (17)	4 (27)	15 (36)	21 (39)	6 (20)
Unknown or could not be evaluated	9 (13)	0	8 (12)	1 (7)	4 (10)	8 (15)	8 (27)
Overall response†							
No. of patients with overall response	28	19	20	6	5	5	2
Percent of patients (95% CI)	41 (29–53)	68 (48–84)	29 (19–41)	40 (16–68)	12 (4–26)	9 (3–20)	7 (1–22)
Disease control‡							
No. of patients with disease control	54	27	49	10	23	25	16
Percent of patients (95% CI)	78 (67–87)	96 (82–100)	71 (59–81)	67 (38–88)	55 (39–70)	46 (33–60)	53 (34–72)
Duration of response							
No. of events/no. of patients with response	23/28	11/19	15/20	6/6	3/5	4/5	2/2
Median duration of response (95% CI) — mo	9.7 (5.6–13.0)	12.6 (5.6–NE)	8.3 (4.2–15.4)	7.5 (2.6–14.3)	24.9 (2.7–24.9)	9.7 (4.2–NE)	4.2 (4.2–4.2)
Progression-free survival							
Progression or death — no. of patients	60	17	58	15	34	50	22
Median progression-free survival (95% CI) — mo	5.4 (4.2–7.0)	12.4 (8.2–NE)	4.1 (2.9–4.8)	4.2 (1.4–6.9)	2.7 (1.4–3.1)	2.7 (1.4–4.1)	3.6 (2.2–4.2)



