FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

RET, MET & BRAF in Non-Small Cell Lung Cancer

Edgardo S. Santos, M.D., FACP
Founding Member, Florida Precision Oncology R & C
Thoracic Oncology
Clinical Affiliate Associate Professor
Charles E. Schmidt College of Medicine
Florida Atlantic University
Aventura-Boca Raton-Miramar/Florida, USA

21st Century Oncology

BE

March 8, 2020

Faculty Disclosures

Edgardo S. Santos, MD, FACP

- ***Speaker Bureau***: Genentech, Boehringer-Ingelheim, Astrazeneca, Pfizer, Novartis, Merck, Amgen, Sanofi-genzyme, Takeda, Celgene, Dova, Astellas, Eli Lilly, Caris, Paradigm Diagnostics, Biodesix, Guardant Health.
- ***Advisor:*** Eli Lilly, BluePrint Medicine, Astrazeneca, Inivata, Oncocyte.
- ***Research Support***: None
- ***Employment:*** None
- ***Stocks/Royalty:*** None

21st Century Oncology

BE

Program Objectives for This Lecture:

RET

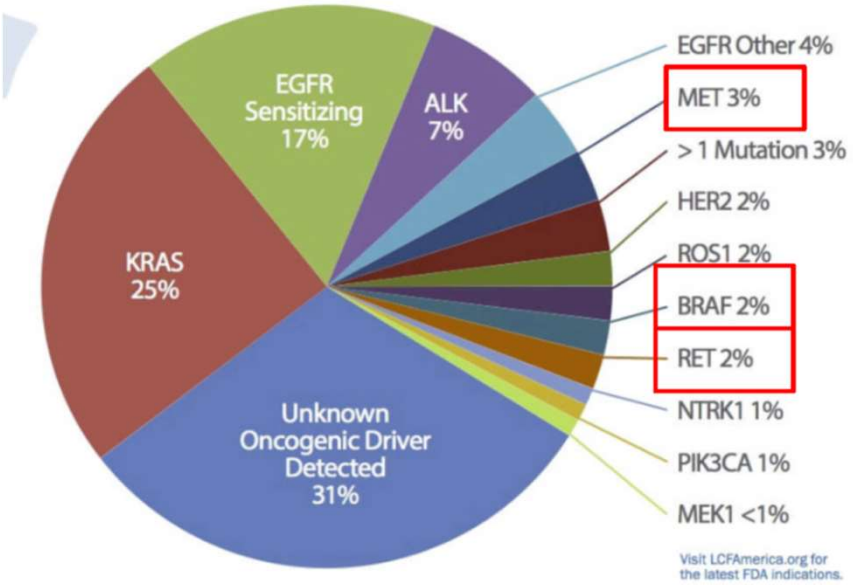
- ARROW (Pralsetinib [BLU-667])
- LIBRETTO-001 (Selpercatinib [LOXO-292]

MET

- VISION (Tepotinib)
- GEOMETRY (Capmatinib)

B-RAF

- BRF113928 (Dabrafenib/Tremetinib)



FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

21st Century Oncology

BE

RET

FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

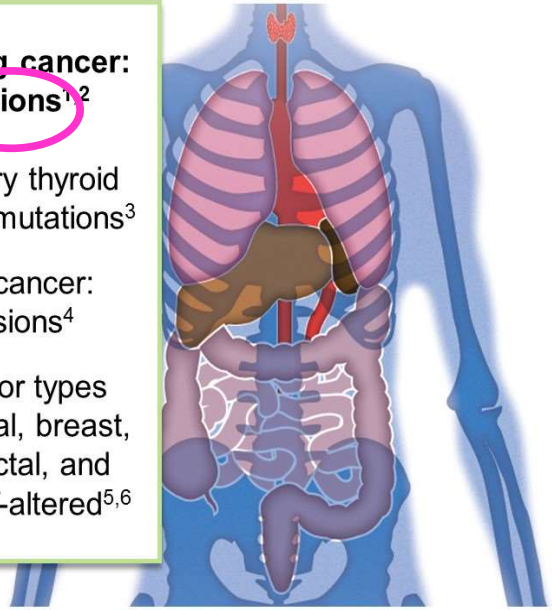
RET Alterations: Diverse Oncogenic Drivers Lacking Targeted Therapeutic Approach

Non-small cell lung cancer: ~1-2% RET fusions[1,2]

Advanced medullary thyroid cancer: ~90% RET mutations[3]

Papillary thyroid cancer: ~20% RET fusions[4]

Multiple other tumor types including esophageal, breast, melanoma, colorectal, and leukemia: <1% RET-altered[5,6]



NSCLC patients with RET fusions have not significantly benefited from existing therapy

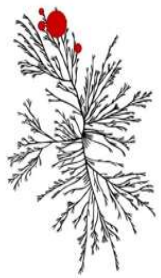
- Chemotherapy: nonspecific, low response rates, significant toxicity
- Checkpoint inhibition: Preliminary evidence for lack of benefit in RET-altered NSCLC[7]
- Multikinase inhibitors: ↓ activity, ↑ off-target toxicity[8,9]

No selective RET inhibitors are approved

NSCLC, non-small cell lung cancer; ORR, overall response rate; PFS, progression-free survival. 1. Lipson, et al. *Nat Med* 2012; 2. Takeuchi, et al. *Nat Med 2012*; 3. Romei, et al. *Oncotarget* 2018; 4. Santoro, et al. *J Clin Invest* 1992; 5. Kato, et al. *Clin Cancer Res* 2017; 6. Ballerini, et al. *Leukemia* 2012; 7. Mazieres, et al. *JCO* 2018; 8. Drilon, et al. *Lancet* 2017; 9. Yoh, et al. *Lancet Respir Med* 2017

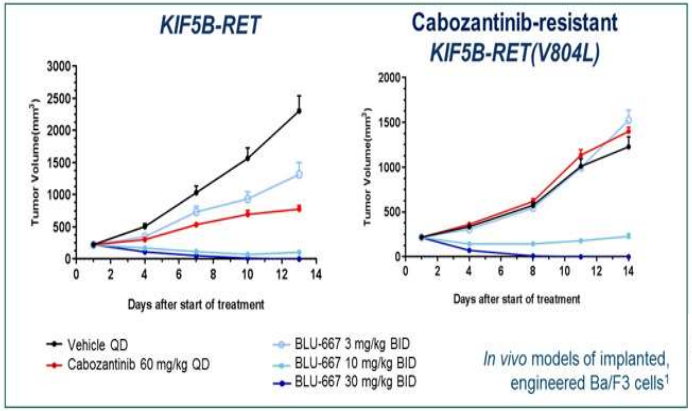
BLU-667 Potently and Selectively Inhibits RET Alterations and Resistance Mutants

BLU-667: High kinome selectivity for RET[a]



BLU-667 vs. pharmacologically relevant kinases:

- ~90-fold more selective for RET than VEGFR2
- 20-fold more selective for RET than JAK1

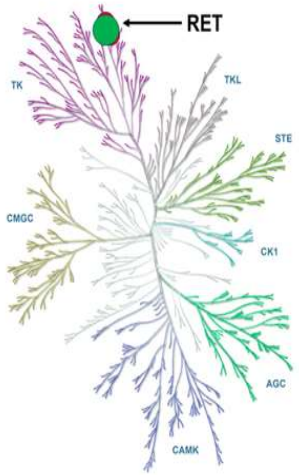


BLU-667 Cellular activity in KIF5B-RET[2]

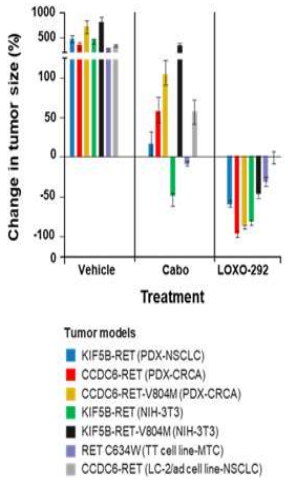
	KIF5B-RET	KIF5B-RET V804L	KIF5B-RET V804M	KIF5B-RET V804E
BLU-667	10.1 nM (1x)	8.1 nM (0.8x)	14.1 nM (1.4x)	8.1 nM (0.8x)

Selpercatinib* (LOXO-292) is a potent and selective RET Inhibitor

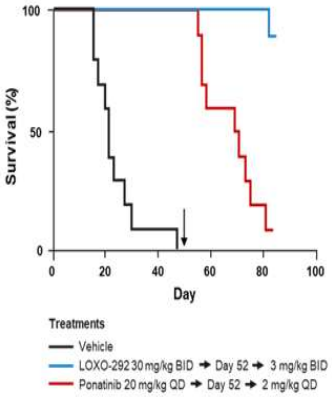
Kinome selectivity
Highly selective for RET



Xenograft models
Multiple fusions/mutations/histologies



Orthotopic brain model
CCDC6-RET orthotopic brain PDX



FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

21st Century Oncology

BE

PRALSETINIB

ARROW: BLU-667 Dose-Escalation and Expansion Study

Part 1: Dose-Escalation (N=62; Complete)[1]

RET-altered advanced solid tumors

BLU-667: 30-600 mg by daily oral administration (QD or BID)

Phase 2 dose determined (400 mg QD) →

ARROW is registered with clinicaltrials.gov (NCT03037385)

Part 2: Expansion Cohorts (Ongoing)

BLU-667 400 mg QD

- Unresectable, advanced solid tumor
- RET alteration status by local tumor testing
- No additional driver mutation
- ECOG PS 0-1
- Asymptomatic brain metastases allowed
- Progressive disease or intolerant to SOC therapy, or not a candidate

Primary objectives:

Overall response rate (RECIST 1.1)

Safety

- RET fusion+ NSCLC, prior platinum (n=80)
- RET fusion+ NSCLC, platinum naïve (n=40)
- MTC, prior cabozantinib or vandetanib (n=60)
- MTC, no prior cabozantinib or vandetanib (n=40)
- Other RET fusion+ tumors (n=40)
- Other RET-mutated tumors (n=20)
- RET-altered, prior selective RET inhibitor (n=20)

21st Century Oncology

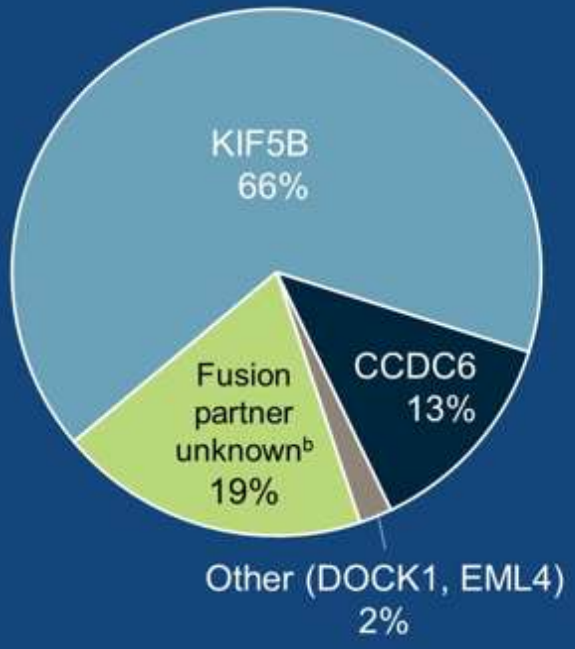
BE

PRALSETINIB

Baseline Characteristics
RET Fusion+ Advanced NSCLC Patients

Characteristic	RET-Fusion+ Advanced NSCLC 400 mg QD Starting Dose	
	All (N=120)	Prior Platinum (N=91)
Age (years), median (range)	60 (28-87)	60 (28-85)
Male, n (%)	59 (49)	45 (49)
ECOG PS, n (%)		
0	46 (38)	33 (36)
1-2	74 (62)	58 (64)
Brain metastases, n (%)	48 (40)	36 (40)
Prior systemic regimens, median (range)	2 (0-11)	2 (1-11)
Any prior anticancer treatment	101 (84)	91 (100)
Chemotherapy, n (%)	92 (77)	91(100)
PD-1 or PD-L1 inhibitor, n (%)	47 (39)	41 (45)
Chemotherapy + PD-(L)1 combination, n (%)	41 (34)	41 (45)
Multikinase inhibitor, n (%)	21 (18)	20 (22)
Smoking history[a]		
Current/Prior	41 (34)	33 (36)
Never	78 (65)	57 (63)
Histology		
Adenocarcinoma	114 (95)	87 (96)
Other	6 (5)	4 (4)

