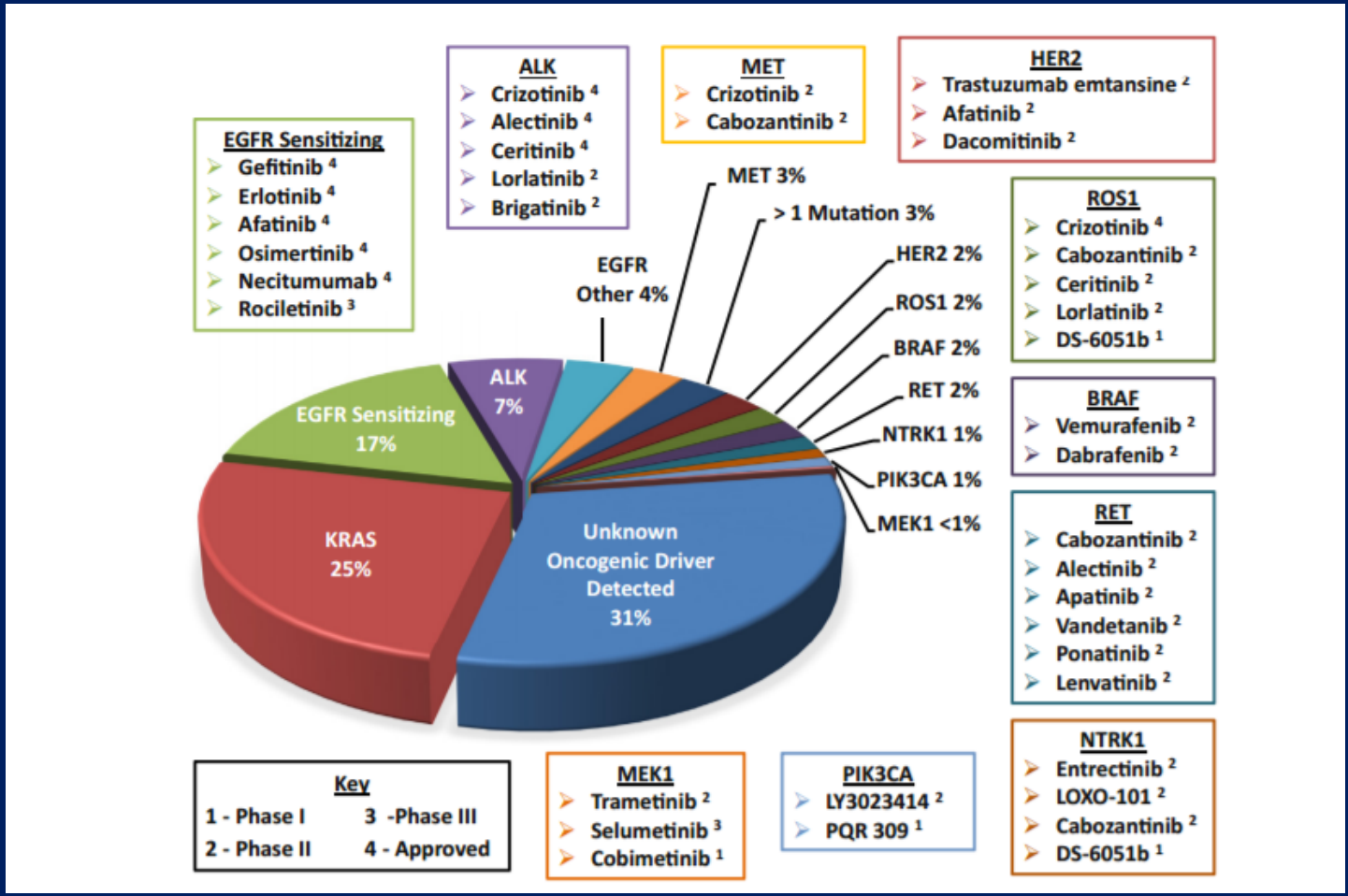
Targeted therapies for patients with uncommon molecular alterations

Tom Stinchcombe

Duke Cancer Institute

Emerging targets and targeted therapies



Tsao et al Journal of Thoracic Oncology 2015

Topics

- *ROS1:* beyond crizotinib
- *BRAF* V600E and non-V600E
- *MET* exon 14 alterations and MET amplification
- *HER2* mutations
- *RET* rearrangements
- *NTRK* fusions

Efficacy of Entrectinib in *ROS1+* NSCLC

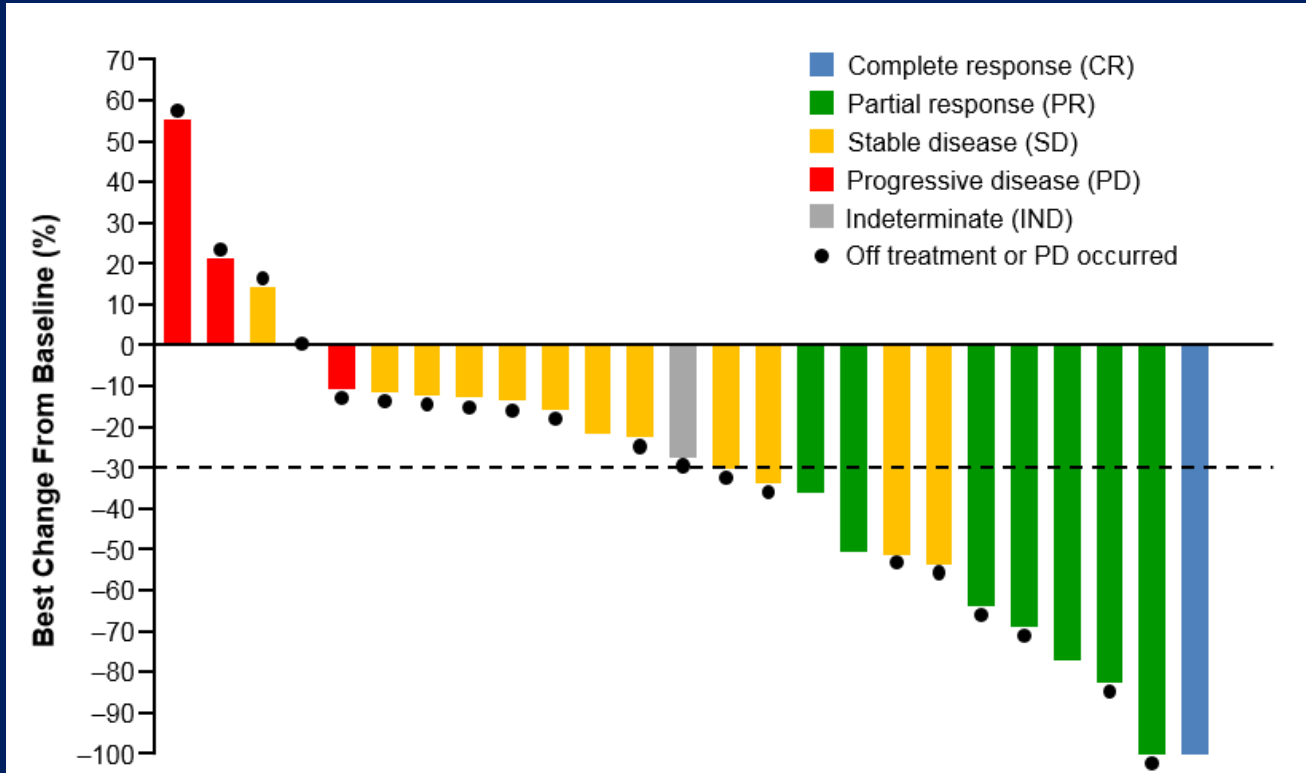
Best Response by BICR, n (%)	Total (N=53)
Objective Response Rate (BICR-ORR)	77.4%
Intracranial BICR-ORR (patients with measurable disease, n=20)	55.0%
Median Duration of Response (BICR-mDOR)	24.6 months
Median Progression-Free Survival (BICR-mPFS) Without CNS disease (n=30) With CNS disease (n=23)	 26.3 months 13.6 months

