Rociletinib
Accelerated Approval NDA for T790M+ EGFR NSCLC Following Failure of TKI

April 12, 2016

Clovis Oncology

Oncologic Drugs Advisory Committee

Introduction

Lindsey Rolfe, MBCHB, MRCP

Chief Medical Officer

Clovis Oncology

NSCLC Associated with High Mortality

- Lung cancer is 2nd most common serious cancer in US[1]
  - >200,000 new cases each year
  - Leading cause of cancer-related death
- NSCLC accounts for almost 85% of lung cancers[2]
- Most NSCLC patients have metastatic disease
  - No cure
  - Treatment focused on reducing tumor burden, controlling disease, and managing symptoms

1. NCI Website; 2. Herbst et al. (2008)

~15% of NSCLC Have EGFR-Activating Mutations[1]

- Majority of patients respond to 1st or 2nd generation EGFR-targeted TKI
- Almost all patients develop acquired resistance to therapy
  - Predominantly due to second EGFR mutation, T790M

1. Linardou et al. (2009)

Rociletinib Designed to Inhibit T790M

- Novel, potent, 3rd generation EGFR-targeting TKI
- Irreversibly inhibits initial-activating EGFR and T790M resistance mutations
  - Without dose limiting skin and GI effects

Proposed Indication for Rociletinib

- Treatment of patients with mutant epidermal growth factor receptor (EGFR) non-small cell lung cancer (NSCLC) who have been previously treated with an EGFR-targeted therapy and have the EGFR T790M mutation as detected by an FDA-approved test

Rociletinib Meets Criteria for Accelerated Approval

- Treats a serious condition
- Advantage over available therapy
  - Single agent chemotherapy and immunotherapy
- ORR endpoint reasonably likely to predict meaningful clinical benefit
- Confirmatory RCT ongoing

Dose Recommendation Evolved Based on Clinical Experience

Date	Activity	Dose	Rationale
June 2015	NDA Submission	500 mg BID	• All doses active • Anticipated response rate at 500 mg would increase as data matured
Dec 2015	FDA Teleconference	625 mg BID	• Higher ORR based on confirmed response at data cut off
Mar 2016	Confirmatory Study Amendment	625 mg BID	• Study 500 mg and 625 mg

Agenda

Unmet Need in EGFR Mutant NSCLC	**David Carbone, MD, PhD** Professor of Medicine/Oncology Director, James Thoracic Center The Ohio State University
Efficacy	**Sergey Yurasov, MD, PhD** Senior Vice President Clinical Development Clovis Oncology
Safety and Dose Selection	**Lindsey Rolfe, MBCHB, MRCP** Chief Medical Officer Clovis Oncology
Clinical Perspective and Benefit-Risk	**Ross Camidge, MD, PhD** Professor of Medicine/Oncology Joyce Zeff Chair in Lung Cancer Research University of Colorado Cancer Center

Additional Experts

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Professor of Medicine and Clinical Pharmacology
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Lankenau Medical Center and Institute for Medical Research
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Unmet Need in EGFR Mutant NSCLC

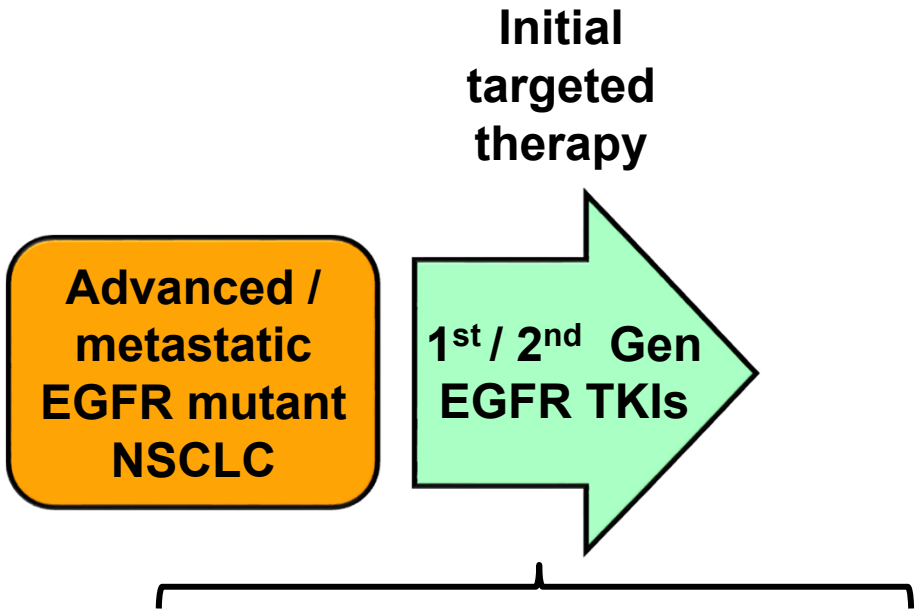
David Carbone, MD, PhD

Professor of Medicine/Oncology

Director, James Thoracic Center

The Ohio State University Medical Center

Maintain Disease Control in Advanced EGFR Mutant NSCLC

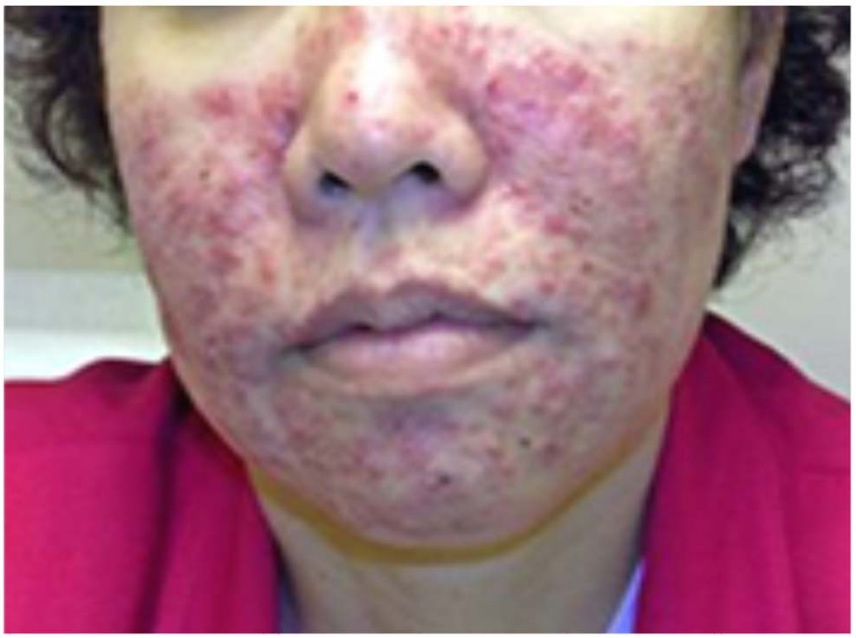


- ORR 50-70%
- DoR 6-12.5 months
- PFS 10-14 months

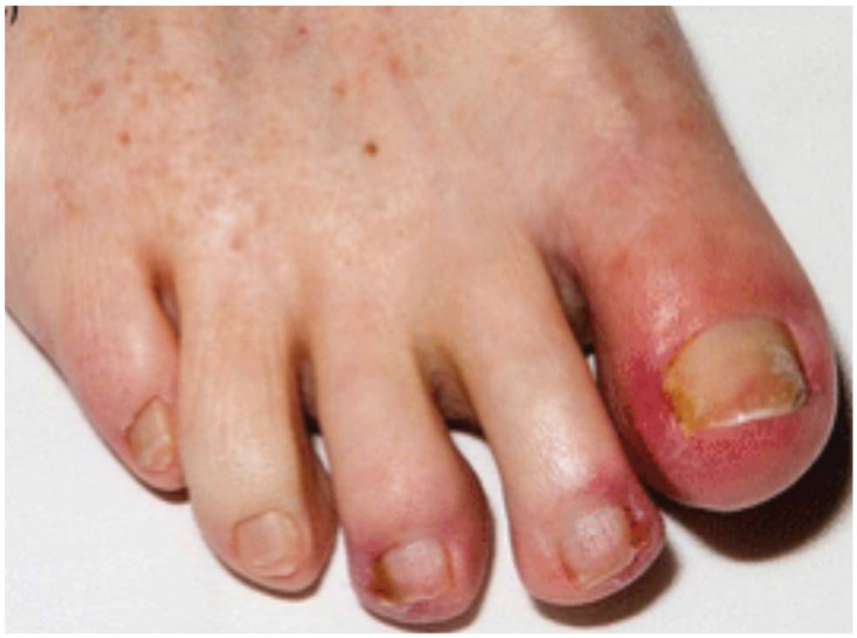
Mok (2009); Rosell (2012); Sequist (2013)