RET Fusion Partner

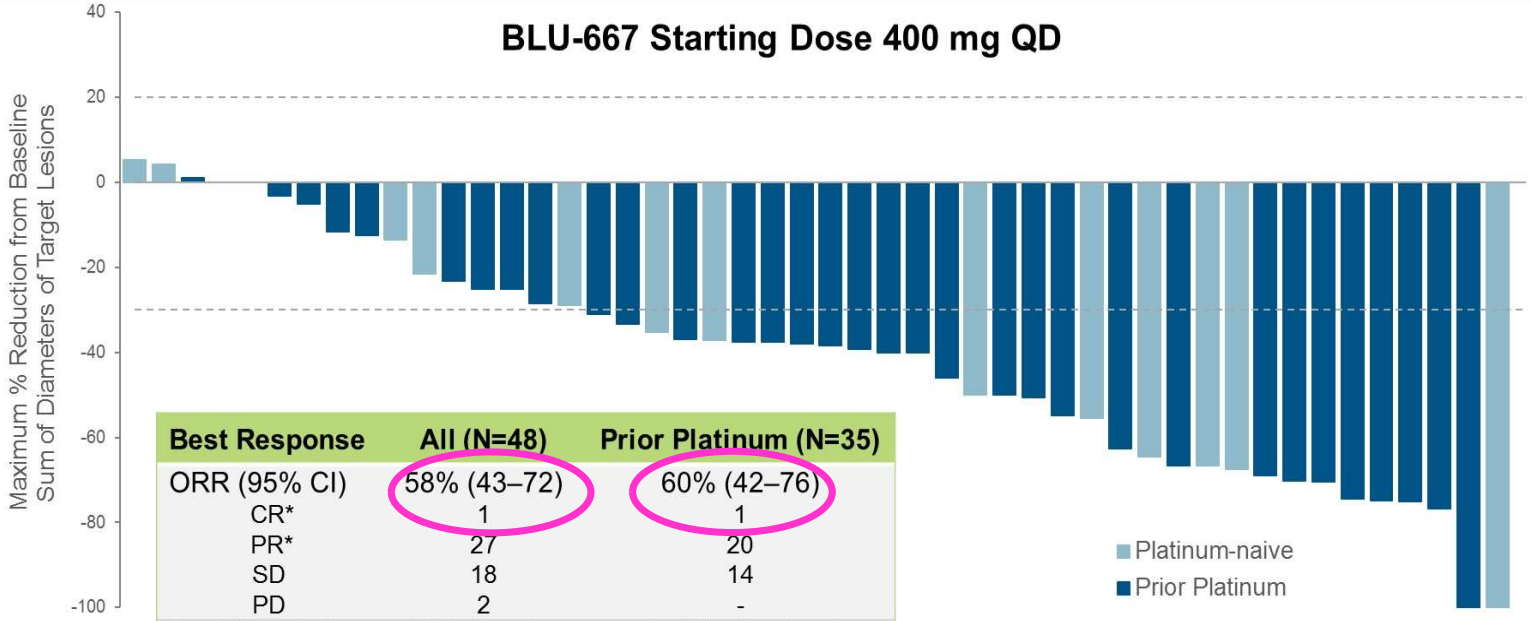


21st Century Oncology

BE

PRALSETINIB

BLU-667 Demonstrates Substantial Antitumor Activity in RET Fusion+ Advanced NSCLC



Best Response	All (N=48)	Prior Platinum (N=35)
ORR (95% CI)	58% (43–72)	60% (42–76)
CR*	1	1
PR*	27	20
SD	18	14
PD	2	-
DCR (95% CI)	96% (86–99)	100% (90–100)

* All responses are confirmed on two consecutive assessments as per RECIST 1.1.

- 5/7 (71%) treatment-naïve patients had confirmed PR

CI, confidence interval; CR, complete response; DCR, disease control rate (best response of SD or better); ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease. Patients enrolled by 14 Nov 18, data cut-off 28 Apr 19. Response-evaluable population includes patients with measurable disease at baseline and ≥1 evaluable post-treatment disease assessment, and excludes 4 patients who previously received >1 cycle of a selective RET inhibitor.

FLORIDA PRECISION ONCOLOGY

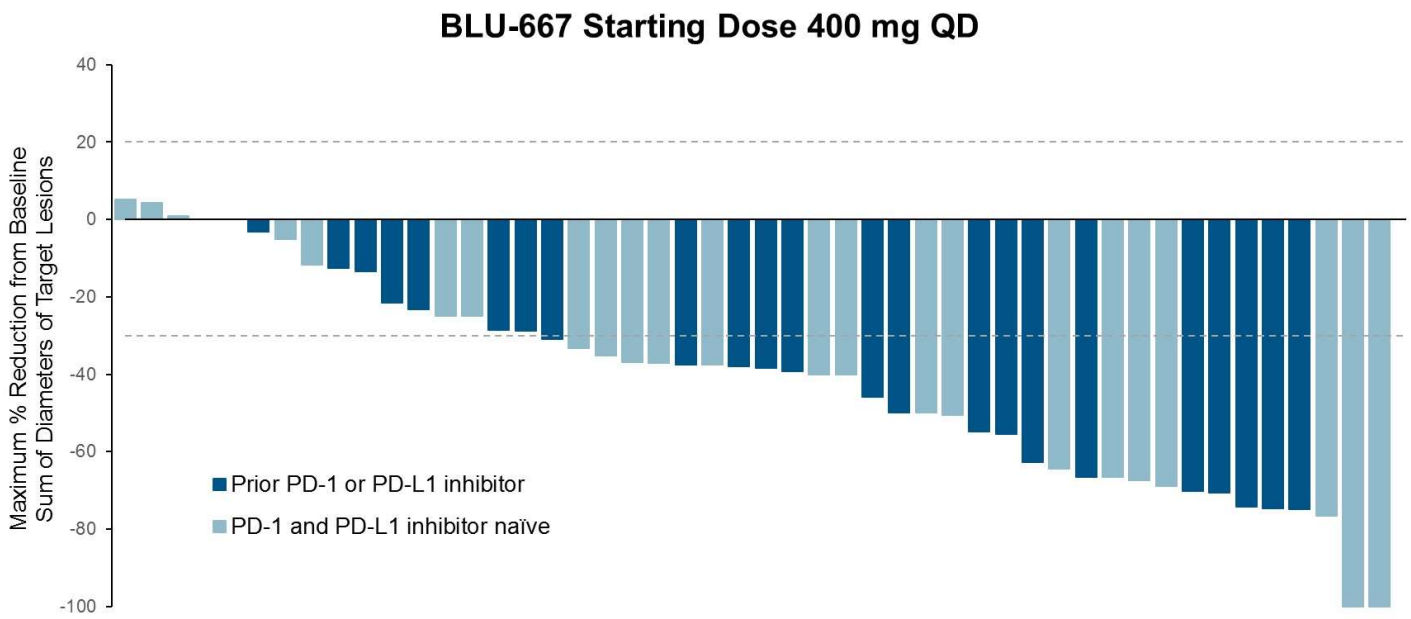
a Division of 21st Century Oncology

21st Century Oncology

BE

PRALSETINIB

BLU-667 is Active Regardless of Prior Checkpoint Treatment



PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: Justin F. Gainor

Patients enrolled by 14 Nov 18, data cut-off 28 Apr 19.

FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

21st Century Oncology

BE

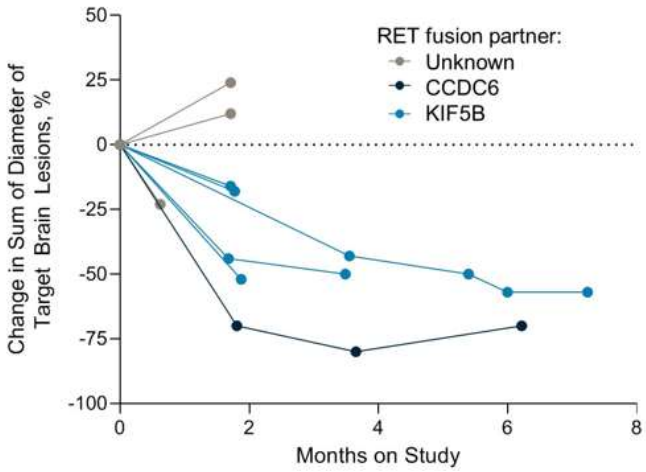
PRALSETINIB

FLORIDA PRECISION ONCOLOGY

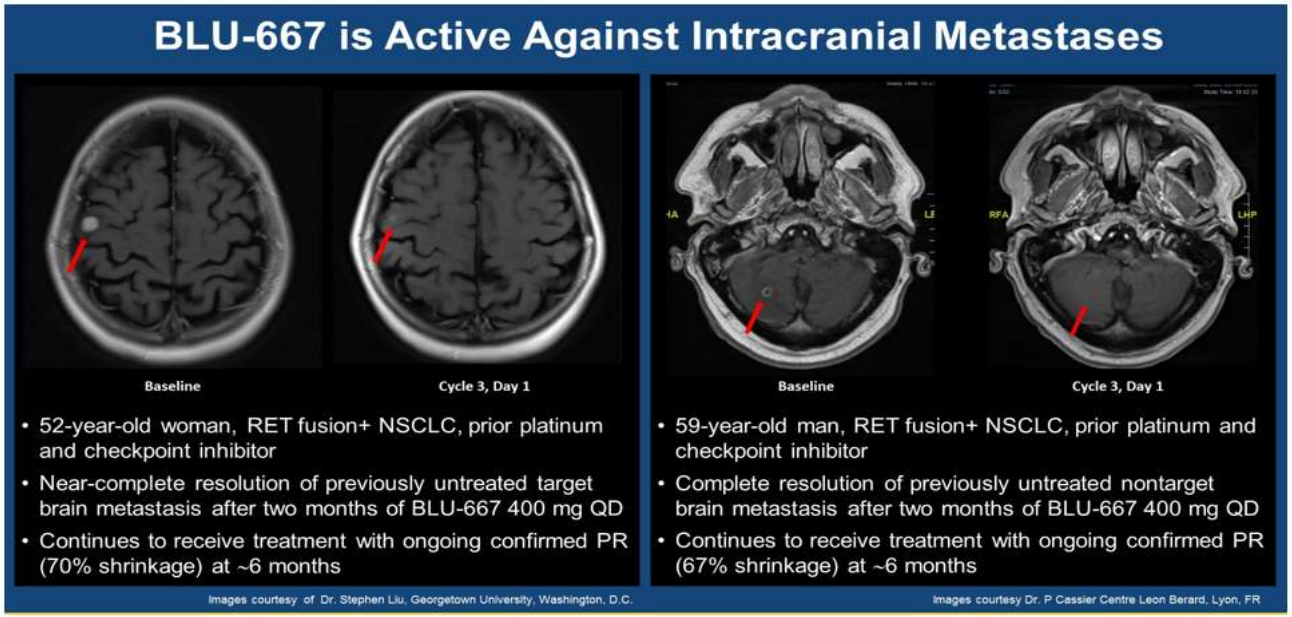
a Division of 21st Century Oncology

BLU-667 is Active Against Intracranial Metastases

Shrinkage of Brain Metastases[a]



- 7 of 9 (78%) patients had shrinkage of measurable brain metastases
- No patients at 400 mg QD starting dose had progression due to new CNS involvement



21st Century Oncology

BE

PRALSETINIB

FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

BLU-667 is Well Tolerated by Patients with RET Fusion+ Advanced NSCLC

	RET Fusion+ Advanced NSCLC 400 mg QD Starting Dose (N=120)			
	Treatment-Emergent (≥15% overall)		Treatment-Related	
Adverse Events	All	Grade ≥3	All	Grade ≥3
Constipation	30%	2%	17%	2%
Neutropenia[a]	26%	13%	26%	13%
AST increased	24%	5%	20%	2%
Fatigue	21%	3%	13%	3%
Hypertension	20%	13%	13%	10%
Anemia	18%	7%	11%	4%
Diarrhea	18%	2%	9%	-
Pyrexia	18%	-	2%	-
ALT increased	17%	3%	13%	2%
Cough	17%	-	3%	-
Dry mouth	17%	-	12%	-

Additional grade ≥3 treatment related AEs (≥2%): increased CPK (3%), leukopenia[b] (3%).