Doebele et al WCLC 2018

BICR = blinded independent central review

Data cutoff date: 13 September 2017

Lorlatinib in *ROS1* + NSCLC

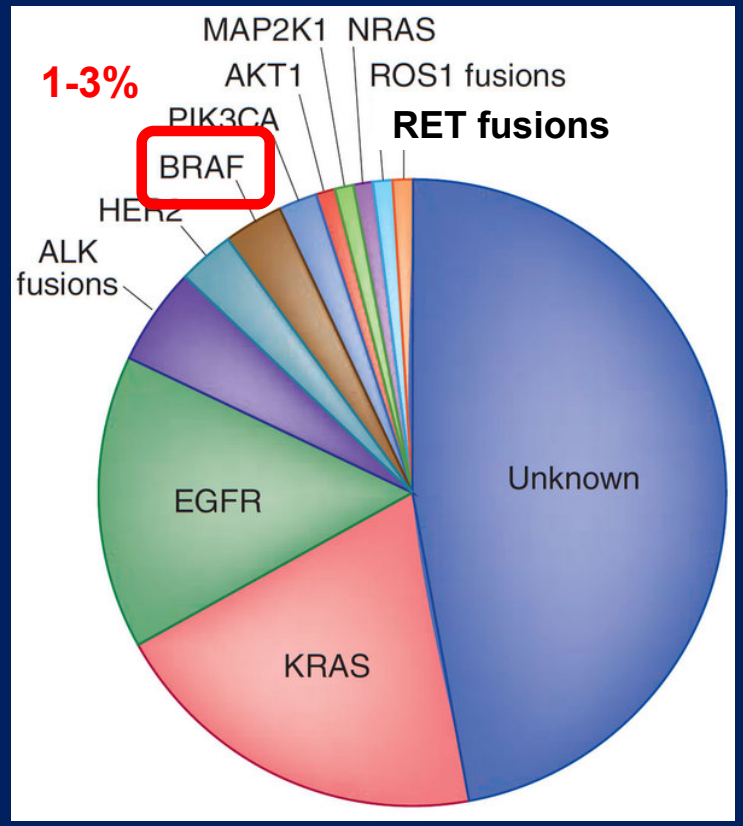


Patients with at least one on-study target lesion assessment as per independent central review were included. If any procedure was different and not interchangeable from the procedure at screening, the percent change from baseline could not be calculated and is not displayed.

TRAEs in ≥10% of Patients, n (%)	Total (N=47)	Grade 3	Grade 4
Hypercholesterolemia*	39 (83.0)	4 (8.5)	0
Hypertriglyceridemia*	28 (59.6)	9 (19.1)	0
Edema*	21 (44.7)	1 (2.1)	0
Peripheral neuropathy*	16 (34.0)	1 (2.1)	0
Cognitive effects*	11 (23.4)	0	0
Weight increased	10 (21.3)	3 (6.4)	0
Dizziness	7 (14.9)	2 (4.3)	0
Mood effects*	6 (12.8)	0	0
Lipase increased	6 (12.8)	3 (6.4)	0
Fatigue*	5 (10.6)	1 (2.1)	0
ALT increased	5 (10.6)	0	0
Arthralgia	5 (10.6)	0	0
Thrombocytopenia	5 (10.6)	0	1 (2.1)

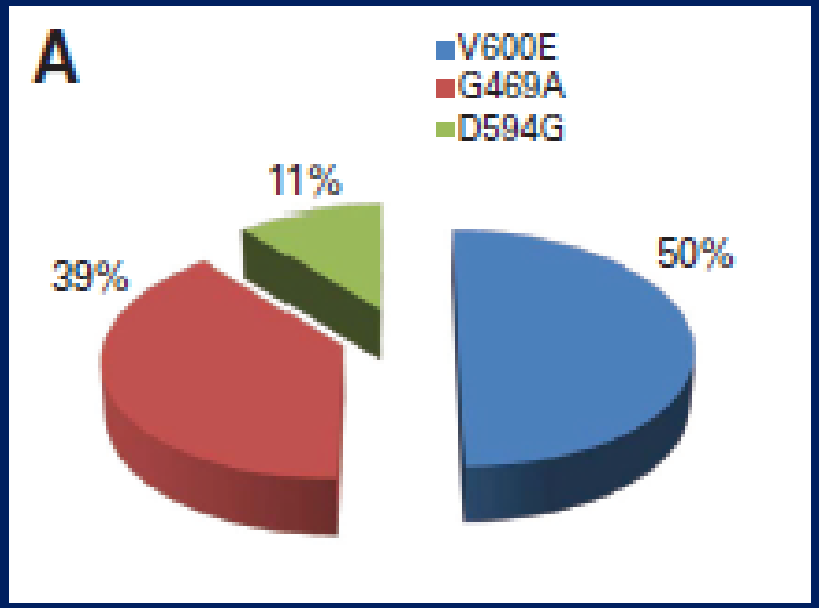
Ou et al WCLC 2018

BRAF mutation in NSCLC



Relative distribution of 'driver' mutations in lung adenocarcinoma.