1st and 2nd Generation EGFR-Targeted TKIs Can Lead to Skin and GI Toxicities

Papulopustular Rash[1]

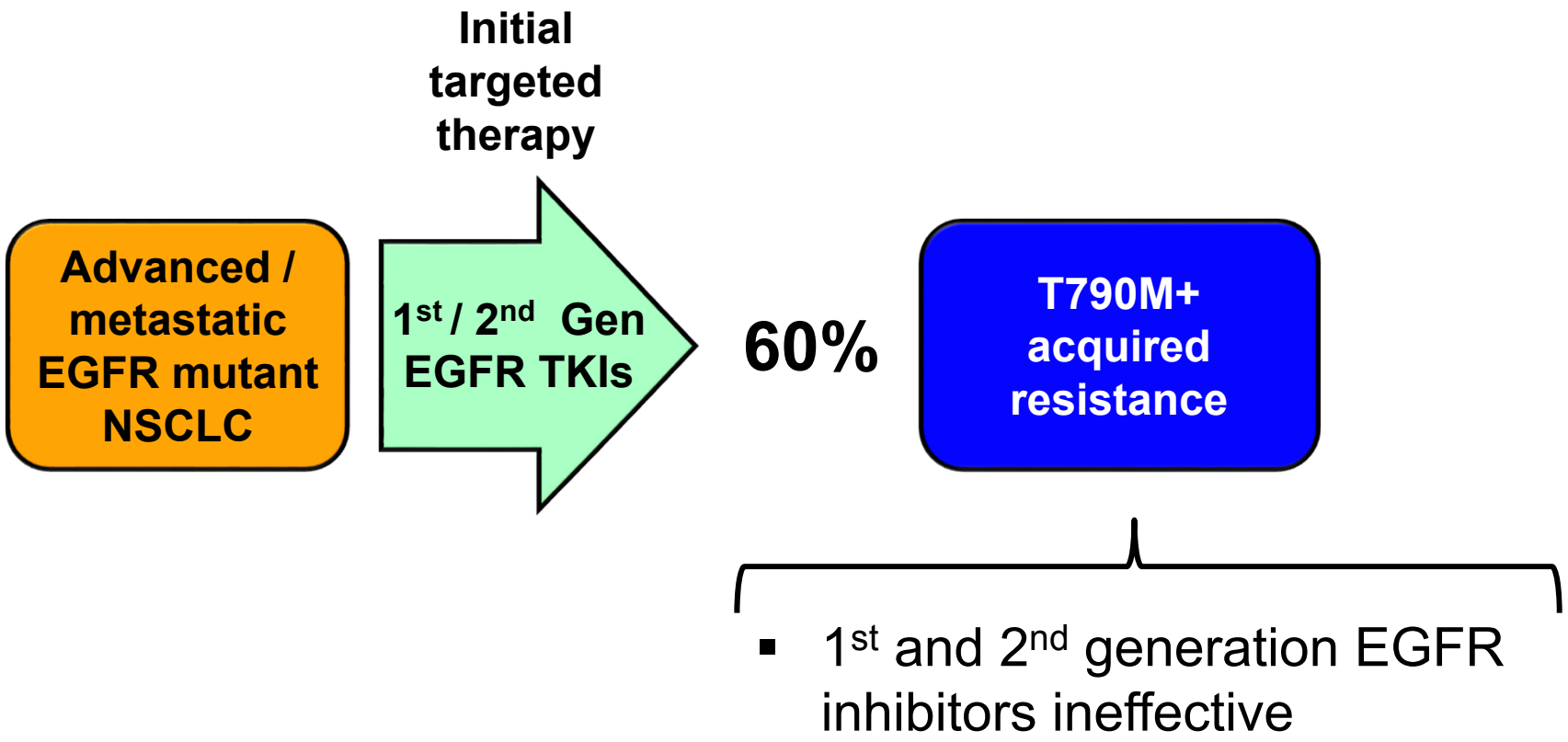


Paronychiae[2]



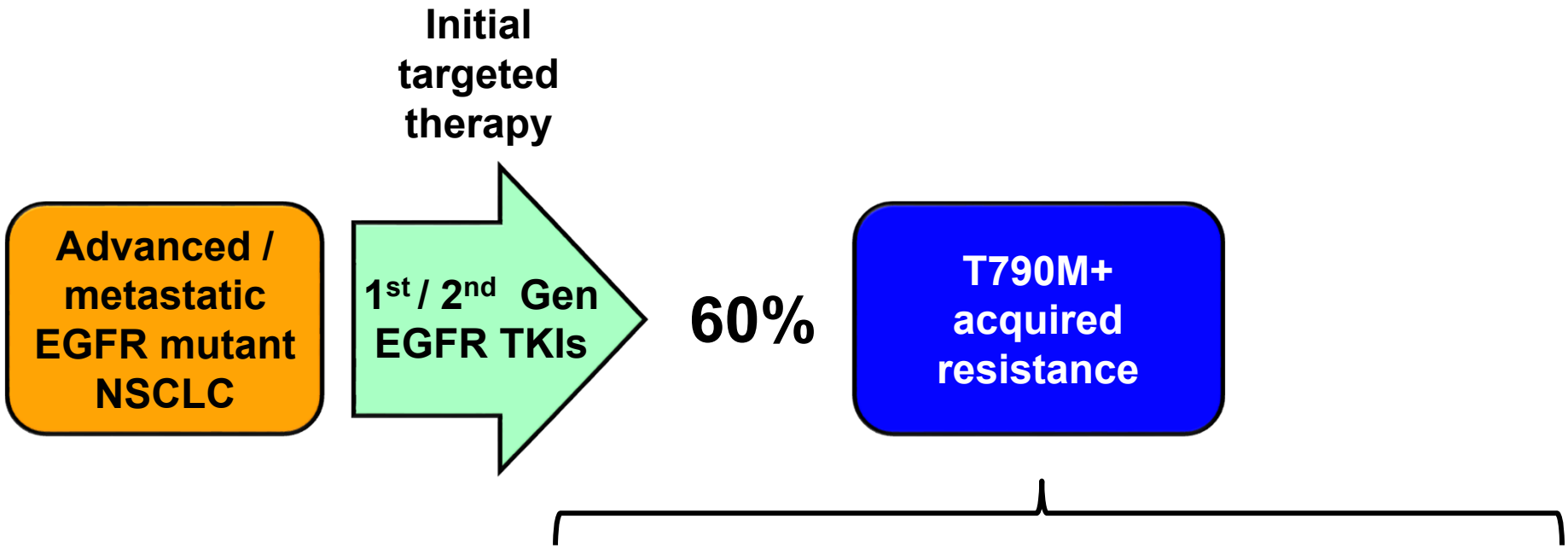
1. White (2011); 2. Melosky (2015)

Progression Due to T790M Mutation



Yu (2013)

Treatment Paradigm After Progression



- 3rd generation EGFR inhibitor
- Platinum-based doublet
- Single-agent chemotherapy, immunotherapy, and anti-VEGFr2 + chemotherapy

Yu (2013)

Second-Line Chemotherapy Offers Little Clinical Benefit

	Single Agent		
	Docetaxel[1]	Docetaxel[2]	Pemetrexed[2]
Territories	US	Global	
ORR*	6.7%	8.8%	9.1%
mDoR (mos)	9.1	5.3	4.6

1. Fossella (2000); 2. Hanna (2004)
*EGFR mutation status: unknown

Significant Toxicities with Second-Line Chemotherapy

	Single Agent		
	Docetaxel[1]	Docetaxel[2]	Pemetrexed[2]
Territories	**US**	**Global**	
Grade ≥ 3 AEs	**54% Grade 4 neutropenia**	**40% Grade 3-4 neutropenia**	**~20%**