Among 120 pts with advanced NSCLC receiving BLU-667 starting dose of 400 mg QD:

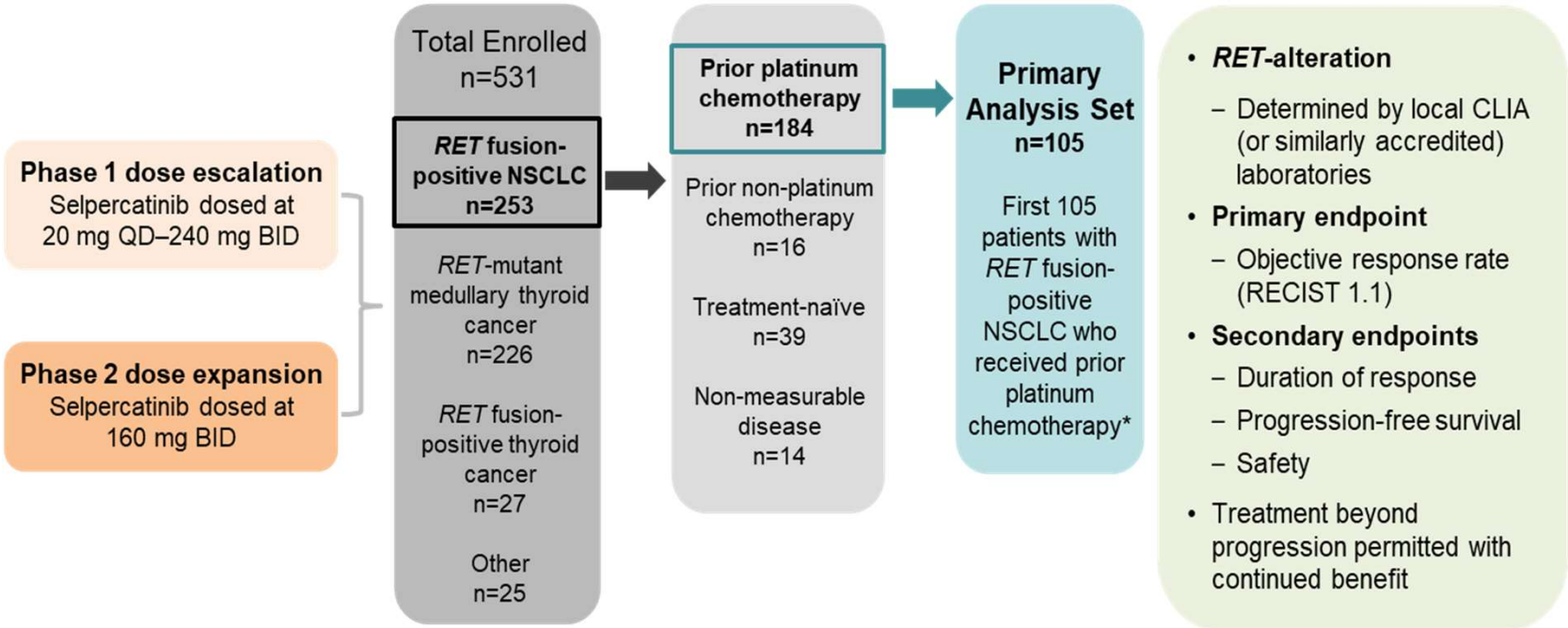
- Treatment-related toxicity is generally low-grade and reversible
- 7% discontinued BLU-667 due to treatment-related toxicity*
  - Pneumonitis, respiratory distress/ hypoxemia, mucositis/colitis, myelosuppression, gait disturbance, anemia

* *Across the entire study (n=276), rate of discontinuation due to treatment-related toxicity is 4%.*

21st Century Oncology

BE

LIBRETTO-001: Selpercatinib in *RET*-altered cancers



FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

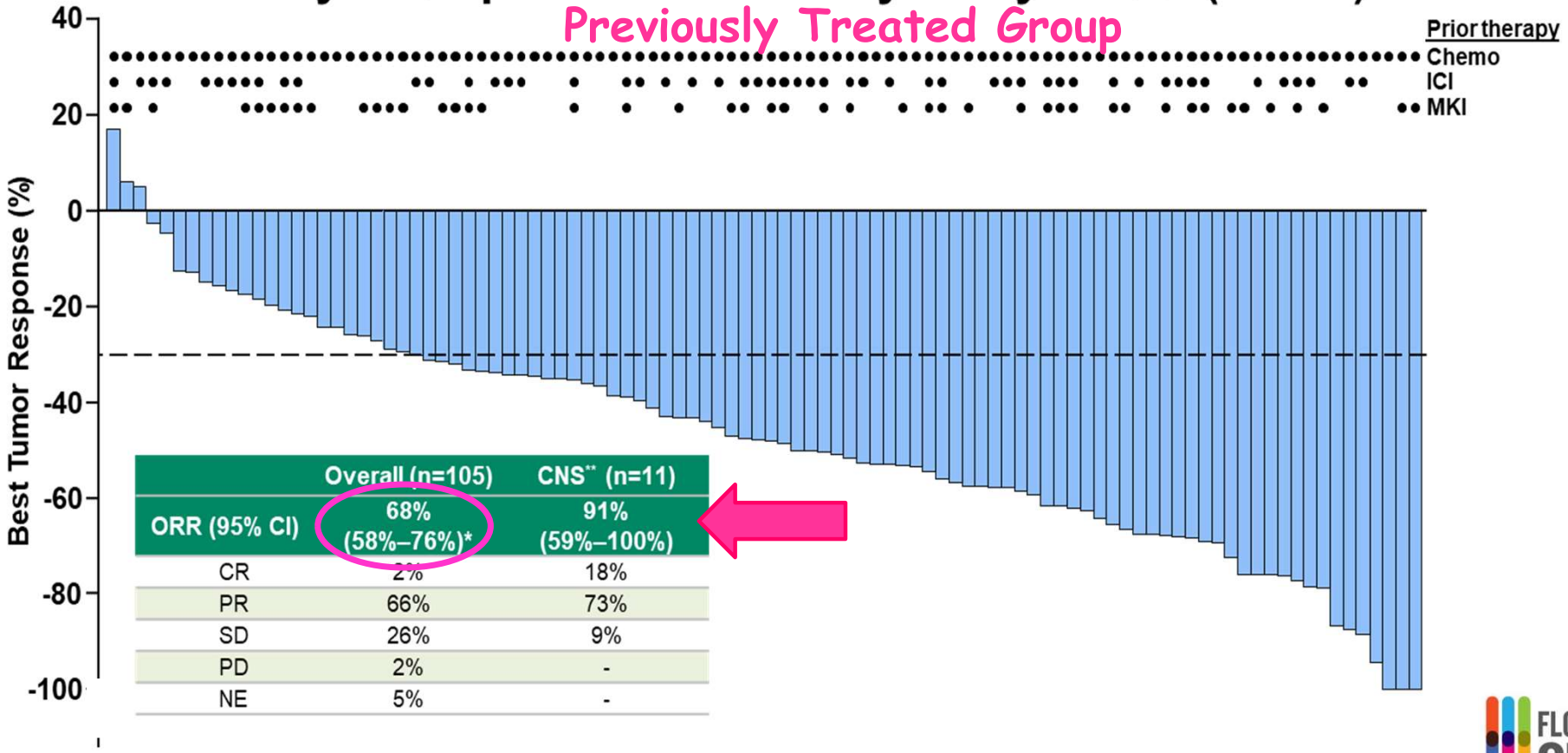
21st Century Oncology

BE

SELPERCATINIB

Efficacy of Selpercatinib: Primary Analysis Set (n=105)

Previously Treated Group



	Overall (n=105)	CNS** (n=11)
ORR (95% CI)	68% (58%–76%)*	91% (59%–100%)
CR	2%	18%
PR	66%	73%
SD	26%	9%
PD	2%	-
NE	5%	-

FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

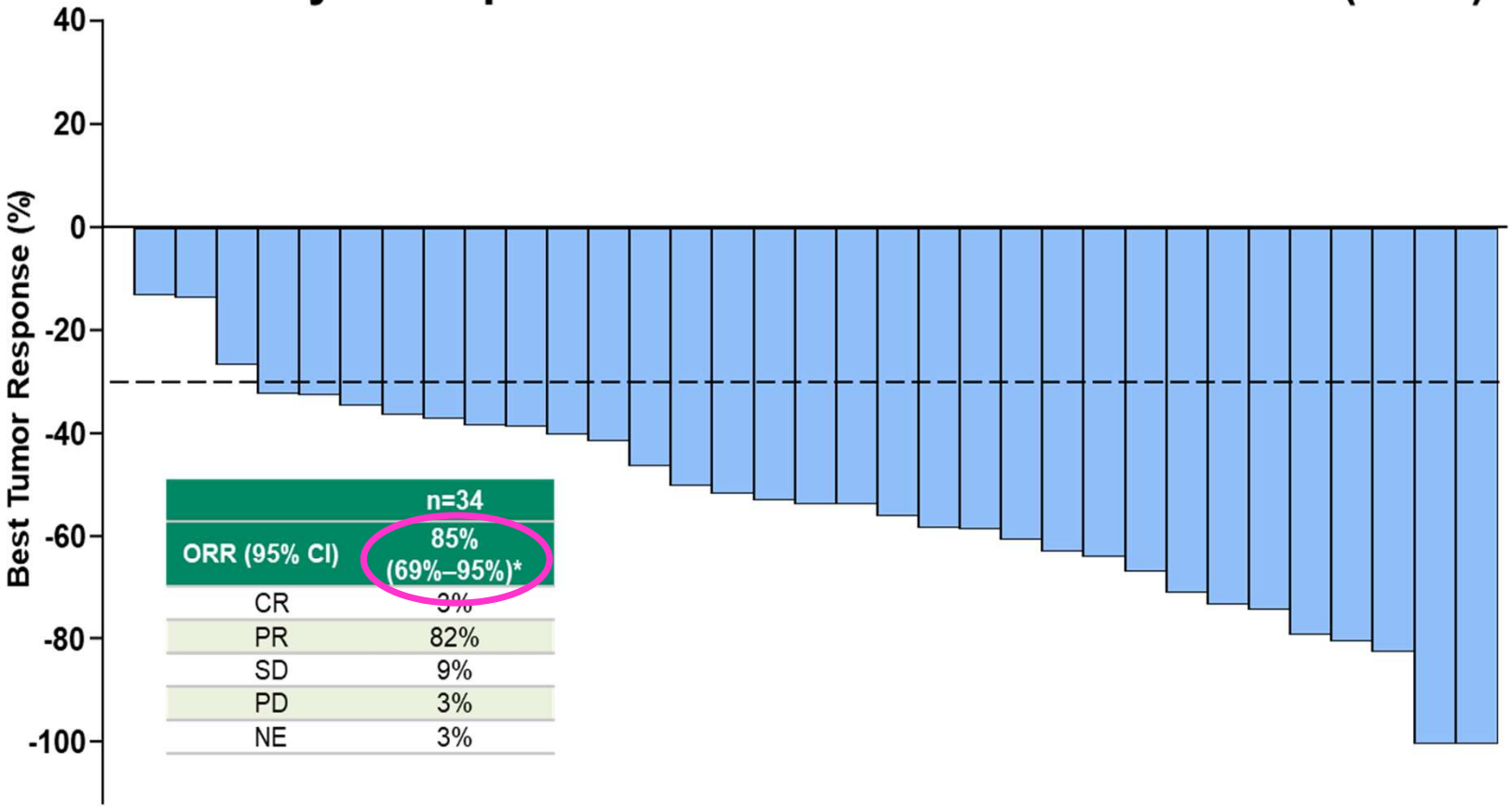
21st Century Oncology

BE

FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

Efficacy of Selpercatinib: Treatment-naïve Patients (n=34)