Pao and Hutchinson 2012



Relative distribution of BRAF mutations in NSCLC.

Paik P et al JCO 2011

BRAF V600E-directed therapy

Agent	ORR	Median DOR (months)	Median PFS (months)	Median OS (months)
Dabrafenib (n=78)	33%	9.6	5.5	12.7
Vemurafenib (n=14)	43%	Not available	Not available	Not available
Vemurafenib (n=19)	42%		7.3	NR
Dabrafenib/Trametinib (n=59)	63.2%	9.0	9.7	NR
Dabrafenib/Trametinib (n=36)	64%	10.4	10.2	24.6 months

Planchard et al Lancet Oncology May 2016, Planchard et al Lancet Oncology July 2016, Planchard et al Lancet Oncology 2017, Hainsworth JCO 2018, Hyman et al NEJM 2015

Dabrafenib alone and with trametinib in *BRAF* V600E NSCLC: Adverse events

Treatment	Grade 3 AE's ≥ 5%	Treatment delivery
Dabrafenib	Squamous cell carcinoma (12%) Asthenia (5%) basal cell carcinoma (5%),	6% discontinued due AE 43% required dose interruption 18% required dose reduction
Dabrafenib/trametinib (previously treated)	Neutropenia (9%) Hyyponatremia (7%) Anemia (6%)	12% discontinued due AE 61% required dose interruption or delay 58% of patients received 80% of planned dabrafenib 75% of patients received 80% planned trametinib
Dabrefenib/trametinib (first-line)	Pyrexia (11%) ALT increase (11%) HTN (11%) Vomiting (8%)	AE's leading to treatment discontinuation (22%), dose interruption (75%), and dose reduction (39%) Dose reduction dabrafenib: 47%, Dose reduction trametinib 28%

Planchard et al Lancet Oncology 2016, Planchard et al Lancet Oncology 2016, Planchard Lancet Oncology 2017

BRAF Non-V600E mutations

First author	Therapy	# of patients	ORR	PFS	OS
Mazieres et al	Vemurafenib	17	0%	1.8 month	5.2 months
Hainsworth et al	Vemurafenib	23*	4%	Not available	Not available
Gautschi et al	Vemurafenib or dabrafenib	6**	17% (1 of 6)	1.5 months	11.8 months

* Number includes patients with all tumor types. Cohort stopped for futility
** Retrospective study and subset analysis for non-V600E

Mazieres et al WCLC 2018, Hainsworth et al JCO 2018, Gautschi et al JTO 2015

MET exon 14 alterations

- Introns flanking *MET* exon 14 in pre-mRNA are spliced out resulting MET mRNA which is translated into functional MET receptor
- *MET* exon 14 encodes the ubiquitin ligase binding site which is used in receptor degradation
- Mutations that disrupt splice sites result in *MET* exon 14 skipping producing a MET receptor that lacks ubiquitin binding site ⟶ reduced degradation of MET protein ⟶ sustained MET activation
- Next generation sequencing the preferred testing method
- *MET* exon 14 skipping mutations in 20-30% of pulmonary sarcomatoid carcinoma, and can be seen in squamous histology
- Median age 73 years

Drilon et al JTO 2017, Liu et al JCO 2016

Crizotinib in *MET* amplified NSCLC: Context matters

MET/CEP7 ratio	N	ORR	PFS
≥1.8 to ≤ 2.2	3	33%	1.8
> 2.2 to < 4.0	14	14.3%	1.9
≥ 4.0	20	40%	6.8

- MET amplified defined by copy number as well. Copy number cut-off vary depending on testing
- MET amplification present in 15-20% of samples of MET exon 14 alteration
- 2/19 patients of *MET* amplified patients had *MET* exon 14 alterations (10.5%)

Camidge et al ASCO 2018

Frequency of *MET* alterations

Molecular alteration	Screening	# of positive cases	Pts included
MET amplification	4191	252 (6.0%)	25 patients
MET mutation	1192	86 (7.2%)	29 patients