- Nausea, fatigue, hair loss and neuropathy
- Neutropenia increases risk for infection and may require hospitalization
- Negatively affects lifestyle and can lead to discontinuation

1. Fossella (2000); 2. Hanna (2004)

Other Approved Treatments Less Active in EGFR Mutant NSCLC Patients

	Nivolumab[1]	Docetaxel + Ramucirumab[2]
Territories	Global	Global
ORR*	19%	23%
mDoR (mos)	17.2	Not reported

1. Borghaei (2015); 2. Garon (2014)
*EGFR mutation status: unknown

Toxicities Related to Other Approved Second-Line Treatments

Regimen	Nivolumab[1]	Docetaxel + Ramucirumab[2]
Territories	**Global**	**Global**
Grade ≥ 3 AEs	**10%**	**79%** (49% Grade 3-4 neutropenia)

- Nivolumab side effect profile benign in majority of patients
  - Small number of severe AEs including colitis, hepatitis, pneumonitis, and rash
- Ramucirumab plus docetaxel has all side effects of docetaxel

1. Borghaei (2015); 2. Garon (2014)

Need for EGFR-Targeted Treatment Options

- Majority of cases diagnosed at stage IV
  - Global median survival only 6 months
- Goal of treatment to control symptoms
  - Achieved by keeping patients on TKIs as long as possible
- All current therapies have unique risk-benefit profiles
  - Allows oncologists to tailor therapy
- No single therapy suited for all patients
- Need for new therapeutic options in EGFR T790M mutant NSCLC