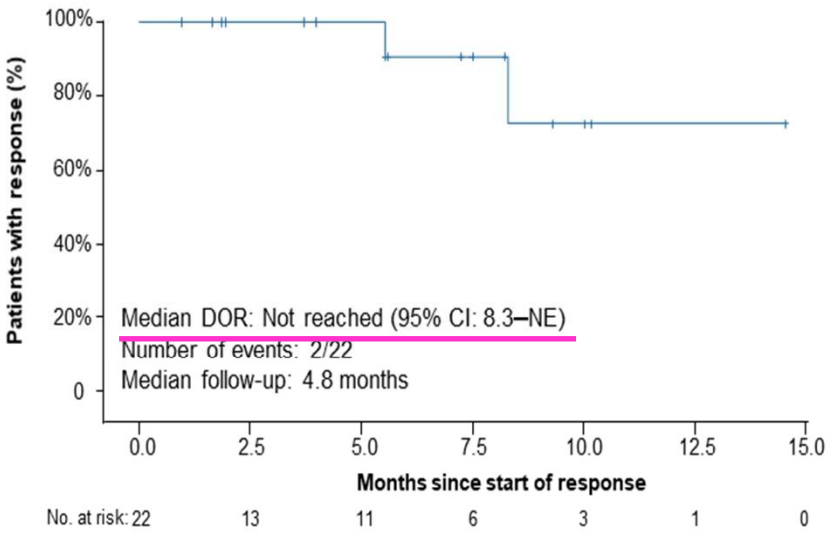
	n=34
ORR (95% CI)	85% (69%–95%)*
CR	3%
PR	82%
SD	9%
PD	3%
NE	3%

21st Century Oncology

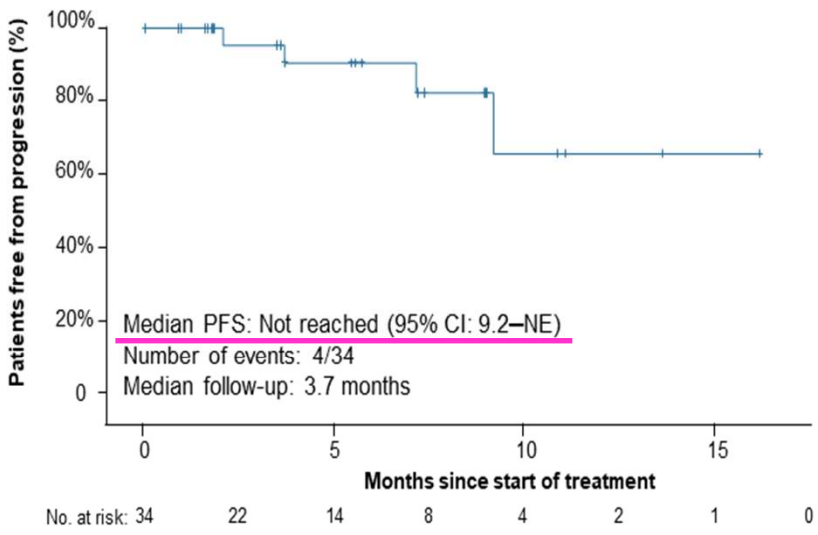
BE

Durability of Selpercatinib Efficacy: Treatment-Naïve

Duration of response



Progression-free survival



FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

21st Century Oncology

BE

Selpercatinib Safety Profile

	LIBRETTO-001 Safety Database, n=531							
	Treatment-emergent AEs (≥15% overall)					Treatment-related AEs		
	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total
Dry mouth	29%	4%	–	–	32%	–	–	27%
Diarrhea	21%	8%	2%	–	31%	1%	–	16%
Hypertension	4%	11%	14%	<1%	29%	8%	<1%	18%
Increased AST	17%	5%	6%	1%	28%	4%	1%	22%
Increased ALT	13%	4%	7%	1%	26%	6%	1%	21%
Fatigue	15%	9%	1%	–	24%	<1%	–	14%
Constipation	19%	3%	<1%	–	22%	<1%	–	11%
Headache	15%	4%	1%	–	20%	<1%	–	7%
Nausea	15%	4%	<1%	–	19%	<1%	–	8%
Peripheral edema	16%	4%	<1%	–	19%	–	–	10%
Increased creatinine	14%	4%	–	<1%	18%	–	–	10%

9 patients (1.7%) discontinued due to treatment-related AEs

Data cut-off. June 17th, 2019. AE- adverse event, Total % for any given AE may be different than the sum of the individual grades, due to rounding.

FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

21st Century Oncology

BE

Conclusion on RET Inhibitors

- Pralsetinib demonstrates a broad and durable antitumor activity in patients with RET+ advanced NSCLC; similarly, Selpercatinib demonstrates a robust and durable response in similar population.

	Pralsetinib	Selpercatinib
ORR (prior platinum)	60%	68%
ORR (naive)	NE	85%
DOR (prior platinum)	NR	20.3 months
DOR (naïve)	NE	NR
Active in CNS met	Yes	Yes
ORR CNS	78% (5/7)	91% (10/11)
Safety profile	most AEs G1/2	most AEs low grade
Discontinuation TRAEs	7%	1.7%

- Pralsetinib has FDA breakthrough therapy designation in RET fusion+ NSCLC that progressed following platinum-based chemotherapy.

- Selpercatinib: New Drug Application (NDA) submission planned by the end of 2019.

FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

21st Century Oncology

BE

MET

FLORIDA PRECISION ONCOLOGY

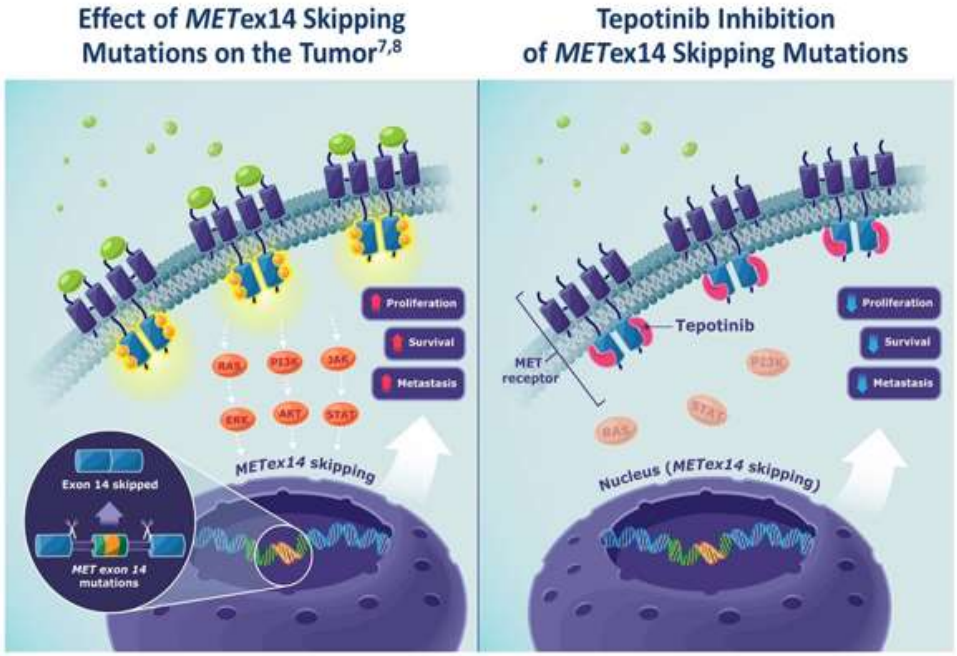
a Division of 21st Century Oncology

21st Century Oncology

BE

*MET*ex14

- *MET* exon 14 skipping (*MET*ex14) alterations are reported in 3–4% of patients with NSCLC[1]
  - Present in 8–32% of sarcomatoid lung carcinomas[2,3]
- *MET*ex14 alterations can be conveniently detected using liquid biopsy (L+) or tissue biopsy (T+)
- *MET*ex14 alterations lead to aberrant activation of MET kinase, but remain sensitive to MET inhibition
  - MET inhibitors have shown clinical activity in patients with *MET*ex14 alterations[1,4–6]



1. Paik PK, et al. Cancer Discov. 2015;5:842–9; 2. Shrock AB, et al. J Thorac Oncol. 2016;11:1493–1502; 3. Tong JH, et al. Clin Cancer Res. 2016;22:3048–56; 4. Felip E, et al. WCLC 2018 [abs. OA12.01]; 5. Drilon A, et al. WCLC 2018 [abs. OA12.02]; 6. Wolf J, et al. Ann Oncol. 2018;29(Suppl 8) [abs. LBA52]; 7. Peschard P, et al. J Biol Chem. 2004; 279:29565–71; 8. Ma PC, et al. Cancer Discov. 2015;5:802–5.

NSCLC, non-small cell lung cancer.

FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

21st Century Oncology

BE

VISION study design

VISION is a single-arm, phase II trial of tepotinib in patients with NSCLC harboring MET alterations (NCT02864992)

Study Design

- **Stage IIIB/IV NSCLC**
  - **All histologies** (including squamous and sarcomatoid)
  - Exclusion of active brain metastases or brain as only measurable lesion
- **Tissue- or blood-based *MET* alterations** (central lab testing)
  - A. *MET*ex14 skipping mutations detected:
    - **Plasma,** LBx (DNA based)
    - OR
    - **Tissue,** TBx (RNA based)
  - B. *MET* amplification only
- **1st , 2nd , 3rd line of therapy**
  - Prior anti-MET therapy was not allowed
  - Prior immunotherapy was allowed

N = up to 120

Cohort A
***MET*ex14 skipping mutations**

→ **Tepotinib 500 mg QD** (21 day cycles until progressive disease [PD])

Cohort B
***MET* amplification**

→ Tepotinib 500 mg QD (21 day cycles until PD)

Selected Endpoints

Primary endpoint

- Objective response rate (ORR) by independent review

Secondary endpoints

- ORR by investigator assessment
- Duration of response
- Objective disease control
- Progression-free survival
- Overall survival
- Safety
- Health-related quality of life

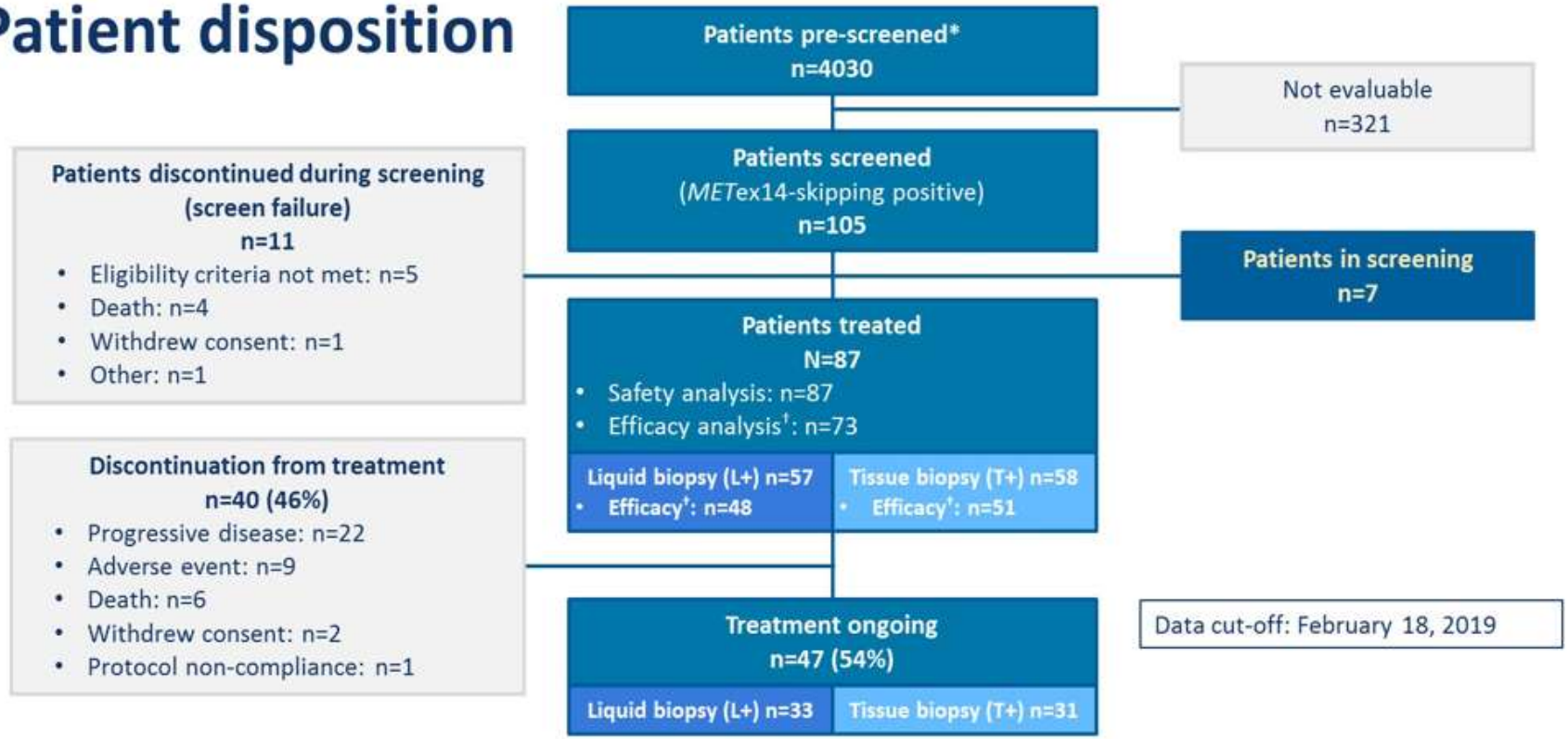
The trial aims for an ORR based on independent review in the range of 40–50% with a lower limit of the corresponding exact 2-sided 95% confidence interval (according to Clopper–Pearson) to exceed an ORR of 20%.