Moro-Sibilot et al WCLC 2018

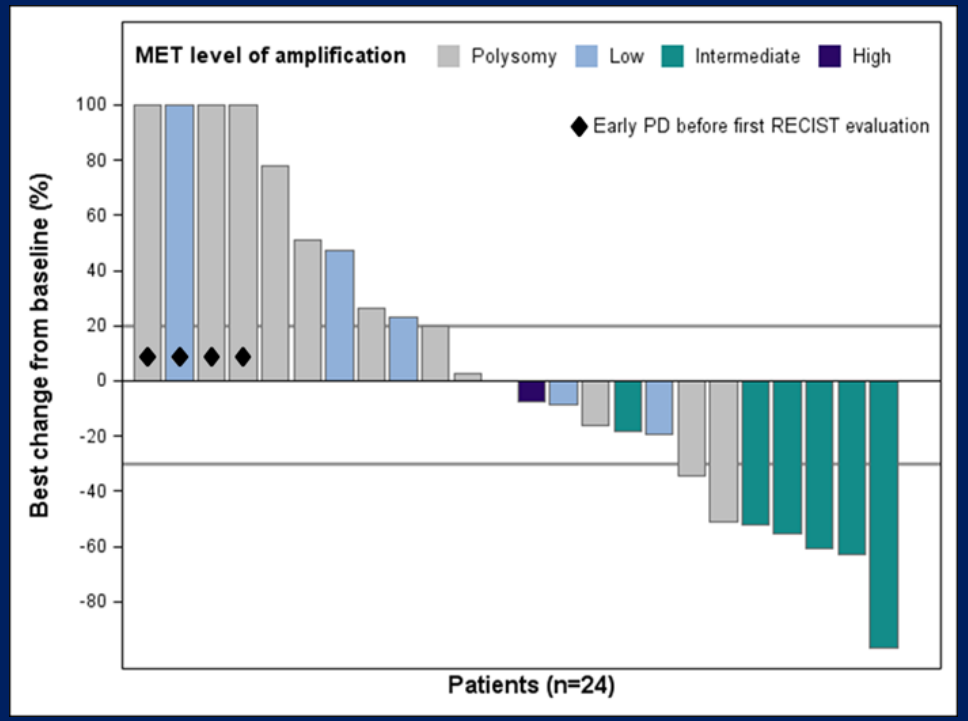
Select patient characteristics

Patient and disease characteristics	*MET* amplification	*MET* mutation
Number	25 Median copy #: 8 (6-12)	28 Exon 14: n=25)
Male	56%	32%
Median age (range)	59 (30-92)	72 (35-85)
Adenocarcinoma	21 (84%)	26 (92%)
Smokers (current and former)	18 (76%)	11 (52%)
Brain metastases	5 (20%)	7 (25%)

Moro-Sibilot et al WCLC 2018

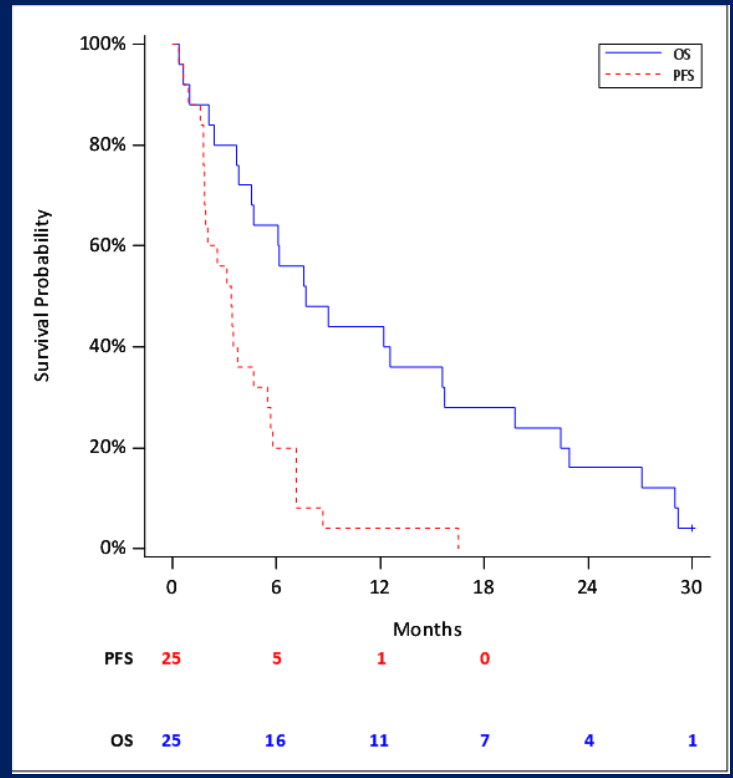
MET amplification

Response



ORR: 32% (8/25)

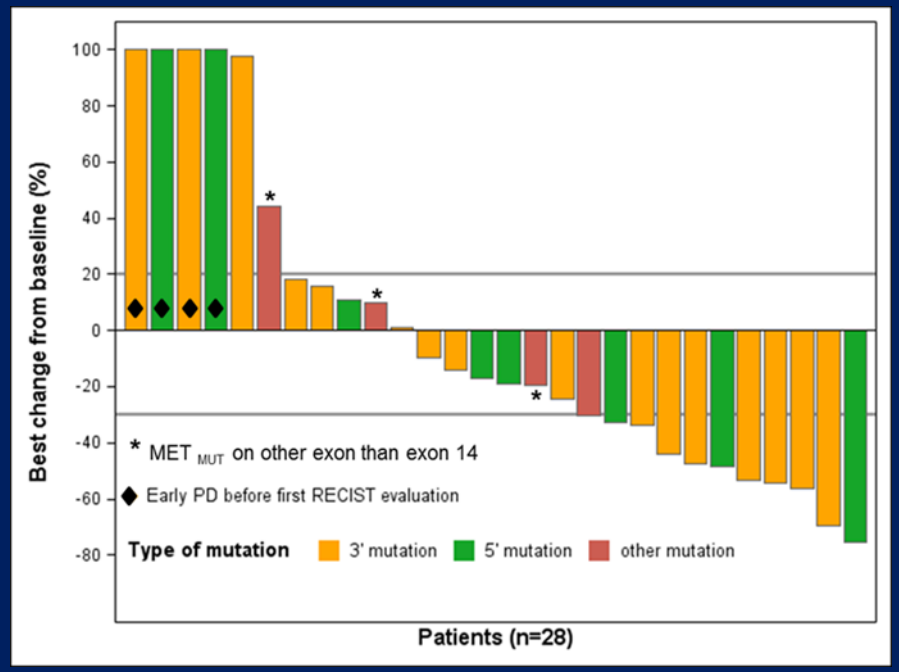
PFS and OS



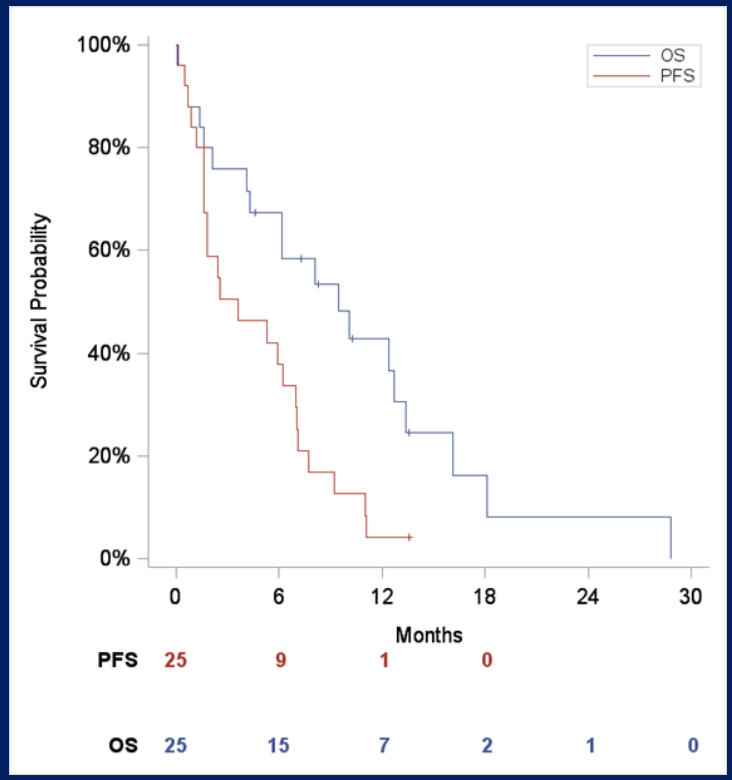
Median PFS: 3.4 months
Median OS: 7.7 months