Efficacy

Sergey Yurasov, MD, PhD

Senior Vice President

Clinical Development

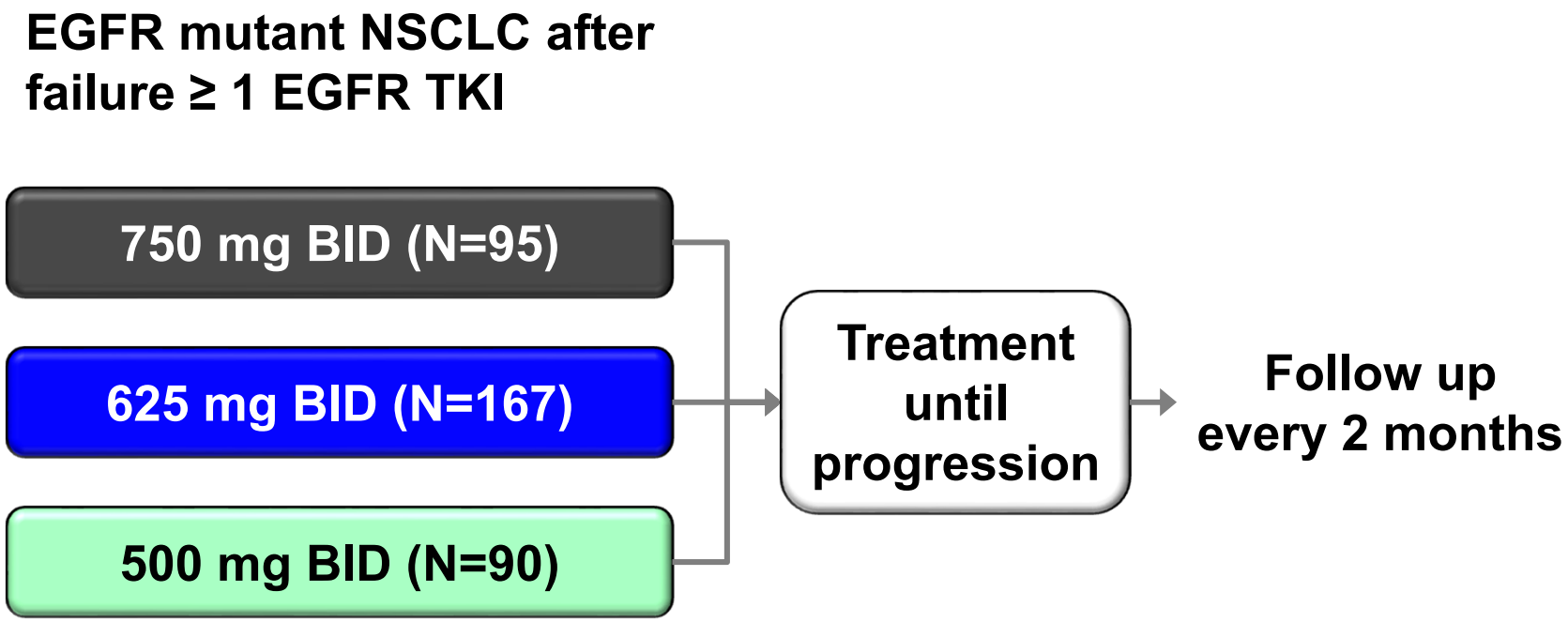
Clovis Oncology

Studies to Support Accelerated Approval

Single-arm Phase 2 studies

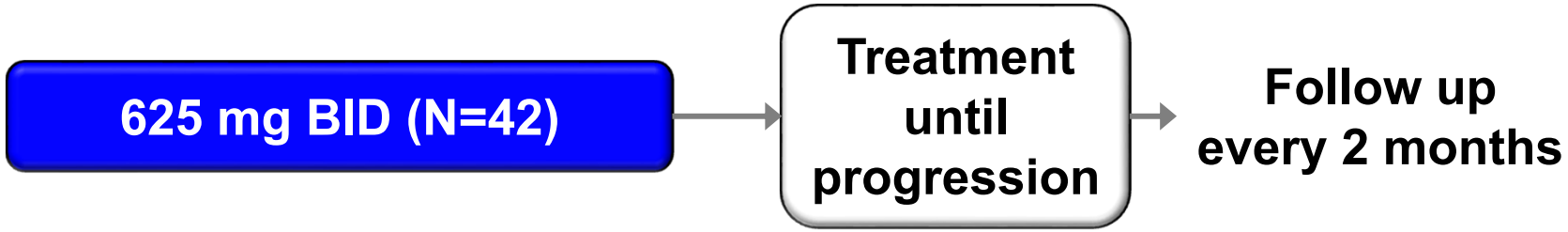
- Study -008
- Study -019

Study -008: Phase 1/2

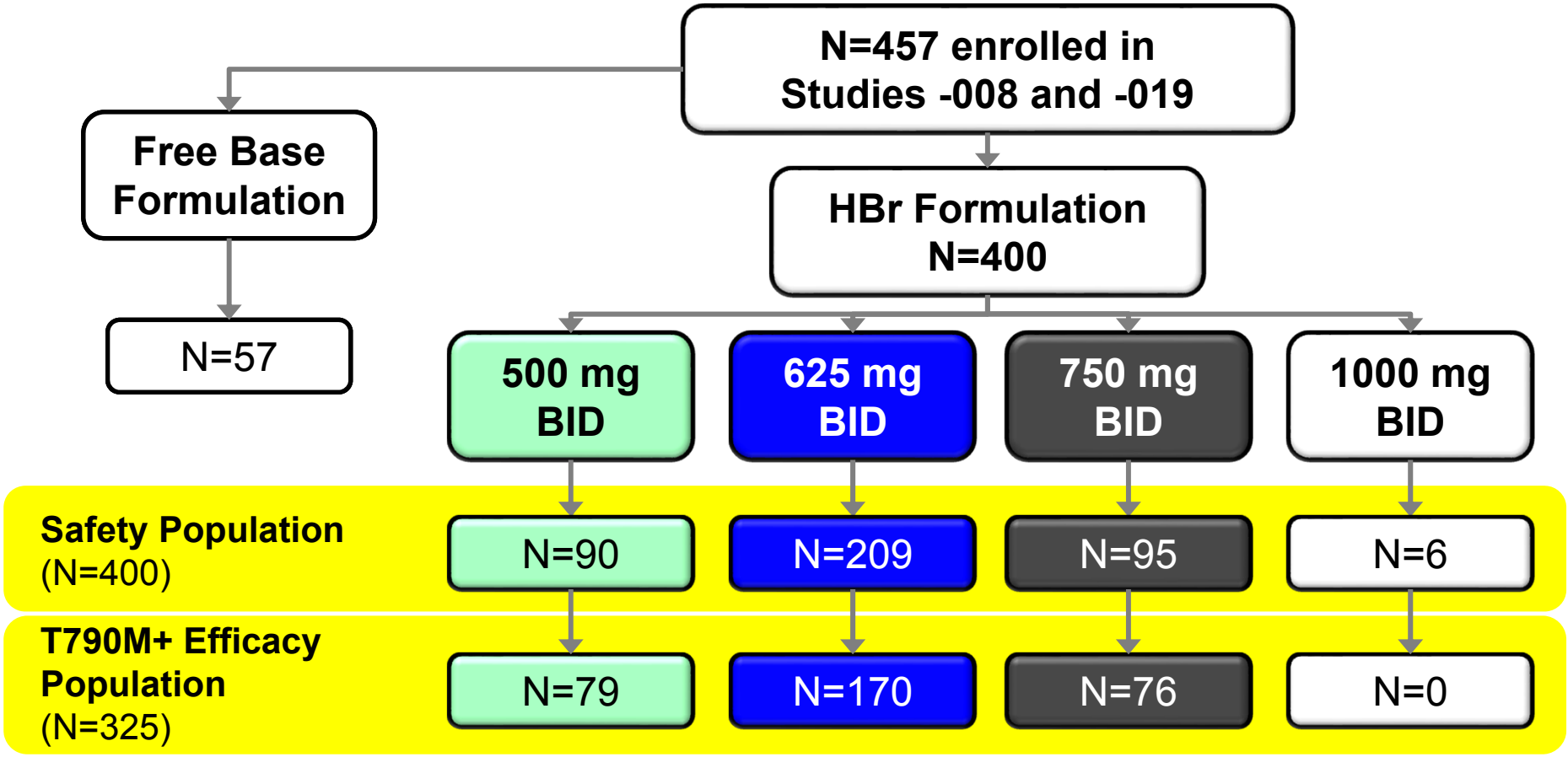


Study -019: Phase 2

T790M+ EGFR NSCLC after 1 EGFR TKI



Patient Enrollment



Key Inclusion Criteria Similar for Studies -008 and -019

- Age ≥ 18 years
- ECOG 0-1
- EGFR mutant NSCLC
- Recurrent disease after prior 1st or 2nd generation EGFR TKIs
- T790M mutation centrally confirmed
- Lines of prior therapy
  - Study -008: one or multiple
  - Study -019: one prior EGFR TKI

Key Exclusion Criteria Similar for Studies -008 and -019

- Medications that prolong QTc
- Prior treatment with T790M targeted therapy
- Unstable CNS metastatic disease

T790M+ Patient Demographics Consistent Across All Doses

Studies -008 and -019	500 mg BID N=79	625 mg BID N=170	750 mg BID N=76
Age, median	62	63	61
Female	75%	69%	66%
United States	77%	82%	87%
Asian ethnicity	19%	25%	25%
ECOG 1	76%	73%	68%

T790M+ Recurrent NSCLC Patient Characteristics

Studies -008 and -019	500 mg BID N=79	625 mg BID N=170	750 mg BID N=76
Time since diagnosis, median (months)	33	23	27
≥ 2 organs involved	82%	81%	84%
Liver	33%	32%	38%
Bone	32%	34%	45%
History of CNS disease	43%	45%	47%

Multiple Prior Therapies

Studies -008 and -019	500 mg BID N=79	625 mg BID N=170	750 mg BID N=76
# of prior therapies, median (range)	3 (1, 8)	2 (1, 13)	2 (1, 9)
≥ 2 prior therapies	73%	60%	57%
Any chemotherapy	68%	52%	53%
Platinum	66%	51%	53%
Pemetrexed	58%	45%	47%
Taxane	19%	18%	21%
≥ 2 prior EFGR TKI	38%	32%	41%

T790M+ Patient Disposition Consistent Across All Doses

Studies -008 and -019	500 mg BID N=79	625 mg BID N=170	750 mg BID N=76
Ongoing	42%	35%	41%
Discontinued	58%	65%	59%
Progressive disease	74%	73%	84%
Adverse event	15%	14%	7%
Death	2%	0	0
Withdrawal by patient	2%	5%	2%
Other*	7%	9%	7%

*Physician decision, lost to follow up, protocol deviation, missing

Primary Endpoint
Objective Response Rate (ORR)

- ORR based on RECIST 1.1
- Independent radiological review (IRR) and Investigator assessment

Studies -008 and -019
Key Secondary Endpoint

- Duration of response (DoR)
  - Measured from first observation of response until disease progression

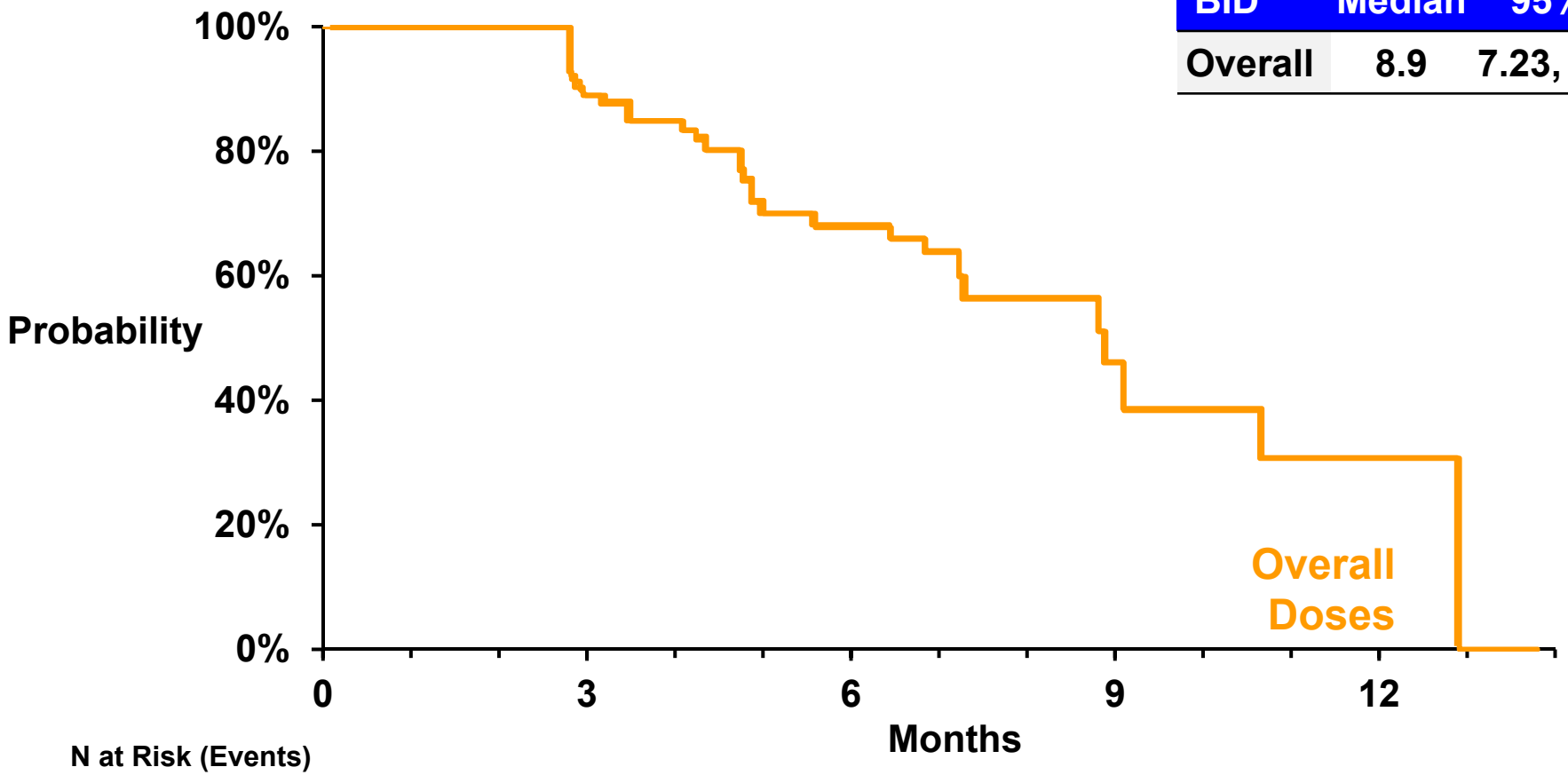
Primary Endpoint
ORR in T790M+ Patients (IRR)