We now report interim data including ORR assessed by independent review and select secondary endpoints

FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

Patient disposition



Enrollment began September 2016.

*Includes 9 patients enrolled in Japan where pre-screening was not required. †Includes patients having ≥2 post-baseline assessments or who discontinued treatment for any reason. One patient was excluded from all efficacy analyses due to insufficient *MET*ex14 data. Patients overlap between L+ and T+.

L+, *MET*ex14-skipping mutation-positive in circulating tumor DNA (ctDNA); T+, *MET*ex14-skipping mutation-positive in tissue.

Efficacy: Best overall response (IRC/Investigator)

Efficacy analysis includes patients having ≥2 post-baseline assessments or who discontinued treatment for any reason.

Tepotinib 500 mg QD	Liquid biopsy (L+)		Tissue biopsy (T+)	
	IRC (n=48)	Investigator (n=47)	IRC (n=51)	Investigator (n=51)
BOR by RECIST 1.1, n (%)				
Complete response	0 (0)	3 (6.4)	0 (0)	3 (5.9)
Partial response	24 (50.0)	23 (48.9)	23 (45.1)	25 (49.0)
Stable disease	8 (16.7)	5 (10.6)	14 (27.5)	11 (21.6)
Progressive disease	7 (14.6)	10 (21.3)	8 (15.7)	6 (11.8)
Not evaluable	9 (18.8)	6 (12.8)	6 (11.8)	6 (11.8)
ORR,* n (%) [95% CI]	24 (**50.0**) [35.2, 64.8]	26 (**55.3**) [40.1, 69.8]	23 (**45.1**) [31.1, 59.7]	28 (**54.9**) [40.3, 68.9]
mDOR, months [95% CI]	**12.4** [5.8, ne]	**17.1** [7.1, ne]	**15.7** [9.0, ne]	**14.3** [5.7, ne]
DCR,† n (%) [95% CI]	32 (**66.7**) [51.6, 79.6]	31 (**66.0**) [50.7, 79.1]	37 (**72.5**) [58.3, 84.1]	39 (**76.5**) [62.5, 87.2]

*ORR, objective response rate: confirmed complete response/partial response.

†DCR, disease control rate: confirmed complete response/partial response or stable disease lasting at least 12 weeks.

L+, *MET*ex14-skipping mutation-positive in ctDNA; T+, *MET*ex14-skipping mutation-positive in tissue.

BOR, best overall response; CI, confidence interval; IRC, independent review committee; mDOR, median duration of response; ne, not estimable.

Efficacy: ORR by line of therapy (IRC/Investigator)

Consistent ORR across treatment lines

Tepotinib 500 mg QD		Liquid biopsy (L+)		Tissue biopsy (T+)	
		IRC (n=48)	Investigator (n=47)	IRC (n=51)	Investigator (n=51)
First line	**ORR,*** n/N (%) [95% CI]	10/17 (**58.8**) [32.9, 81.6]	12/17 (**70.6**) [44.0, 89.7]	8/18 (**44.4**) [21.5, 69.2]	9/18 (**50.0**) [26.0, 74.0]
Second line	**ORR,*** n/N (%) [95% CI]	8/15 (**53.3**) [26.6, 78.7]	7/14 (**50.0**) [23.0, 77.0]	9/18 (**50.0**) [26.0, 74.0]	11/18 (**61.1**) [35.7, 82.7]
≥Third line	**ORR,*** n/N (%) [95% CI]	6/16 (**37.5**) [15.2, 64.6]	7/16 (**43.8**) [19.8, 70.1]	6/15 (**40.0**) [16.3, 67.7]	8/15 (**53.3**) [26.6, 78.7]
≥Second line	**ORR,*** n/N (%) [95% CI]	14/31 (**45.2**) [27.3, 64.0]	14/30 (**46.7**) [28.3, 65.7]	15/33 (**45.5**) [28.1, 63.6]	19/33 (**57.6**) [39.2, 74.5]
	mDOR, months [95% CI]	**12.4** [5.6, ne]	**ne** [17.1, ne]	**12.4** [3.7, ne]	**17.1** [5.7, ne]

Efficacy analysis includes patients having ≥2 post-baseline assessments or who discontinued treatment for any reason.

*ORR, objective response rate: confirmed complete response/partial response.

L+, *MET*ex14-skipping mutation-positive in ctDNA; T+, *MET*ex14-skipping mutation-positive in tissue.

CI, confidence interval; IRC, independent review committee; mDOR, median duration of response; ne, not estimable.

21st Century Oncology

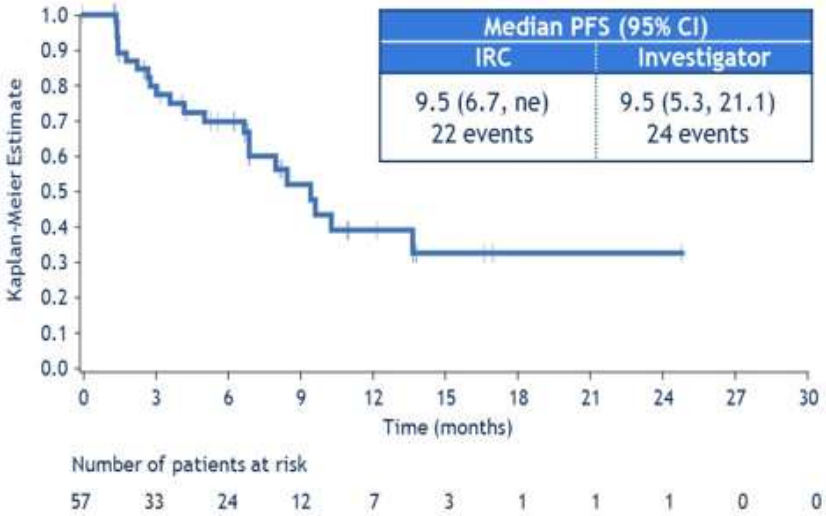
BE

Efficacy: Progression-free survival

PFS across all treatment lines

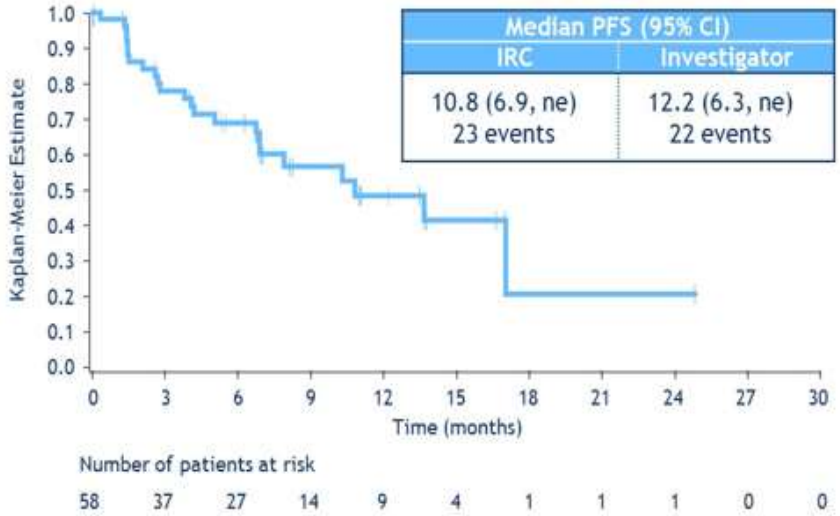
Liquid biopsy (L+) (n=57)

PFS by IRC



Tissue biopsy (T+) (n=58)

PFS by IRC



33/57 L+ patients and 31/58 T+ patients remain on treatment.

Median follow-up for PFS (IRC): 6.9 months (95% CI 5.5, 11.0).

L+, *MET*ex14-skipping mutation-positive in ctDNA; T+, *MET*ex14-skipping mutation-positive in tissue.
IRC, independent review committee; ne, not estimable; PFS, progression-free survival.

FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

Durable response to tepotinib

Courtesy of Dr Mazières from CHU de Toulouse, IUCT-Oncopole, Toulouse, France

- 73-year old female patient, non-smoker, adenocarcinoma with *MET*ex14 mutation, PD-L1 30%, and PI3KCA mutation (E542A)
- First-line tepotinib ongoing since May 2018
- PR was achieved at 18 weeks and is still ongoing

PR, partial response; SD, stable disease.

BE

Safety: Treatment-related adverse events

	Tepotinib 500 mg QD (N=87)	
	Any Grade	Grade 3
Any treatment-related AE, n (%)	71 (81.6)	17 (19.5)
Treatment-related AEs reported in ≥5% patients, n (%)		
Peripheral edema	42 (48.3)	7 (8.0)
Nausea	20 (23.0)	0
Diarrhea	18 (20.7)	1 (1.1)
Blood creatinine increased	11 (12.6)	0
Asthenia	8 (9.2)	1 (1.1)
Amylase increase	7 (8.0)	2 (2.3)
ALT increased	6 (6.9)	2 (2.3)
AST increased	5 (5.7)	1 (1.1)
Hypoalbuminemia	5 (5.7)	0

Data cut-off: February 18, 2019

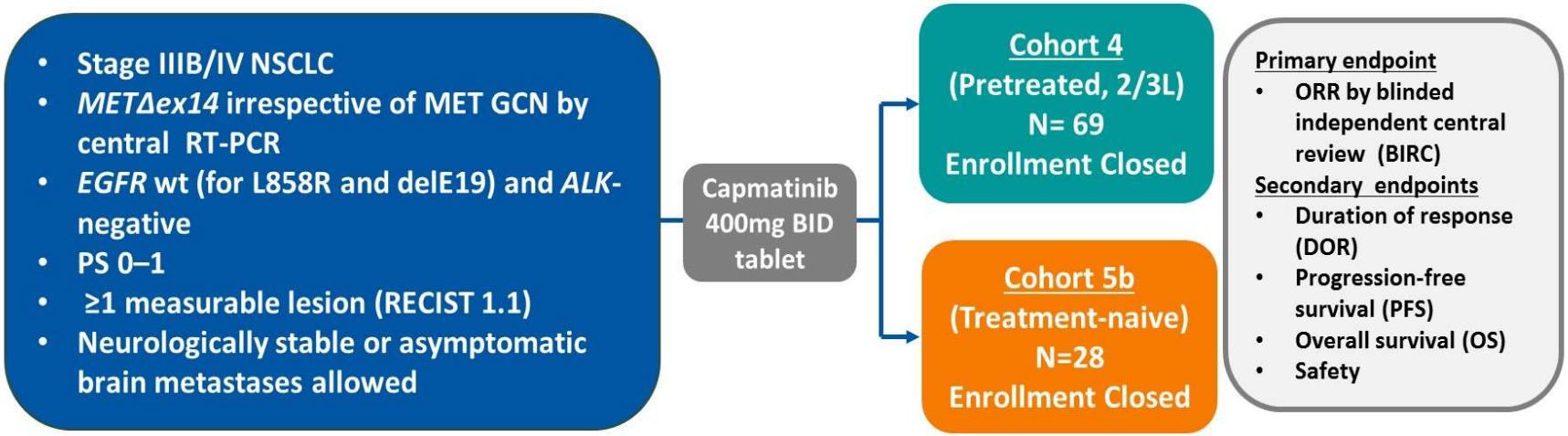
Treatment-related adverse event (investigator assessment).
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