Moro-Sibilot et al WCLC 2018

MET exon 14 mutation



ORR 40% (10/25)

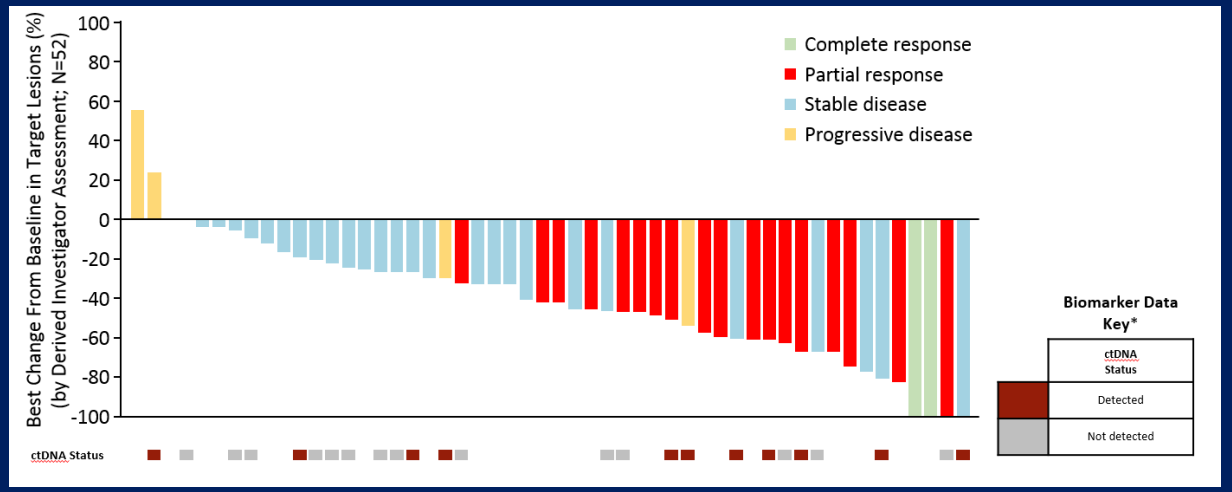


Moro-Sibilot et al WCLC 2018

Median PFS 3.6 months
Median OS: 9.5 months

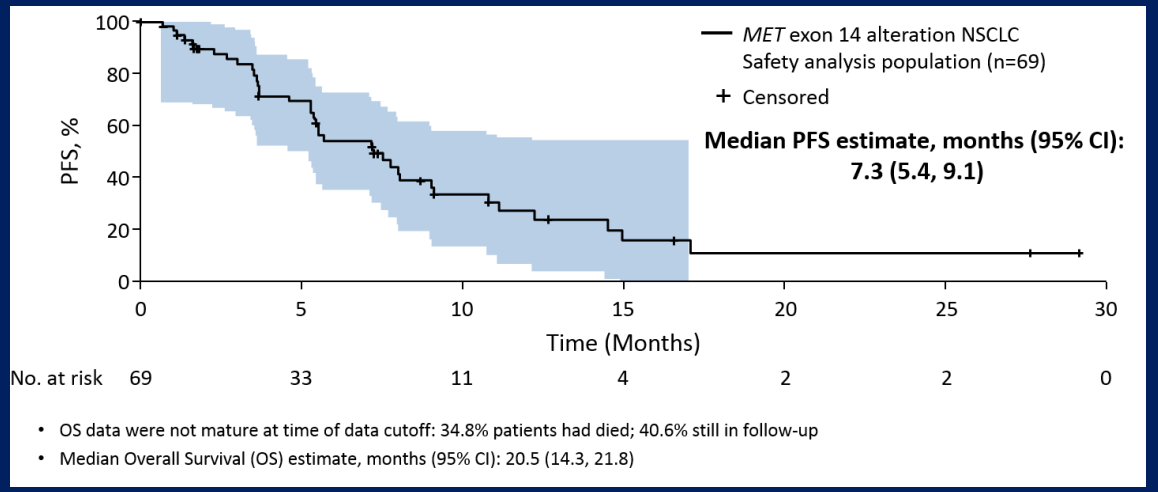
Crizotinib in *MET* exon 14 alterations

Responses



ORR: 32% (28/65)
DOR: 9.1 months

Progression-free survival



Median OS: 20.5 months

Drilon et al WCLC 2018

Novel agents MET exon 14 agents

Agent	Patient population	ORR	PFS
Capmatinib (INC280)	MET exon 14 Pre-treated	39% 27/69	Not available
Capmatinib (INC280)	MET exon 14 Treatment naïve	72% (18/25)	Not available
Tepotinib	MET exon 14 Pre-treated	35% (14/40)	Not available

Wolf et al ESMO 2018, Felip et al WCLC 2018

RET rearranged NSCLC

- *RET* rearrangements are detected in 1-2% of adenocarcinomas, 8% among patients who are *EGFR* and *ALK* negative
- *RET* proto-oncogene is rearranged with partner gene: *KIF5B* most common but others are *CCDC6*, *NCOA4, or TRIM33*
- Multi-targeted TKI's investigated in prospective phase 2 studies
- Frequent dose reductions for "off target" toxicities were observed, often related to VEGF and/or EGFR activity

Gautschi et al JCO 2017, Yoh et al Lancet Respiratory 2017, Drilon et al Lancet Oncology 2016, Lee et al Annals of Oncology 2017