Studies -008 and -019	500 mg BID N=79	625 mg BID N=170	750 mg BID N=76	Overall* N=325
ORR (95% CI)	23% (14, 34)	32% (25, 40)	33% (23, 45)	30% (25, 36)
CR	0	1%	0	0.3%
PR	23%	32%	33%	30%
SD	48%	33%	33%	37%
PD	13%	19%	18%	17%
Not evaluable	17%	16%	16%	16%

* Overall includes 500, 625, 750 mg BID

Studies -008 and -019 Duration of Response by IRR in T790M+ Patients

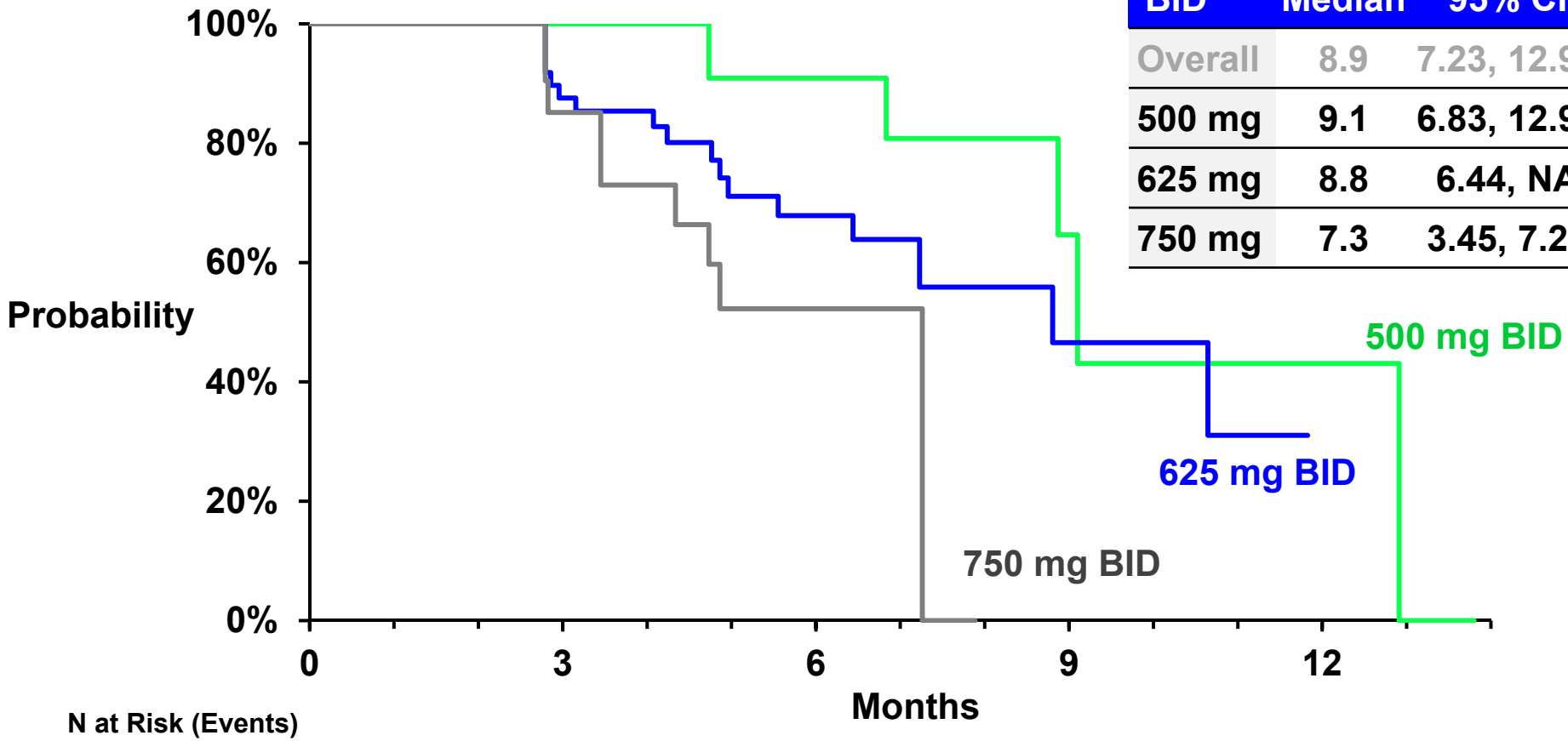
BID	Median	95% CI
Overall	8.9	7.23, 12.91



N at Risk (Events)														
Overall	98(0)	98(0)	86(0)	69(9)	57(12)	40(20)	34(22)	25(24)	13(26)	10(28)	5(29)	4(30)	1(30)	1(30)	0(31)

Studies -008 and -019 Duration of Response by IRR in T790M+ Patients

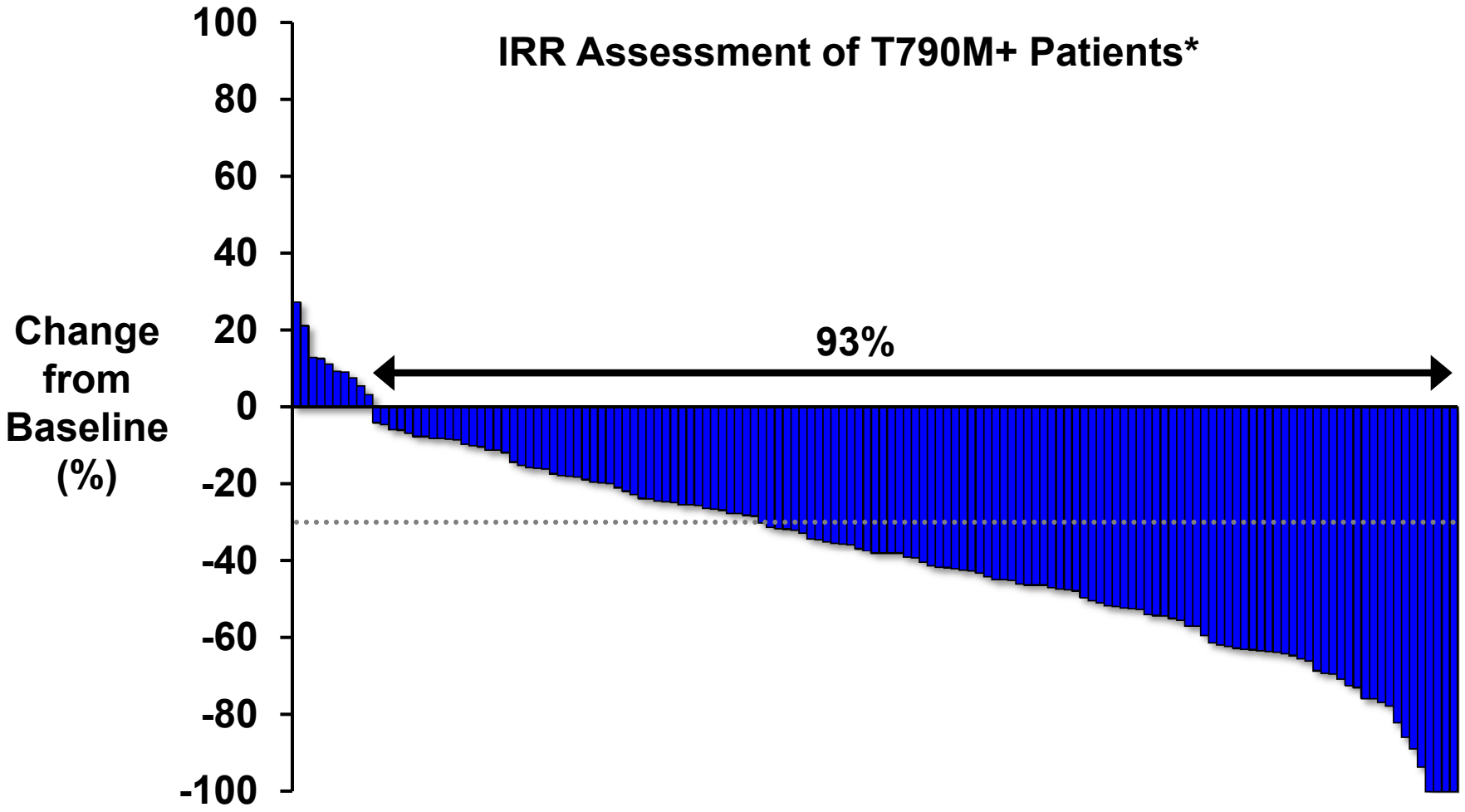
BID	Median	95% CI
Overall	8.9	7.23, 12.91
500 mg	9.1	6.83, 12.91
625 mg	8.8	6.44, NA
750 mg	7.3	3.45, 7.26