- No grade 4 or grade 5 treatment-related AEs
- Other relevant treatment-related AEs (any grade) include:
  - lipase increased (4.6%)
  - fatigue (3.4%)
  - vomiting (3.4%)
- Treatment-related AEs led to permanent discontinuation in 4 patients:
  - two patients due to peripheral edema
  - one patient due to interstitial lung disease
  - one patient due to diarrhea and nausea

21st Century Oncology

BE

GEOMETRY mono-1: A phase II trial of capmatinib in patients with advanced NSCLC harboring *MET exon14 skipping* mutation



Study methodology:

- Cohort 4 and 5b are each analyzed separately and have independent statistical hypothesis
- Primary (ORR) and key secondary (DOR) endpoints based on BIRC including 2 parallel independent radiology reviewers (+ additional one for adjudication)
- Efficacy endpoints based on BIRC and investigator assessment per RECIST 1.1

Data cut off: April 15, 2019; median duration of follow-up for DOR: 9.7 months in Cohort 4 and 9.6 months in Cohort 5b
Additional data on *MET* mutated patients will be generated in Cohort 6 (2L; N~30) and Cohort 7 (1L; N~27)

FLORIDA PRECISION ONCOLOGY
a Division of 21st Century Oncology

21st Century Oncology

BE

Baseline characteristics

Baseline characteristics		Cohort 4 (2/3L) N = 69	Cohort 5b (1L) N = 28
Age (years)	Median (range)	71 (49-90)	71 (57-86)
Race, n (%)	Caucasian	49 (71.0)	24 (85.7)
	Asian	19 (27.5)	4 (14.3)
	Other	1 (1.4)	0
Sex, n (%)	Female/Male	40 (58.0)/29 (42.0)	18 (64.3)/10 (35.7)
Smoking history, n (%)	Never smoker	40 (58.0)	18 (64.3)
	Former smoker	27 (39.1)	9 (32.1)
	Current smoker	2 (2.9)	1 (3.6)
ECOG status, n (%)	0	16 (23.2)	7 (25.0)
	1	52 (75.4)	21 (75.0)
	2	1 (1.4)	0
Histology, n (%)	Adenocarcinoma	53 (76.8)	25 (89.3)
	Squamous	6 (8.7)	2 (7.1)
	Others*	10 (14.5)	1 (3.6)
Key metastatic site of cancer, n (%)	Brain†	11 (15.9)	3 (10.7)
	Liver	16 (23.2)	4 (14.3)
	Bone	41 (59.4)	16 (57.1)
	Adrenal	11 (15.9)	6 (21.4)
Concurrent MET amplification, n (%)	<4 GCN	18 (26.1)	4 (14.3)
	≥4-6 GCN	15 (21.7)	10 (35.7)
	≥6-<10	17 (24.6)	3 (10.7)
	≥10 GCN	11 (15.9)	4 (14.3)
	Missing	8 (11.6)	7 (25.0)

*all other histologies including 5 sarcomatoid/carcinosarcoma

†12 identified in medical history and 2 identified at baseline CT scan

FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

21st Century Oncology

BE

Prior therapies

Prior therapies		Cohort 4 (2/3L) N = 69	Cohort 5b (1L) N = 28
Number of prior lines of therapy, n (%)	1 2 3	51 (73.9) 16 (23.2) 2 (2.9)	NA
Prior therapies* (any line), n (%)	Platinum based chemo Immunotherapy Single agent chemo Targeted therapy	61 (88.4) 18 (26.1) 9 (13.0) 3 (4.3)	NA

*pretreated patients were MET inhibitor naïve

FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

21st Century Oncology

BE

Best overall response (pretreated cohort 4)

All responses confirmed per RECIST 1.1

Response rates consistent between BIRC and investigator assessment

	Cohort 4 (2/3L) N=69	
	BIRC	**Investigator**
Best overall response, n (%)		
Complete Response	0	1 (1.4)
Partial Response	28 (40.6)	28 (40.6)
Stable Disease	25 (36.2)	22 (31.9)
Non-CR/non-PD	1 (1.4)	2 (2.9)
Progressive Disease	6 (8.7)	7 (10.1)
Not evaluable*	9 (13.0)	9 (13.0)
Overall response rate (ORR) %, (95% CI)	**40.6 (28.9, 53.1)**	**42.0 (30.2, 54.5)**
Disease control rate (DCR) %, (95% CI)	**78.3 (66.7, 87.3)**	**76.8 (65.1, 86.1)**

*not qualifying for confirmed CR or PR and without SD after more than 6 weeks or progression within the first 12 weeks

BIRC, blinded independent review committee; CI, confidence interval; CR, complete response; DCR, disease control rate (CR+PR+SD+non-CR/non-PD); ORR, overall response rate (CR+PR); PD, progressive disease; PR, partial response; SD, stable disease

FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

21st Century Oncology

BE

Best overall response (treatment naive cohort 5b)

All responses confirmed per RECIST 1.1

Response rates consistent between BIRC and investigator assessment

	Cohort 5b (1L) N=28	
	BIRC	**Investigator**
Best overall response, n (%)		
Complete Response	1 (3.6)	0
Partial Response	18 (64.3)	17 (60.7)
Stable Disease	8 (28.6)	10 (35.7)
Progressive Disease	1 (3.6)	1 (3.6)
Overall response rate (ORR) %, (95% CI)	**67.9 (47.6, 84.1)**	**60.7 (40.6, 78.5)**
Disease control rate (DCR) %, (95% CI)	**96.4 (81.7, 99.9)**	**96.4 (81.7, 99.9)**

BIRC, blinded independent review committee; CI, confidence interval; CR, complete response; DCR, disease control rate (CR+PR+SD+non-CR/non-PD); ORR, overall response rate (CR+PR); PD, progressive disease; PR, partial response; SD, stable disease

FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

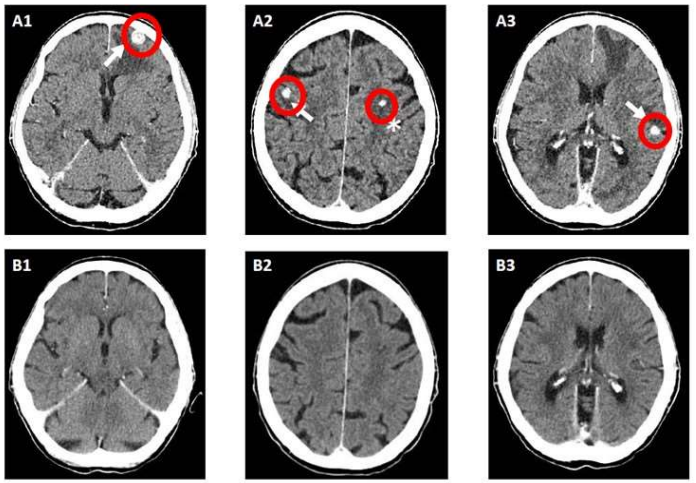
21st Century Oncology

BE

BIRC neuro-radiologist review confirms activity against brain metastases

- 13 evaluable patients with brain metastasis at baseline by BIRC [3.3 brain lesions/patient (range 1–8)].
- 54% (n=7/13) had intracranial response*:
  - 4 patients had complete resolution of all brain lesions
  - The other 3 responding patients had:
    - complete resolution in 3 lesions, -50% reduction in 1 lesion, stabilization in remaining 4 lesions (total of 7 lesions)
    - Complete resolution in 2 lesions, stabilization in 1 remaining lesion (total of 3 lesions)
    - Complete resolution in 1 lesion, stabilization in 3 remaining lesions (total of 4 lesions)
- Intracranial responses were as fast as responses in extracranial lesions.
- Intracranial disease control achieved in 12/13 patients.

* All responses were confirmed at next staging



- 73 year old, female patient with multiple brain metastases treated with WBRT and pembrolizumab (PD-L1 85%).
- Progression after 3 cycles, both systemic and intracranial [3 new metastases and progression on pre-existing lesions].
- Feb 2018: start of capmatinib.
- Brain response since first CT scan; complete resolution of all lesions by 2nd post baseline CT scan at 12 weeks.
- Systemic PR; patient still ongoing and in response after 15+ months.

CT images courtesy Dr. Johan Vansteenkiste (University Hospitals KU Leuven), informed consent by the patient.

FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

21st Century Oncology

BE

Safety summary

Favorable and manageable safety profile

Most common adverse events-treatment related (≥10%, all grades), n (%)	All Patients N = 334	
	All grades	Grade 3/4
Any	282 (84.4)	119 (35.6)
Peripheral edema	139 (41.6)	25 (7.5)
Nausea*	111 (33.2)	6 (1.8)
Increased blood creatinine†	65 (19.5)	0
Vomiting*	63 (18.9)	6 (1.8)
Fatigue	46 (13.8)	10 (3.0)
Decreased appetite*	42 (12.6)	3 (0.9)
Diarrhea	38 (11.4)	1 (0.3)

- Safety determined in the largest dataset of *MET* dysregulated‡ NSCLC patients (N=334).
- Median treatment exposure time: 14.9 weeks
- Capmatinib was well tolerated with few Grade 3/4 events [only 15 patients (4.5%) had Grade 4 events]
- Dose adjustment due to treatment related AE: 73 (21.9%)
- Discontinuation due to treatment related AE: 37 (11.1%)
  - Most frequent (≥ 1%): peripheral edema (n=6, 1.8%), pneumonitis (n= 5, 1.5%) and fatigue (n=5, 1.5%)
- Serious treatment related AEs: 43 (12.9%)

* Capmatinib administered in fasting conditions; food restriction removed in new cohorts 6 and 7

† Capmatinib is known to inhibit creatinine transporters

‡ *MET* mutated/amplified

FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

21st Century Oncology

BE

Conclusion on MET Inhibitors

- Tepotinib has durable clinical activity in patients with NSCLC harboring METex14 mutation and Capmatinib has demonstrated clinically meaningful activity in the same driver mutation population.

	Tepotinib	Capmatinib
ORR (naïve)	L+: 58%; T+:44%	67.9%
ORR (≥2 lines)	L+: 45%; T+:45%	40.6%
DOR (naïve)	14.3 months	11.1 months
DOR (≥2 lines)	L+: 12.4 mo; T+: 12.4 mo	9.7 months
Active in CNS met	Yes	Yes
Safety profile	G3: 19.5%; no G4	G3/4: 35.6%; G4: 4.5%
Discontinuation TRAEs	4.6%	11.1%

- Capmatinib: Orphan Drug Designation and Breakthrough Therapy Designation granted to this agent.

FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

21st Century Oncology

BE

B-RAF

FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

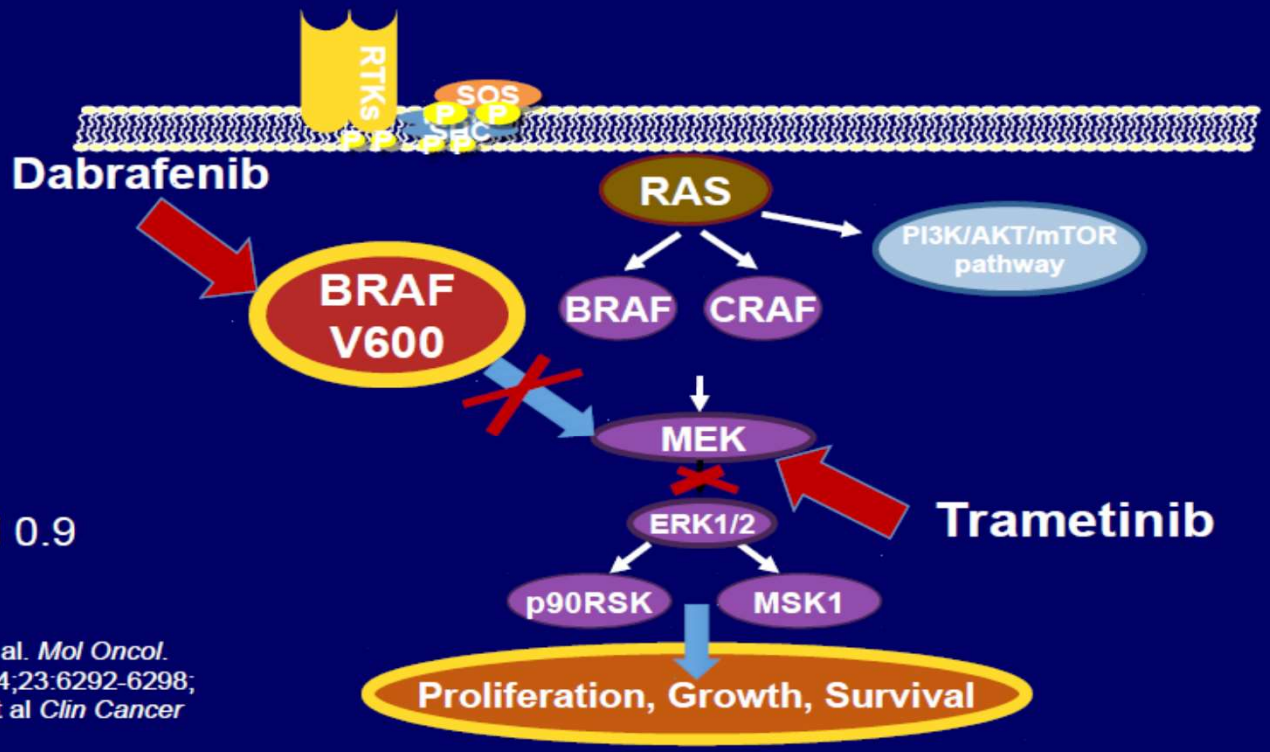
Dabrafenib Inhibits BRAF V600 Kinase and Trametinib Inhibits Downstream MEK Signaling

Dabrafenib mode of action

- Reversible, small molecule
- BRAF inhibitor
- ATP competitive
- BRAF V600E: IC_{50} 0.65 nM

Trametinib mode of action

- Reversible, small molecule
- MEK1 and MEK2 allosteric inhibitor
- MEK1 and MEK2: IC_{50} 0.7 and 0.9 nM



Davies H, et al. *Nature*. 2002;417:949-954; Platz A, et al. *Mol Oncol*. 2008;1:395-405; Karasarides M, et al. *Oncogene*. 2004;23:6292-6298; Long, et al. *N Engl J Med*. 2014;371:1877; Gilmartin et al *Clin Cancer Res* 2011;17:989.

21st Century Oncology

BE

B-Raf/MEK Inhibitors

- Dabrafenib/Trametinib
  - Melanoma (metastatic and adjuvant)
  - Lung cancer (metastatic)
- Cobimetinib/Vemurafenib*
  - Melanoma (metastatic)
  - Erdheim-Chester Disease*
- Binimetinib/Encorafenib
  - Melanoma (metastatic)
  - Colon Cancer (metastatic)** (with cetuximab)

FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

21st Century Oncology

BE

Study Design: Dabrafenib plus Trametinib in Patients with B-RAF V600E Metastatic Non-Small Cell Lung Cancer

Key Eligibility Criteria[1-3]

- *BRAF* V600E metastatic NSCLC
- No prior exposure to BRAF or MEK inhibitor
- Absence of *EGFR* mutation or *ALK* rearrangement[a]
- Adult patients (≥18 years of age)

- Major efficacy outcomes: ORR, DOR[1,2,a,b]
- Additional outcomes[3-5,a,b]
  - OS, PFS, safety

N=171

Cohort A
Previously treated patients
Dabrafenib 150 mg po twice daily
(n=78)

Cohort B
Previously treated patients
Dabrafenib 150 mg po twice daily
Trametinib 2 mg po daily
(n=57)

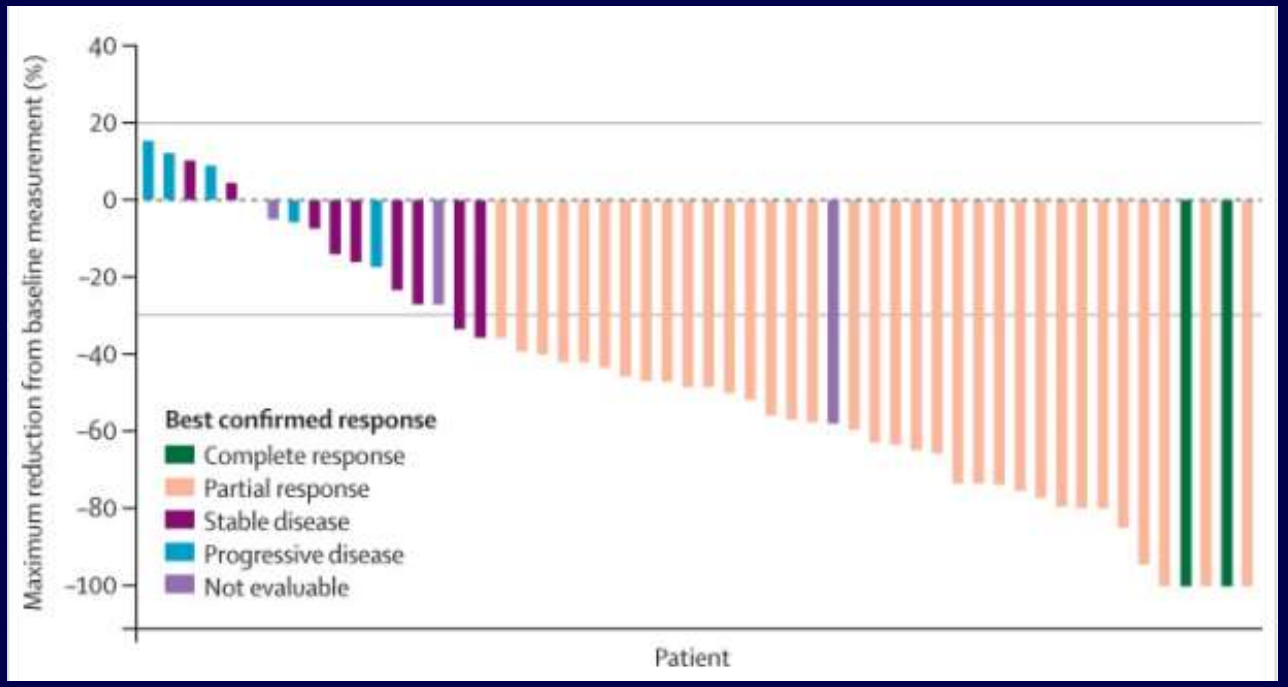
Cohort C
First line patients
Dabrafenib 150 mg po twice daily
Trametinib 2 mg po daily
(n=36)

A phase 2, multicenter, non-randomized, non-comparative, open-label trial

FLORIDA PRECISION ONCOLOGY
a Division of 21st Century Oncology

Dabrafenib + Trametinib: Best Confirmed Response in ≥ 2nd Line; BRF113928 Trial.

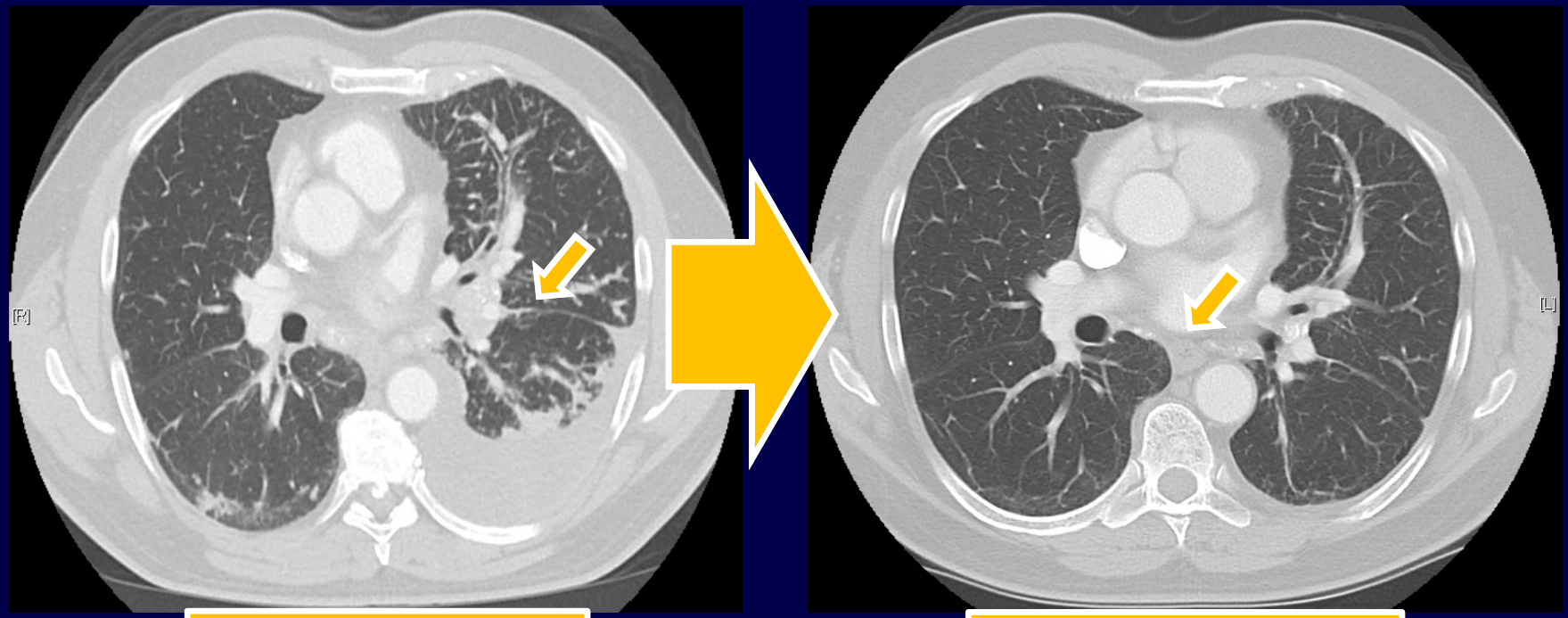
- Clinically meaningful anti-tumor activity with a higher ORR when compared indirectly with dabrafenib monotherapy in BRAF V600E mutated NSCLC
  - ORR = 63% and DCR = 75% for dabrafenib plus trametinib
  - ORR = 33% and DCR = 56% for dabrafenib as monotherapy



Planchard D, et al. Lancet Oncol. 2016;17:642-650. Planchard D, et al. Lancet Oncol. 2016;[in press].