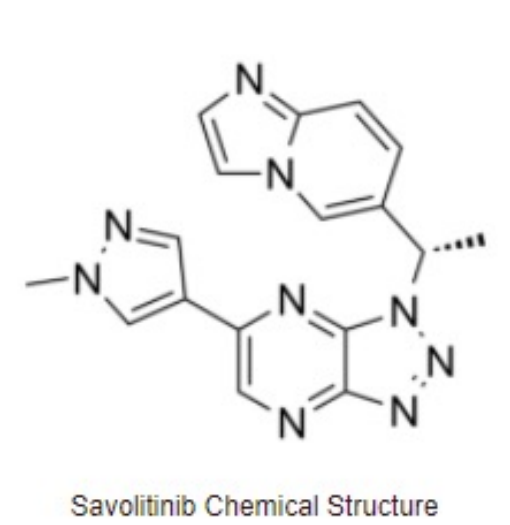
Wolf et al NEJM 2020

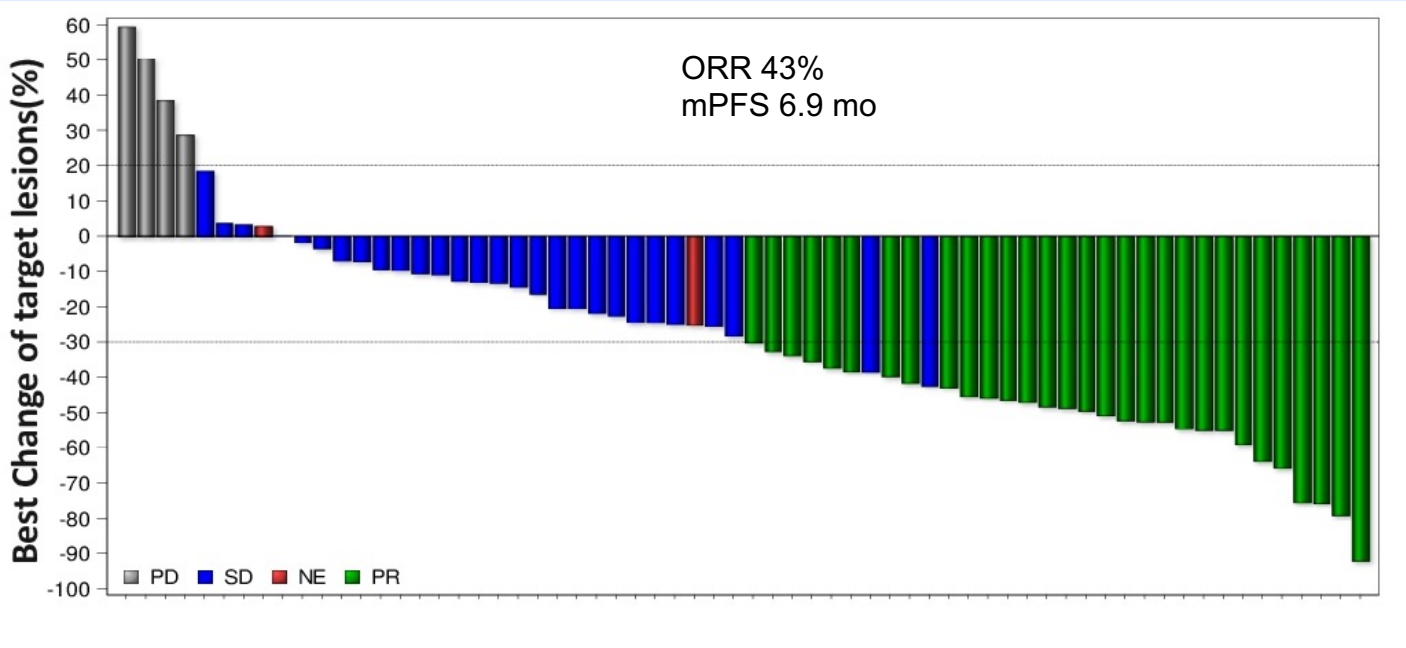
Savolitinib NCT02897479 study design



Lu et al, ASCO 2020