N at Risk (Events)

500 mg BID	18(0)	18(0)	14(0)	13(0)	12(0)	10(1)	10(1)	8(2)	7(2)	5(3)	2(4)	2(4)	1(4)	1(4)	0(5)
625 mg BID	55(0)	55(0)	51(0)	42(6)	33(7)	24(11)	18(13)	14(14)	6(15)	5(16)	3(16)	2(17)	0(17)		
750 mg BID	25(0)	25(0)	21(0)	14(3)	12(5)	6(8)	6(8)	3(8)	0(9)						

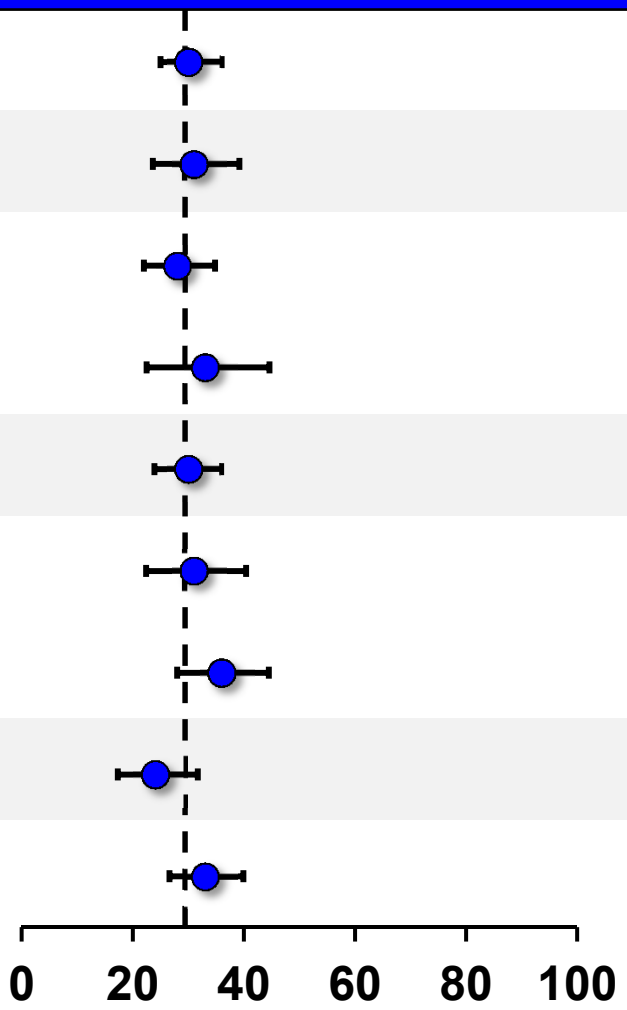
93% of Patients Had Target Lesion Reduction on Rociletinib 625 mg BID



* IRR Reviewer 1

Consistent ORR Across Major Subgroups, All Doses Combined (IRR)

T790M+ Subgroup	n	ORR (95% CI)
Overall (+)	325	
Age ≥ 65 years	145	
White	203	
Asian	76	
ECOG 1	236	
Patients with liver metastasis	110	
Patients with bone metastasis	139	
History of CNS metastases	146	
≥ 2 prior therapies	203	



Rociletinib Demonstrates Clinically Meaningful Efficacy

- All doses combined (n=325)
  - ORR: 30% by IRR
  - DoR: 8.9 months
- 625 mg BID (n=170)
  - ORR: 32% by IRR
  - DoR: 8.8 months
- Similar responses across all major subgroups
  - Including patients with poor prognostic factors

Safety and Dose Selection

Lindsey Rolfe, MBCHB, MRCP

Chief Medical Officer

Clovis Oncology

Safety Exposure

Studies -008 and -019	500 mg BID N=90	625 mg BID N=209	750 mg BID N=95
Duration of Treatment			
Median (weeks)	22.4	18.3	25.1
<6 months	63%	63%	53%
>6 months	37%	37%	47%

Overall Safety*

Patients with ≥ 1 Event Studies -008 and -019	500 mg BID N=90	625 mg BID N=209	750 mg BID N=95
Any AE	100%	99%	100%
Grade 3/4 AE	57%	56%	65%
AE leading to dose modification	60%	63%	74%
AE leading to discontinuation	20%	22%	20%
SAE	44%	46%	47%
AE with outcome of death	13%	17%	15%

- 86% of AEs with outcome of death due to disease progression

*Includes AEs of disease progression

Overview of AEs
All Grades (>25% Any Group)

AEs by Preferred Term Studies -008 and -019	500 mg BID N=90	625 mg BID N=209	750 mg BID N=95
Any AE	100%	99%	100%
Diarrhea	56%	55%	53%
Nausea	51%	53%	52%
Hyperglycemia SMQ	54%	55%	66%
Fatigue	47%	41%	47%
Decreased appetite	32%	34%	42%
QT prolonged SMQ	33%	37%	35%
Vomiting	30%	33%	28%
Constipation	22%	30%	23%
Headache	27%	22%	17%
Muscle spasms	28%	22%	26%
Weight decreased	27%	19%	40%

AEs Grade 3/4 (≥ 4% Any Group)

AEs by Worst Grade Preferred Term Studies -008 and -019	500 mg BID N=90	625 mg BID N=209	750 mg BID N=95
Any Grade 3/4 AE	57%	56%	65%
Hyperglycemia SMQ	31%	32%	42%
QT prolonged SMQ	8%	13%	16%
Fatigue	4%	5%	4%
Anemia	3%	5%	1%
Diarrhea	0%	4%	3%
Hypokalemia	0%	4%	3%
Pneumonia	1%	4%	5%
Hyponatremia	4%	3%	5%
Nausea	3%	3%	4%
Asthenia	2%	2%	5%
Neoplasm progression	3%	2%	7%
Pancreatitis	4%	2%	0
Vomiting	7%	2%	5%
Weight decreased	0	1%	4%

Diarrhea and Cutaneous AEs Generally Mild

AEs by Preferred Term Studies -008 and -019	500 mg BID N=90		625 mg BID N=209		750 mg BID N=95	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Diarrhea	56%	0	51%	4%	49%	3%
Rash, combined terms	10%	0	10%	<1%	10%	0
Paronychia	1%	0	0	0	1%	0
Stomatitis	4%	0	2%	0	1%	0

AEs Leading to Dose Modification, All Grades (≥ 4% in Any Group)

AEs by Preferred Term Studies -008 and -019	500 mg BID N=90	625 mg BID N=209	750 mg BID N=95
Any AEs Leading to Dose Modification	60%	63%	74%
Hyperglycemia SMQ	24%	23%	47%
QT prolonged SMQ*	11%	12%	14%
Nausea	9%	13%	15%
Diarrhea	3%	12%	11%
Fatigue	4%	11%	17%
Decreased appetite	2%	7%	7%
Vomiting	7%	7%	6%
Asthenia	2%	2%	5%
Pancreatitis	4%	2%	0
Thrombocytopenia	2%	1%	4%
Malignant neoplasm progression	0	1%	4%
Muscle spasm	0	0	4%

*QT prolongation required dose interruption followed by dose reduction

AEs Leading to Discontinuation (≥ 2%)

AEs by Preferred Term Studies -008 and -019	500 mg BID N=90	625 mg BID N=209	750 mg BID N=95
Any AEs Leading to Discontinuation	20%	22%	20%
Malignant neoplasm progression	9%	11%	12%
QT prolonged SMQ	3%	3%	3%
Hyperglycemia SMQ	2%	1%	0
Pneumonia	1%	1%	2%
Pneumonitis SMQ	0	1%	2%
Nausea	0	0	2%