Dabrafenib + Trametinib: Outcome

- 65 years old male patient (former smoker) with V600E BRAF mutation



Baseline, October 2014

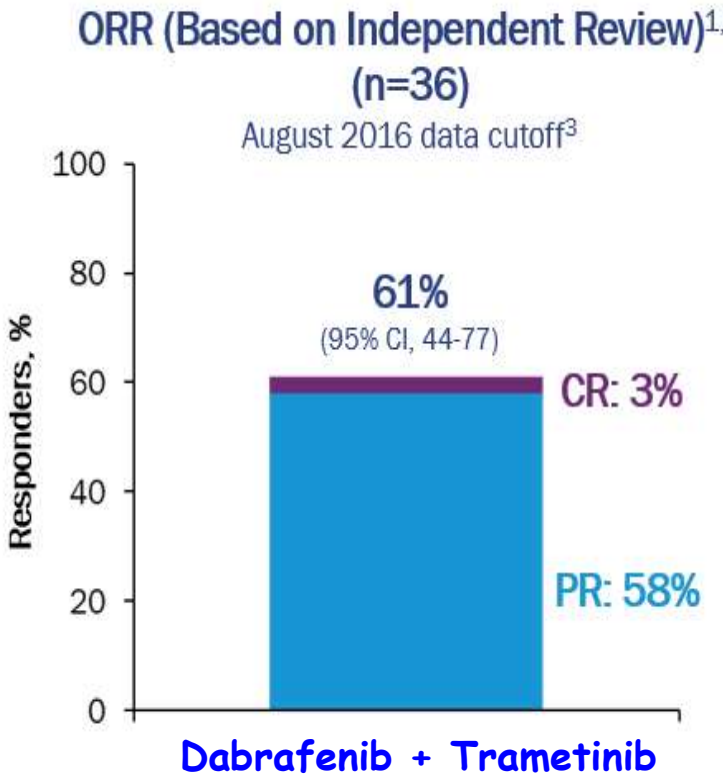
+8 months (May 2015)

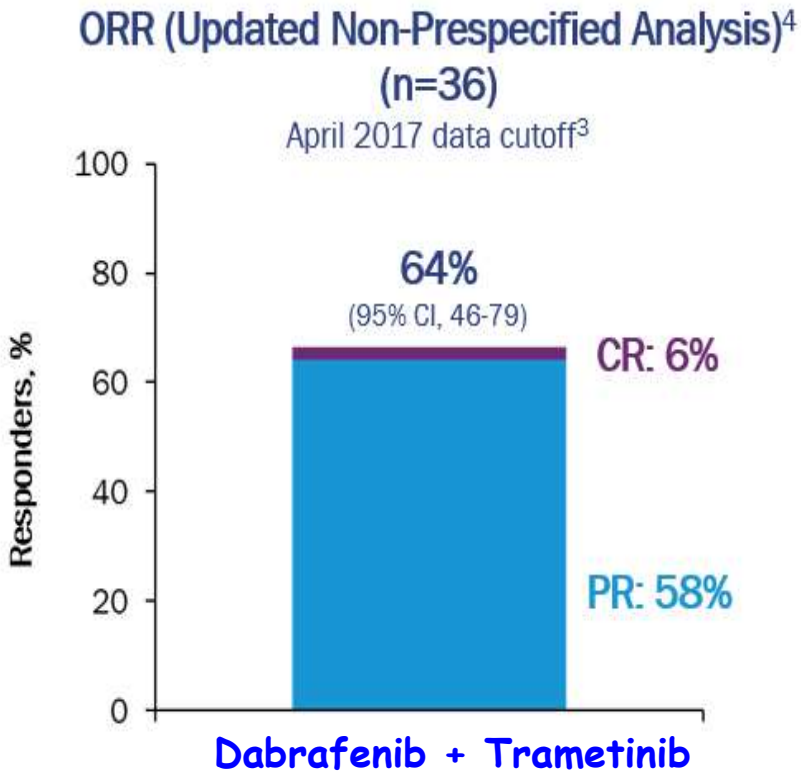
Images courtesy of B. Johnson. DFCI.

21st Century Oncology

BE

First-Line: Dabrafenib + Trametinib in Patients With B-Raf V600E Metastatic NSCLC: Overall Response Rate





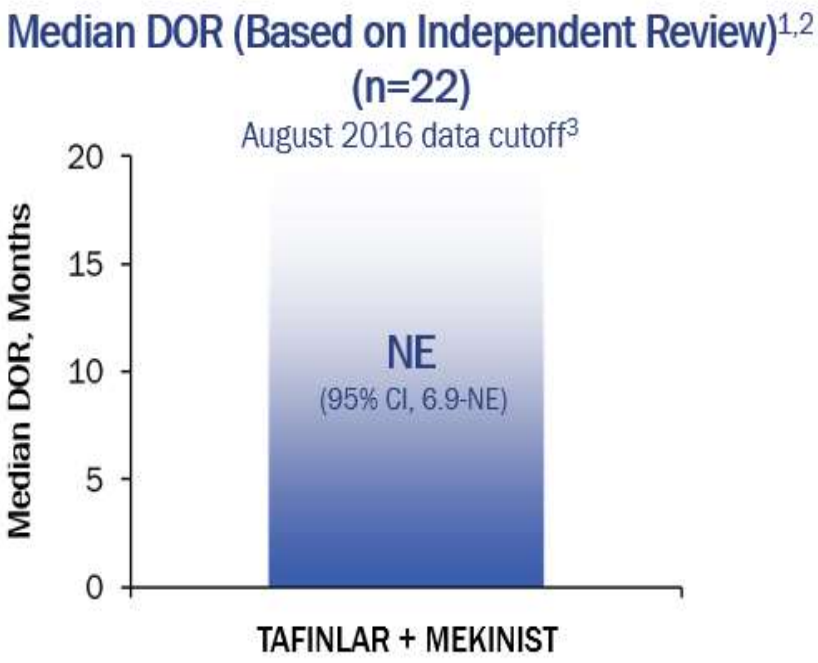
FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

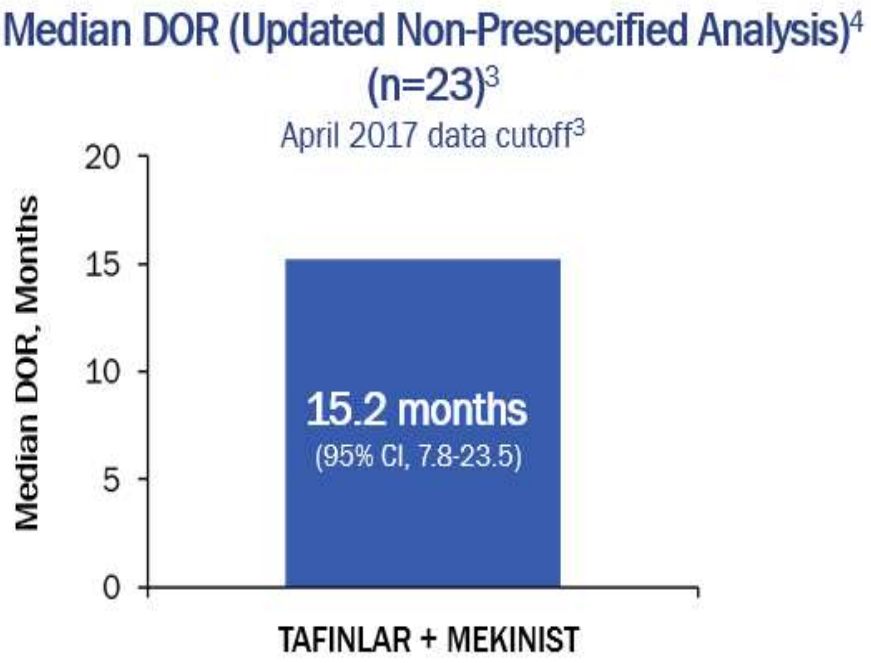
21st Century Oncology

BE

First-Line: Dabrafenib + Trametinib in Patients With B-Raf V600E Metastatic NSCLC: Overall Response Rate



59% of responders achieved DOR ≥6 months



82% responders achieved DOR ≥6 months

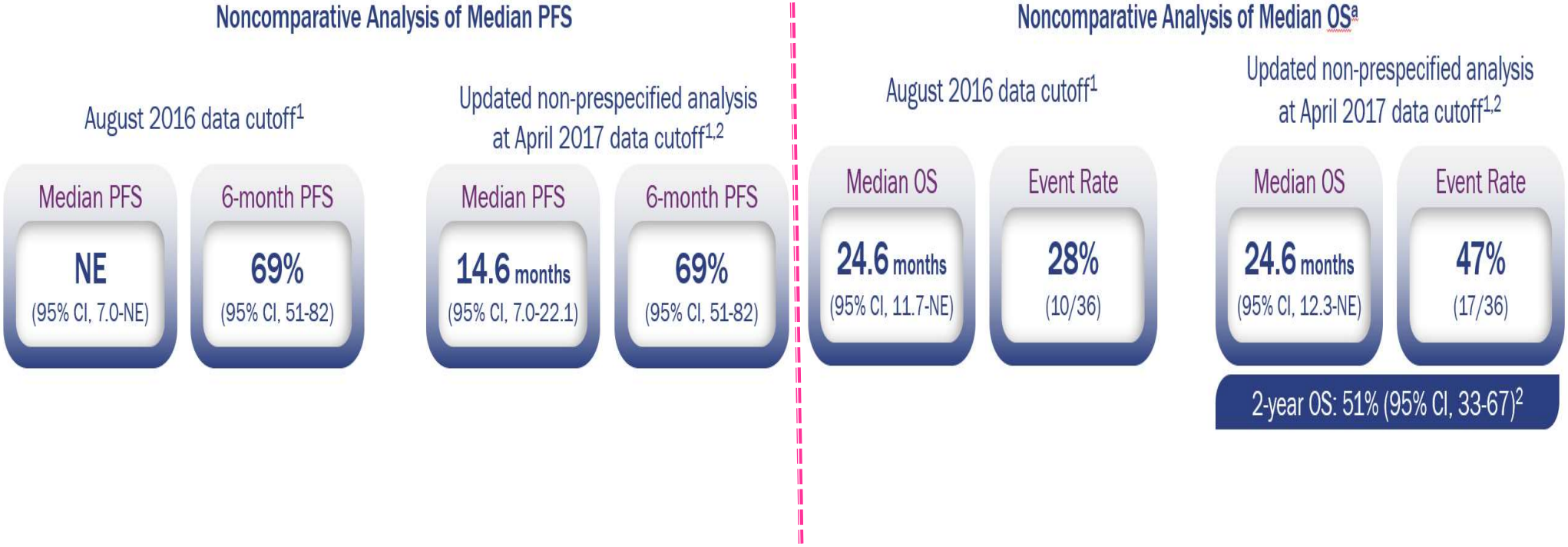
FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

21st Century Oncology

BE

First-Line: Dabrafenib + Trametinib in Patients With B-Raf V600E Metastatic NSCLC: Overall Response Rate



FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

21st Century Oncology

BE

MA03.05: BRAF Mutations Are Associated with Increased Benefit from PD1/PDL1 Blockade Compared with Other Oncogenic Drivers in Non-Small Cell Lung Cancer – Negrao MV, et al

- **Key results**
  - BRAF V600E mutations were significantly associated with high PD-L1 expression ($p<0.05$), while BRAF non-V600E and KRAS were significantly associated with high TMB (both $p<0.01$)

	KRAS	BRAF	Classic EGFR	EGFR exon 20	HER2
ORR, %	24	62	4	10	8
mPFS, months (95%CI)					
MDACC	2.8 (2.2, 3.3)	7.4 (NE)	1.8 (1.2, 2.4)	2.7 (1.7, 3.8)	1.9 (1.6, 2.1)
CGDB	3.7 (3.3, 4.5)	BRAF V600E 9.8 (7.6, NA) BRAF nonV600E 5.4 (3.0, 16.0.0	2.5 (1.8, 3.1)	3.7 (2.3, 7.3)	3.0 (1,8, NA)

- **Conclusion**
  - In patients with oncogenic-driven NSCLC, there are distinct patterns of response to immune checkpoint inhibitors with BRAF mutations being associated with the best outcomes

Negrao MV, et al. J Thorac Oncol 2019;14(suppl):Abstr MA03.05

FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

21st Century Oncology

BE

Conclusion

EMERGING BIOMARKERS TO IDENTIFY NOVEL THERAPIES FOR PATIENTS WITH METASTATIC NSCLC

Genetic Alteration (ie, Driver event)	Available Targeted Agents with Activity Against Driver Event in Lung Cancer
High-level *MET* amplification or *MET* exon 14 skipping mutation	**Tepotinib** **Capmatinib**
RET rearrangements	**Praseltinib** **Selpercatinib**
ERBB2 (HER2) mutations	Ado-trastuzumab emtansine[9]
Tumor mutational burden (TMB)*	Nivolumab + ipilimumab[10] Nivolumab[11]

NCCN Guidelines Version ?.2020- NON-SMALL CELL LUNG CANCER

FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology

21st Century Oncology

BE

Question.

The most common Grade 3/4 adverse event found with MET inhibitors is:

a. Neutropenia
b. Nausea
c. Diarrhea
d. Peripheral Edema
e. Fatigue

Answer.

Peripheral edema is an adverse event that has been described with MET inhibitors such as crizotinib as well as novel and more potent MET inhibitors such as tepotinib and capmatinib. In the VISION study, the incidence of grade 3 peripheral edema was 8%; in the GEOMETRY study, peripheral edema grade 3-4 was seen in 7.5%. Moreover, in the discontinuation rate due to adverse event, peripheral edema was the most common cause.

FLORIDA PRECISION ONCOLOGY

a Division of 21st Century Oncology