Savolitinib activity in METex14





Lu et al, ASCO 2020

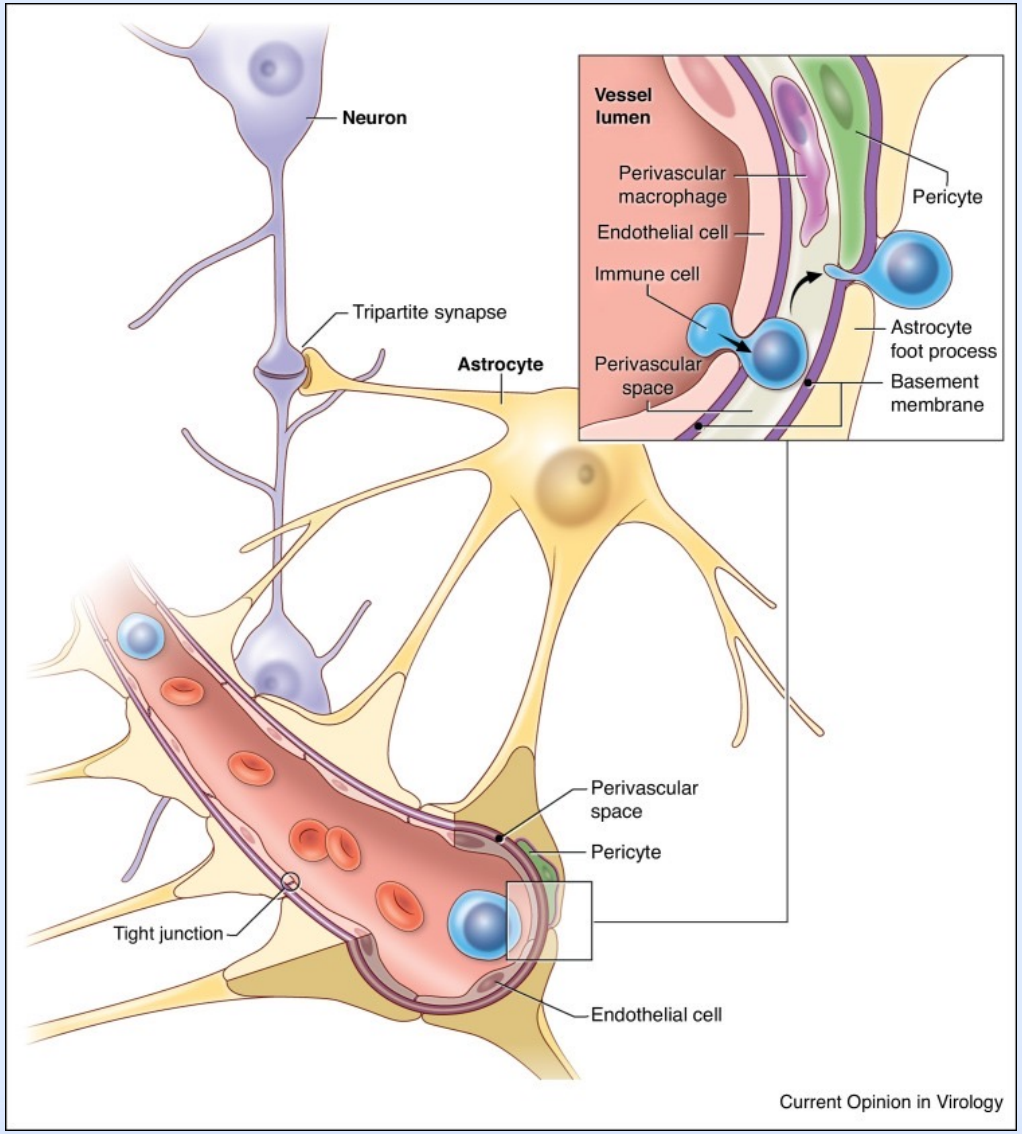
Type I MET inhibitors in MET exon 14 skipping