SAEs (≥ 3% in Any Group)

SAEs by Preferred Term Studies -008 and -019	500 mg BID N=90	625 mg BID N=209	750 mg BID N=95
Any SAE	44%	46%	47%
Malignant neoplasm progression	12%	17%	17%
Hyperglycemia SMQ	13%	6%	7%
Pneumonia	2%	4%	6%
Pancreatitis SMQ	4%	2%	0%
Nausea	3%	2%	1%
Headache	0	<1%	3%
Vomiting	6%	<1%	1%

Events with Outcome of Death

Deaths by Preferred Term Studies -008 and -019	500 mg BID N=90	625 mg BID N=209	750 mg BID N=95
Any AE with Outcome of Death[1]	13%	17%	15%
Malignant neoplasm progression[2]	10%	16%	13%
Pneumonia	1%	<1%	1%
Sudden death	0%	<1%	1%
Aspiration	1%	0	0
Sepsis	1%	0	0

1. 86% due to disease progression; 2. Judged unrelated to rociletinib by investigator

Events of Torsade de Pointes / QTc Prolongation SMQ

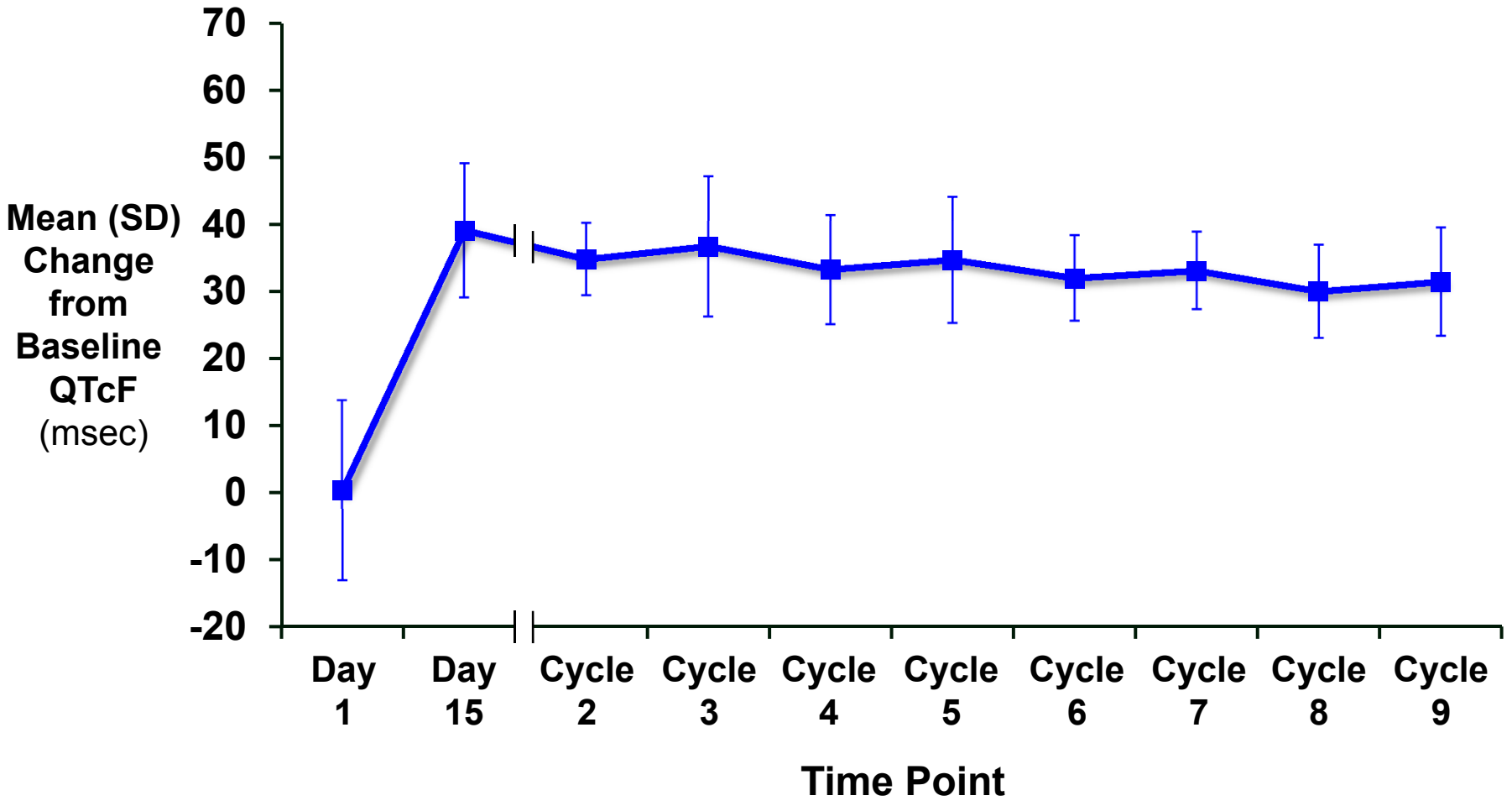
QTc Prolongation SMQ Studies -008 and -019	500 mg BID N=90	625 mg BID N=209	750 mg BID N=95
All AEs	33%	37%	35%
Grade ≥ 3 AE	8%	13%	16%
AE leading to dose modification	11%	12%	14%
AE leading to discontinuation	3%	3%	3%
SAE	1%	4%	2%
AE with outcome of death	0	<1%	1%

QTc Lab Values

QTcF Results* Studies -008 and -019	500 mg BID N=90	625 mg BID N=209	750 mg BID N=95
Post Baseline			
450 to 480 ms	31%	35%	34%
481 to 500 ms	9%	10%	12%
≥ 501 ms	12%	12%	18%
Change from Baseline			
30 to 60 ms	50%	39%	40%
>60 ms	26%	33%	45%

* Average of QTc per ICH guidelines

QTc Measurements (625 mg BID)



Proposed QT Prolongation Risk Minimization Strategy

- Plan agreed with FDA
  - REMS program
  - Black box warning
- Proposed labeling

Proposed QT Prolongation Risk Minimization Strategy (1)

- REMS program and messages
  - Rociletinib prolongs QTc interval
  - Torsades de pointes and sudden death have occurred
  - ECG and electrolytes must be monitored
  - Rociletinib not recommended in patients with prolonged QT at baseline
  - Communication to HCPs
  - Assessment plan
  - Identification, education of new prescribers

Proposed QT Prolongation Risk Minimization Strategy (2)

- Black box warning
  - Clear information on which patients are not suitable for rociletinib
  - Based on baseline risk factors that increase risk of QT complications

Proposed QT Prolongation Risk Minimization Strategy (3)

- Proposed label
  - Patient selection
  - ECG monitoring during therapy
    - Day 8, 15, and periodically
  - Warning to check electrolytes before starting therapy
  - Co-administered drugs to avoid
  - Dose reductions and dose interruptions to manage QT prolongation

Hyperglycemia SMQ

Hyperglycemia SMQ Studies -008 and -019	500 mg BID N=90	625 mg BID N=209	750 mg BID N=95
All AEs	54%	55%	66%
Grade 3/4 AE	31%	32%	42%
AE leading to dose modification	24%	23%	47%
AE leading to discontinuation	2%	1%	0
SAE	13%	6%	7%
AE with outcome of death	0	0	0

Hyperglycemia Management

- Regular glucose monitoring appropriate
- Manage hyperglycemia using agents that target insulin resistance
  - Dose reductions may be used if not otherwise manageable
- Hyperglycemia detected and monitored by blood or urine testing (widely available)

Other AESIs

- Pancreatitis
  - Acute pancreatitis in 15 patients (4%)
  - All recovered and continued drug
  - After NDA cutoff, 1 fatal case reported (625 mg BID)
- Cataracts
  - Appears to be late effect
  - 41 patients reported as of January 2016

Rociletinib 625 mg BID Well-Defined, Manageable, Differentiated Safety Profile

- 37% treatment duration >6 months
- Starting dose of 625 mg BID may be reduced to manage adverse events
- Prescriber education to manage QTc prolongation and hyperglycemia
- Differs from other EGFR TKIs
  - Higher rates of hyperglycemia and QTc prolongation
  - Minimal cutaneous toxicities