Phase 2 trials of RET inhibitors

Agent	# of patients	ORR	PFS	Dose reduction
Vandetanib	17	47% (n=9) 95% CI: 24-71%	4.7 months 95% CI: 2.8-8.5	53% of patients
Vandetanib	18	18% (n=3)	4.5 months	22% of patients
Cabozantinib	26	28% (n=7) 95% CI: 12-49%	5.5 months 95% CI: 3.8-8.4	73% of patients
Platinum-based chemotherapy*	84	51% (n=33) 95% CI: 38-63	7.8 months 95% CI: 5.3-10.2	

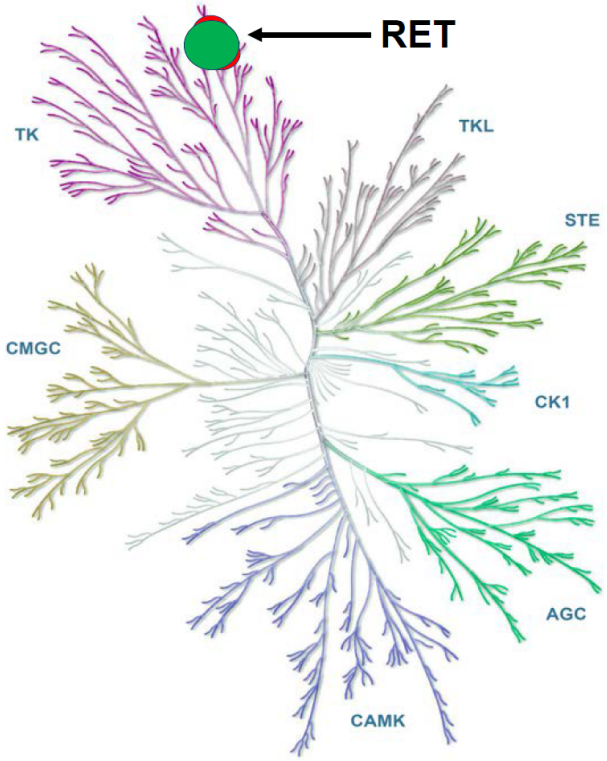
- 0f 84 patients 66 received platinum-pemetrxed
- Median OS 24.8 months

Yoh et al Lancet Respiratory 2017, Drilon et al Lancet Oncology 2016, Lee et al Annals of Oncology 2017

LOXO-292 is a potent and selective RET inhibitor

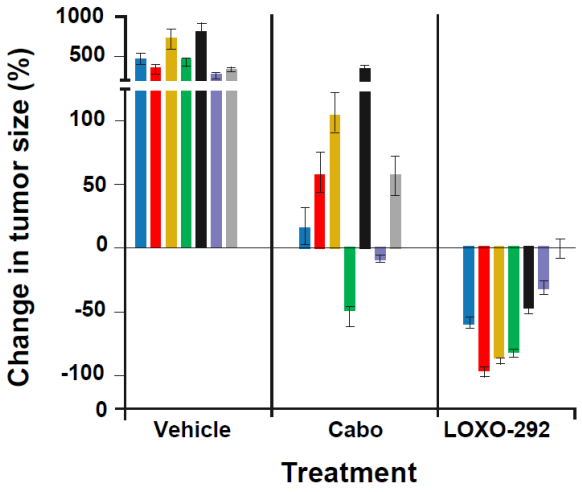
Kinome selectivity

Highly selective for RET



Xenograft models

Multiple fusions/mutations/histologies

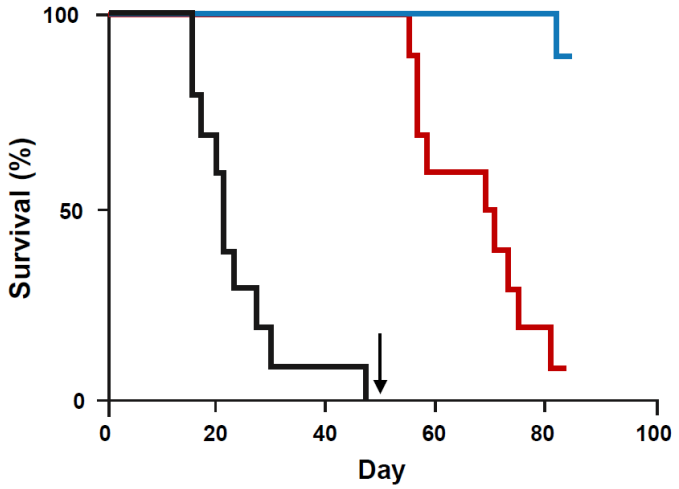


Tumor models

- KIF5B-*RET* (PDX-NSCLC)
- CCDC6-*RET* (PDX-CRCA)
- CCDC6-*RET*-V804M (PDX-CRCA)
- KIF5B-*RET* (NIH-3T3)
- KIF5B-*RET*-V804M (NIH-3T3)
- RET C634W (TT cell line-MTC)
- CCDC6-*RET* (LC-2/ad cell line-NSCLC)