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

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

Blood Brain Barrier

- Some cancer drugs have difficulty entering the brain due to this 'barrier'
- Crizotinib is an example where relatively lower effectiveness in brain metastases has been observed

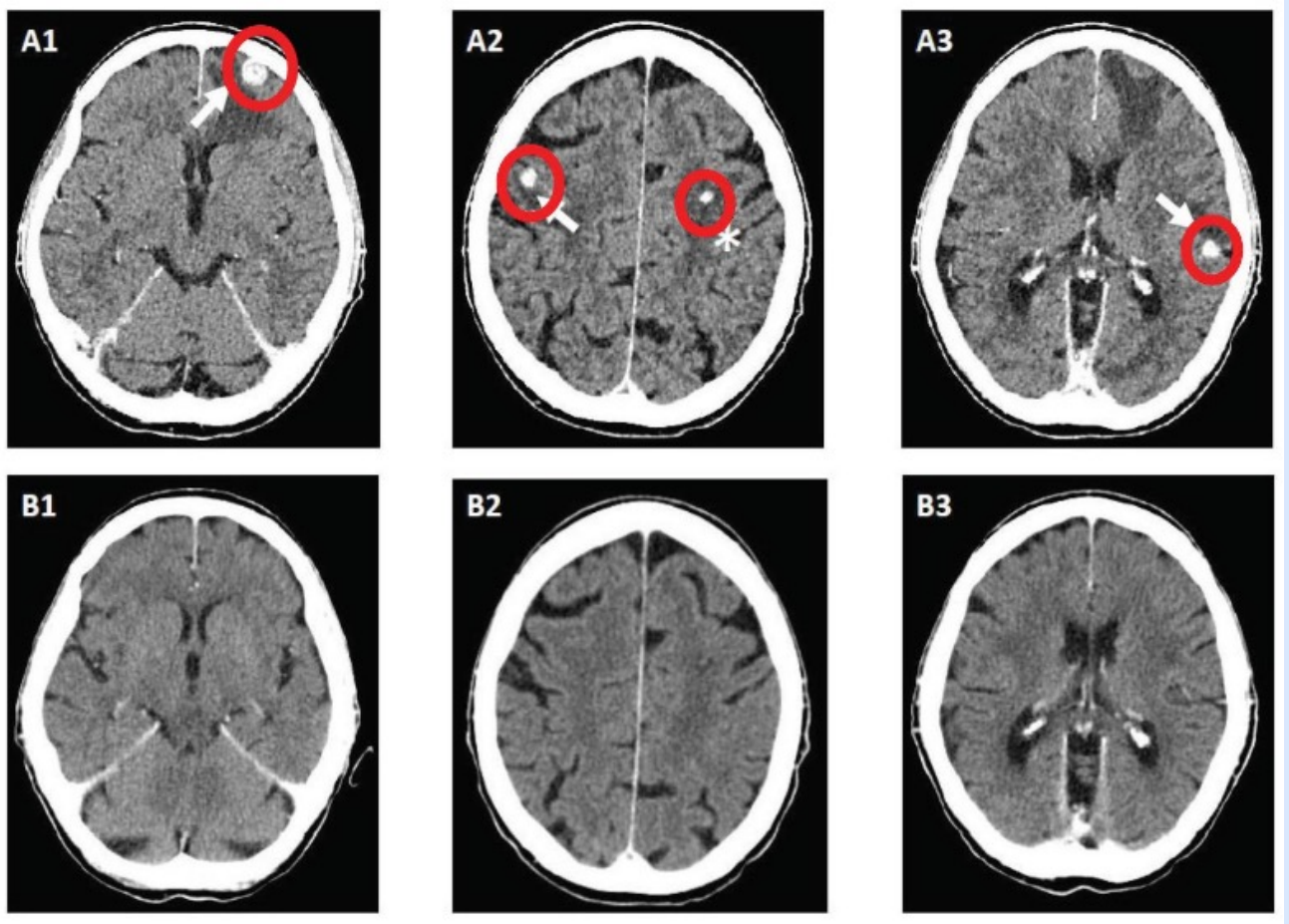


Manglani et al Curr Opin Virol 2018

Costa et al JCO 2011

CNS Activity – Capmatinib and Tepotinib

- Capmatinib, 54% (n=7/13) intracranial response
  - Intracranial disease control achieved in 12/13 patients
- Tepotinib, 55% (n=6/11) intracranial response



Wolf et al NEJM 2020

Crizotinib - Safety

- Adverse events led to a dose reduction in 38% of patients and discontinuation in 7%

Patients — no. (%) (N=69)	Any Grade	Grade 1	Grade 2	Grade 3§	Grade 4§
Any AE*†	65 (94)	14 (20)	30 (44)	17 (25)	3 (4)
Edema‡	35 (51)	23 (33)	11 (16)	1 (1)	0
Vision disorder‡	31 (45)	30 (44)	1 (1)	0	0
Nausea	28 (41)	20 (29)	8 (12)	0	0
Diarrhea	27 (39)	20 (29)	7 (10)	0	0
Vomiting	20 (29)	18 (26)	2 (3)	0	0
Fatigue	16 (23)	7 (10)	9 (13)	0	0
Constipation	14 (20)	11 (16)	2 (3)	1 (1)	0
Decreased appetite	13 (19)	8 (12)	5 (7)	0	0
Elevated transaminases‡	12 (17)	6 (9)	3 (4)	3 (4)	0
Bradycardia‡	11 (16)	9 (13)	1 (1)	1 (1)	0
Dysgeusia	10 (14)	10 (15)	0	0	0
Neuropathy‡	7 (10)	6 (9)	1 (1)	0	0

Drilon et al, Nat Medicine 2019

Capmatinib - Safety

- Most common were peripheral edema and GI effects
- Adverse events led to a dose reduction in 23% of patients and discontinuation in 11%

Variable	All Cohorts (N=364)	
	Total	Grade 3 or 4
Adverse events		
Any event — no. (%)	355 (98)	244 (67)
Most common events — no. (%)†		
Peripheral edema	186 (51)	33 (9)
Nausea‡	163 (45)	9 (2)
Vomiting‡	102 (28)	9 (2)
Blood creatinine increased	89 (24)	0
Dyspnea	84 (23)	24 (7)
Fatigue	80 (22)	16 (4)
Decreased appetite‡	76 (21)	3 (1)