Orthotopic brain model

CCDC6-RET orthotopic brain PDX



Treatments

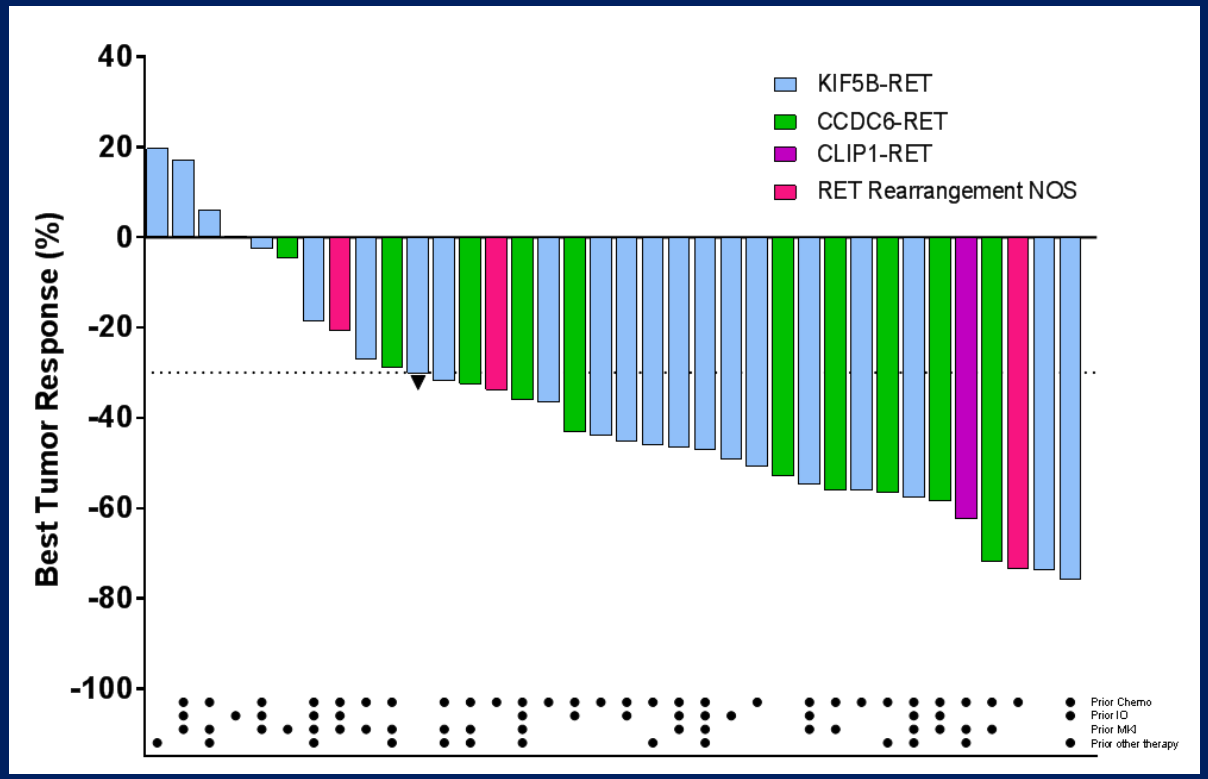
- Vehicle
- LOXO-292 30 mg/kg BID → Day 52 → 3 mg/kg BID
- Ponatinib 20 mg/kg QD → Day 52 → 2 mg/kg QD

Oxnard et al WCLC 2018

Subbiah et al. Ann Oncol 2018; Cabo = cabozantinib; PDX = patient-derived xenograft; NSCLC = non-small cell lung cancer; CRC = colorectal cancer; MTC = medullary thyroid cancer; BID = twice-daily; QD = once-daily

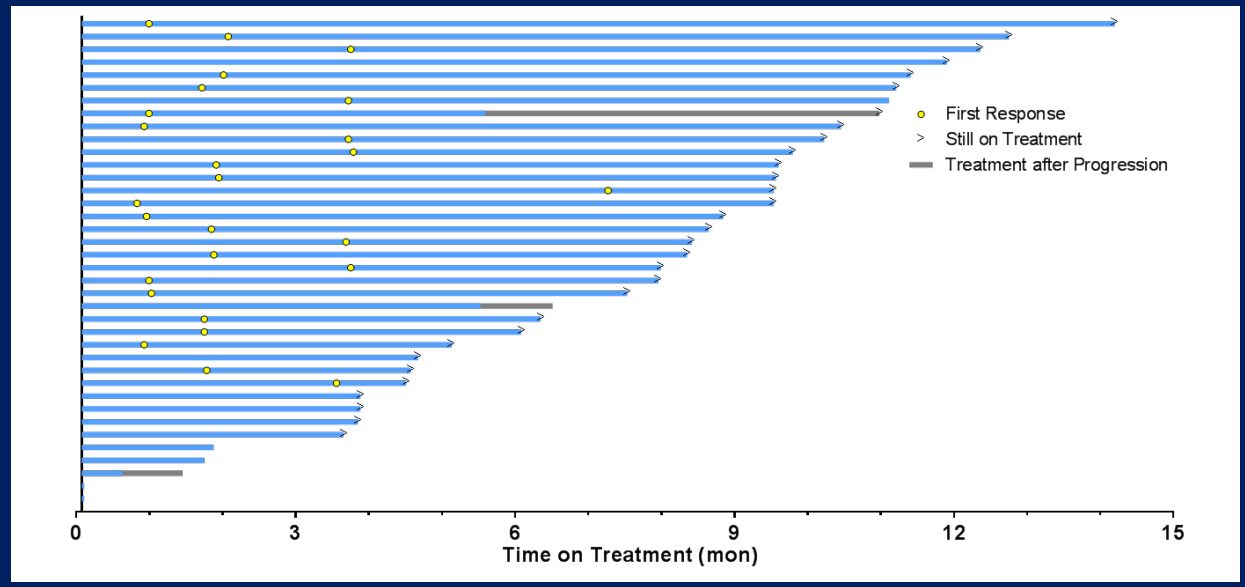
Efficacy of LOXO-292 in RET fusion NSCLC

Responses



ORR: 68% (26/38)

Swimmers plot



24/26 responses on going at time of analysis

Oxnard et al WCLC 2018

LOXO-292 safety profile

	All doses and patients, n=82							
	Treatment-emergent AEs (≥10% overall)					Treatment-related AEs		
	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total
Diarrhea	15%	7%	1%	-	23%	1%	-	11%
Fatigue	9%	13%	-	-	22%	-	-	17%
Dry Mouth	21%	-	-	-	21%	-	-	13%
Constipation	17%	2%	-	-	20%	-	-	4%
Hypomagnesemia	12%	1%	-	-	13%	-	-	2%
Cough	11%	1%	-	-	12%	-	-	1%
Headache	10%	1%	1%	-	12%	-	-	1%
Nausea	9%	4%	-	-	12%	-	-	5%

- Most treatment-emergent AEs were Grade 1 in severity and judged not related to LOXO-292
- Four patients experienced treatment-related AEs ≥ grade 3: diarrhea, increased ALT/AST, thrombocytopenia (DLT @ 240mg BID), tumor lysis syndrome (DLT @ 240mg BID)
- Dose exploration ongoing at 200 mg BID

AE = adverse event; DLT = dose limiting toxicity; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Note: Total %s for any given AE may be different than the sum of the individual grades, due to rounding. Patients enrolled as of April 2, 2018. Follow-up as of July 19, 2018.