Variable	All Cohorts (N=364)	
	Total	Grade 3 or 4
Constipation	66 (18)	3 (1)
Diarrhea	64 (18)	2 (1)
Cough	58 (16)	2 (1)
Back pain	54 (15)	3 (1)
Pyrexia	50 (14)	3 (1)
ALT increased	48 (13)	23 (6)
Asthenia	42 (12)	13 (4)
Pneumonia	39 (11)	17 (5)
Weight loss	36 (10)	2 (1)
Noncardiac chest pain	35 (10)	4 (1)

Wolf et al NEJM 2020

Tepotinib - Safety

- Median time to onset of events was 3-11 weeks after initiation
- Led to a dose reduction in 33% of patients and discontinuation in 11%

Table 2. Adverse Events (Safety Population).*

Adverse Events	Safety Population (N=152)			
	All Grades	Grade 1 or 2	Grade 3	Grade 4
	number of patients (percent)			
Any adverse event†	135 (89)	93 (61)	38 (25)	3 (2)
Peripheral edema	96 (63)	85 (56)	11 (7)	0
Nausea	39 (26)	38 (25)	1 (1)	0
Diarrhea	33 (22)	32 (21)	1 (1)	0
Blood creatinine increased	27 (18)	26 (17)	1 (1)	0
Hypoalbuminemia	24 (16)	21 (14)	3 (2)	0
Amylase increased	17 (11)	13 (9)	3 (2)	1 (1)
Lipase increased	13 (9)	9 (6)	4 (3)	0
Asthenia	12 (8)	11 (7)	1 (1)	0
Decreased appetite	12 (8)	11 (7)	1 (1)	0
Pleural effusion	12 (8)	8 (5)	4 (3)	0
Alopecia	12 (8)	12 (8)	0	0
Fatigue	11 (7)	10 (7)	1 (1)	0
Alanine aminotransferase increased	11 (7)	7 (5)	3 (2)	1 (1)
Aspartate aminotransferase increased	10 (7)	7 (5)	2 (1)	1 (1)
Vomiting	9 (6)	9 (6)	0	0
General edema	9 (6)	5 (3)	4 (3)	0
Upper abdominal pain	8 (5)	8 (5)	0	0

Paik et al NEJM 2020

Capmatinib- Practical concerns

- Capmatinib starting dose: 400 mg orally twice daily
  - Available in 200 mg or 150 mg tablets
  - Can be taken with or without food

- Elimination half-life of capmatinib - 6.5 hours

Tepotinib- Practical concerns

- Tepotinib starting dose: 450 mg orally once daily
  - Available in 225 mg tablets
  - Should be taken with food

- Elimination half-life of tepotinib - 32 hours

MET TKIs - Practical concerns

- Labs including liver function tests should be checked prior to and during therapy
- Let your oncologist know if you develop shortness of breath or respiratory symptoms
- For edema, compression stockings and leg elevation are recommended; diuretics not always helpful
- Be aware of potential drug interactions (including grapefruit!)

Conflict of Interest

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

Dr. Andreas Saltos has received travel reimbursement from Daiichi Sankyo, and research funding (to his institution) from Novartis, Daiichi Sankyo, Eli Lilly, Mersana, Genmab, AstaZeneca and Turning Point Therapeutics.

Dr. Heist has received honoraria for consulting/advisory boards from Novartis, EMD Serono, Daichii Sankyo, Tarveda, Apollomics, Boehringer Ingelheim. She has also received research funding (to institution, not to self) from Novartis, Daichii Sankyo, Genentech/Roche, Mirati, Turning Point, BMS, Agios, Corvus, Abbvie, Incyte, Corvus, Lilly

MET
CRUSADERS