Oxnard et al WCLC 2018

Phase 1 trial of BLU-667 in patients with advanced RET-altered solid tumors

- 53 patients enrolled: 29 medullary thyroid cancer and 19 NSCLC
- MTD 400 daily with dose-limiting toxicities of hyponatremia and hypertension
- Grade ≥ 3 AE's: increased liver tests, hypertension, diarrhea, fatigue, neutropenia
- Response evaluable patients (n=40): CR 1 (3%), PR 17 (43%), SD 20 (50%), PD 2 (5%)
- ORR in RET-fusion NSCLC: 50%
- 41 of 51 RET altered patients remain on treatment

Subbiah et al AACR 2018, Subbiah et al Cancer Discovery 2018

NTRK gene rearrangements

- Gene rearrangements on *NTRK1*, *NTRK2*, and *NTRK3* and multiple gene partners
- FISH and NGS can identify alteration
- Screened 1,378 cases of NSCLC, *NTRK1* gene rearrangements identified in 0.1%
- Present in papillary thyroid cancer, cholangiocarcinoma, glioblastoma, sarcomas
- Larotrectinib potent and selective inhibitor of all 3 TRK proteins

Vaishnavi et al Nature Medicine 2013, Farago et al JTO 2015, Stransky et al Nature Communications 2014, Drilon et al NEJM 2018

Larotrectinib in *TRK*-fusion cancers

Diseases

Tumor type	#/ percentage
Salivary gland tumor	12 (22%)
Soft tissue sarcoma	11 (20%)
Infantile fibrosarcoma	7 (13%)
Thyroid cancer	5 (9%)
Colon cancer	4 (7%)
Lung cancer	4 (7%)
Melanoma	4 (7%)
GIST	3 (5%)
Cholangiocarcinoma	2 (4%)
Appendix	1 (2%)
Breast	1 (2%)
Pancreas	1 (2%)

Efficacy

Parameter	Result
ORR	75% (41/55)
Median time to response	1.8 months
Median duration of response	NR
Median PFS	NR
1-year PFS	55%

Drilon et al NEJM 2018

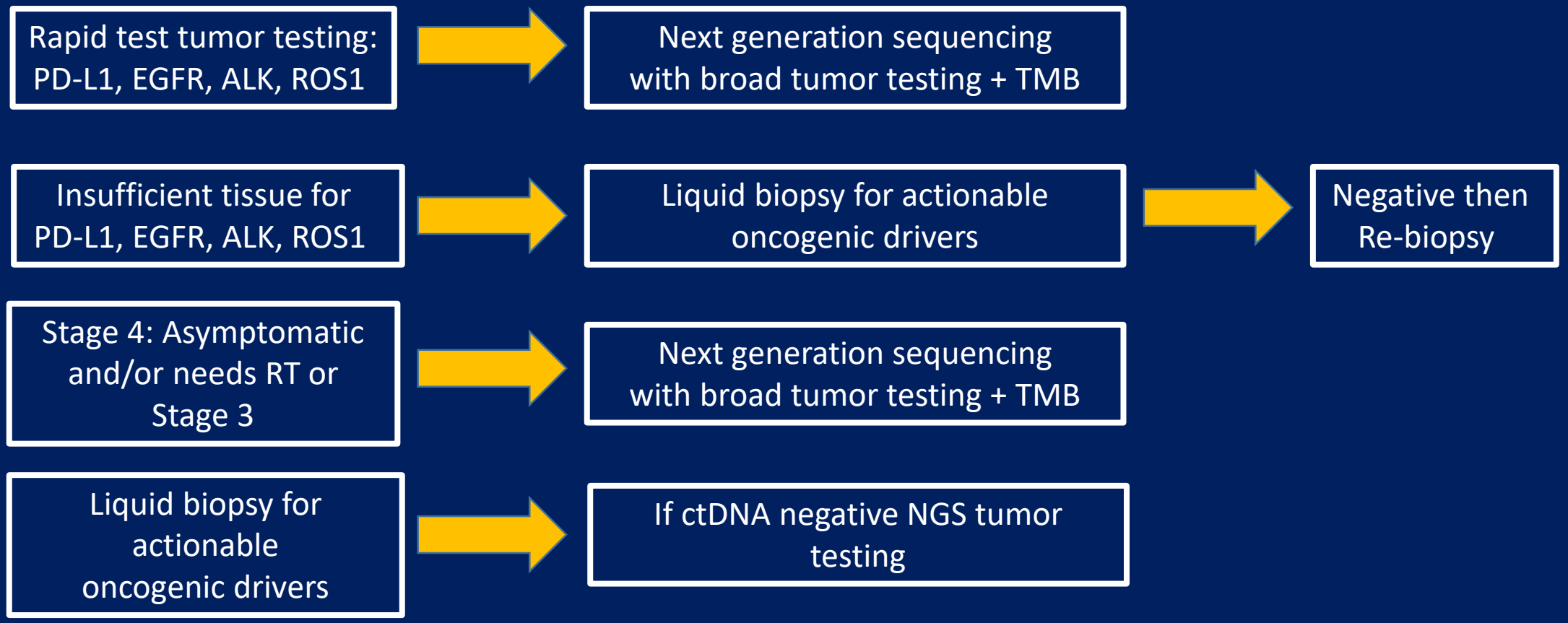
Emerging targeted agents for patients with metastatic NSCLC

Genetic Alteration (i.e. driver event)	Available targeted agent
High level *MET* amplification or *MET* exon 14 skipping mutation	Crizotinib
RET rearrangements	Cabozantinib, vandetanib
HER2 mutations	Ado-trastuzumab emtansine
Tumor mutation burden	Nivolumab +/- ipilimumab

Note: All recommendations are category 2A unless otherwise indicated
Clinical trials: NCCN believes that the best management of any patient with cancer is a clinical trial. Participation in clinical trials is especially encouraged.

https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf-accessed 2/19/2018 Version 3.2019

Testing strategies: one size does not fit all



My thoughts

- *ROS1* crizotinib the standard therapy. Novel first and second-line agents may become available
- *BRAF* V600E: dabrafenib and trametinib standard option
- *MET* exon 14 and MET amplified promising target: crizotinib active, but need to develop new agents
- *HER2* mutant: current TKI's limited activity, and T-DM1 promising but needs further validation
- RET inhibitor LOXO-292 reveals promising activity and tolerable side effects. BLU-667 in development as well
- Supports wider used on NGS or broad testing methods for rare mutations