Justification for 625 mg BID Dose Based on Benefit-Risk

Rociletinib 625 mg BID Selected Dose Based on Efficacy and Safety

Studies -008 and -019	500 mg BID	625 mg BID	750 mg BID
Efficacy	N=79	N=170	N=76
ORR (95% CI) by IRR	23% (14, 34)	32% (25, 40)	33% (23, 45)
Safety	N=90	N=209	N=95
Any Grade 3/4 AE	57%	56%	65%

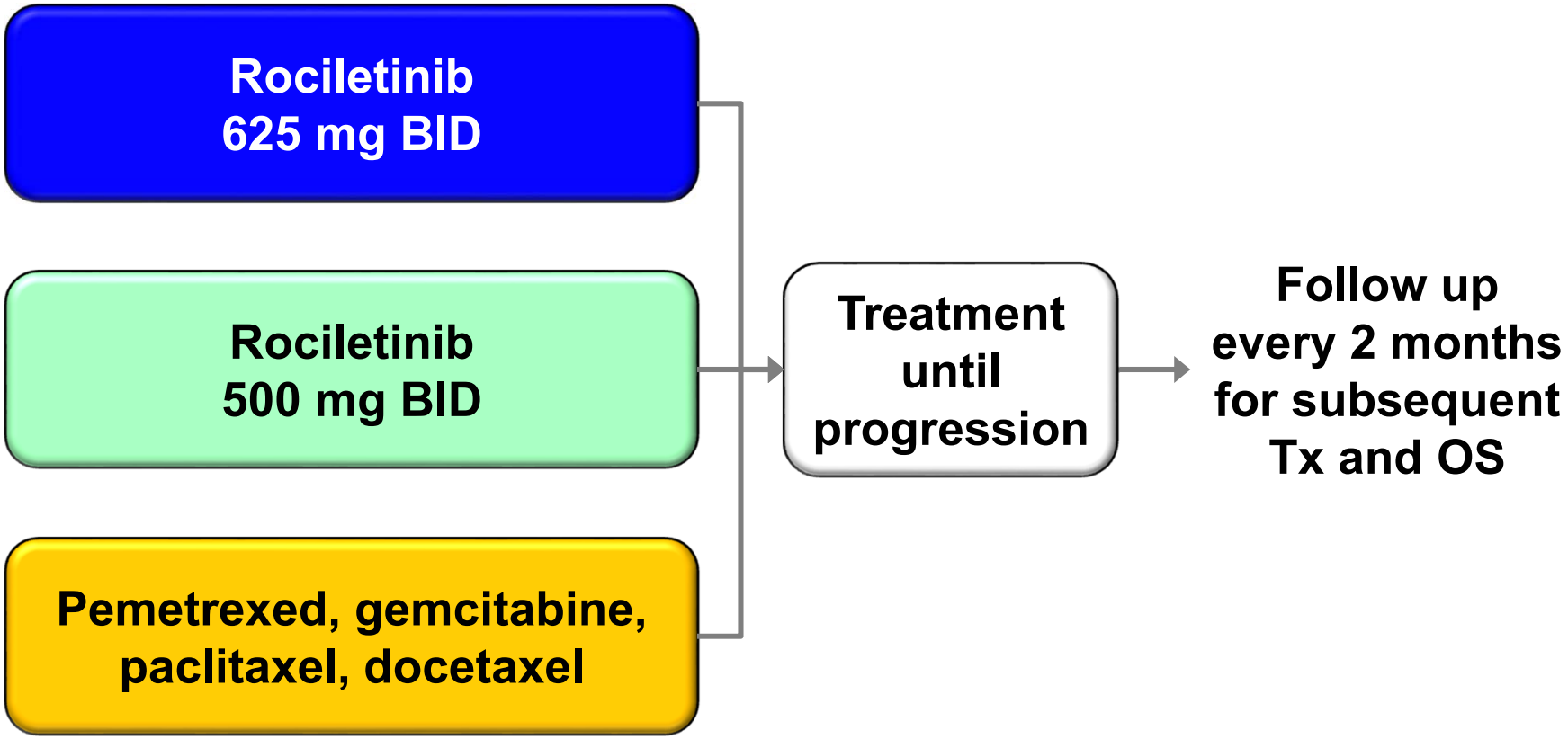
- 625 mg BID dose for accelerated approval

Rociletinib Confirmatory Study

Confirmatory RCT Compared to Investigator's Choice Cytotoxic Chemotherapy

- Eligible patients
  - ≥ 1 previous line of EGFR inhibitor therapy
  - Cytotoxic chemotherapy, platinum-containing doublet
- Primary endpoint: PFS
- Secondary endpoints: ORR, DoR, OS

Confirmatory Randomized Study Design



Confirmatory Study Expected to Complete in 2018

- 137 patients enrolled as of April 8, 2016
  - Tracking to projection
- Open more centers outside of US
- Complete in timely manner

Clinical Perspective and Benefit-Risk

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Why Rociletinib 625 mg BID?

Studies -008 and -019	500 mg BID	625 mg BID	750 mg BID
Efficacy	N=79	N=170	N=76
ORR (95% CI)	23% (14, 34)	32% (25, 40)	33% (23, 45)
DoR, median (months)	9.1	8.8	7.3
Safety	N=90	N=209	N=95
Any Grade 3/4 AE	57%	56%	65%
AE leading to dose modification	60%	63%	74%

Rociletinib 625 mg BID Should Be Starting Dose

- Clinical goal: maximize response rate with tolerable safety profile
- Higher proportion of patients responded to 625 mg BID than 500 mg BID dose
- Side effects at both 500 mg BID and 625 mg BID doses comparable and manageable

Majority of Grade 3/4 AEs Related to Hyperglycemia and QTc Lab Values

Studies -008 and -019	500 mg BID N=90	625 mg BID N=209	750 mg BID N=95
Any Grade 3/4 AE	57%	56%	65%
Hyperglycemia SMQ	31%	32%	42%
QTc prolongation SMQ	8%	13%	16%

Hyperglycemia Commonly Managed without Serious Consequences

Hyperglycemia SMQ Studies -008 and -019	500 mg BID N=90	625 mg BID N=209	750 mg BID N=95
Grade 3 (>250 – 500 mg/dL)	26%	29%	39%
Grade 4 (>500 mg/dL)	6%	3%	3%
SAE	13%	6%	7%

- Management informed by understanding of mechanism of action (active metabolite causing IR/IGF1R inhibition)

QT Prolongation Rarely Clinically Significant

QT prolongation SMQ Studies -008 and -019	500 mg BID N=90	625 mg BID N=209	750 mg BID N=95
Grade 3 (>500 ms)*	7%	10%	15%
Grade 4 (>500 ms, and life-threatening signs or symptoms)*	1%	1%	0%
SAE	1%	4%	2%

* QT preferred term

Rociletinib Provides Important, Different Option for T790M+ NSCLC

- Single-agent chemotherapy
  - ORR <10%
  - Toxicities and inconvenience of intravenous chemotherapy
- Combination ramucirumab plus docetaxel
  - ORR = 23%
  - Severe toxicities in ~80% of patients that alter QoL
- Immunotherapy[1]
  - Likely less active in EGFR mutant lung cancer
  - NCCN guidelines suggest not enough data to recommend for/against

1. Rizvi (2015)

Favorable Benefit-Risk Profile and Need for Immediate Availability

- Patients with T790M positive disease have limited options
- Rociletinib allows patients to maintain disease control longer through oral therapy
  - Delay less effective, less proven and/or less attractive options (chemo/immunotherapy)
- Unique safety profile/mechanism gives physicians flexibility to individualize treatment
- Results merit accelerated approval

Rociletinib: Accelerated Approval NDA for T790M+ EGFR NSCLC Following Failure of TKI

April 12, 2016

Clovis Oncology

Oncologic Drugs Advisory Committee

Question and Answer Session

Backup Slides Shown

Patients with Initial PR Not Confirmed (By IRR in Efficacy Population)

	500mg BID N=12	625mg BID N=13
PD (Overall)	8	11
AE	1	0
Died	1	1
SD next scan	0	1
Missing	2	0

Activity Maintained with Dose Reductions (Efficacy Population)

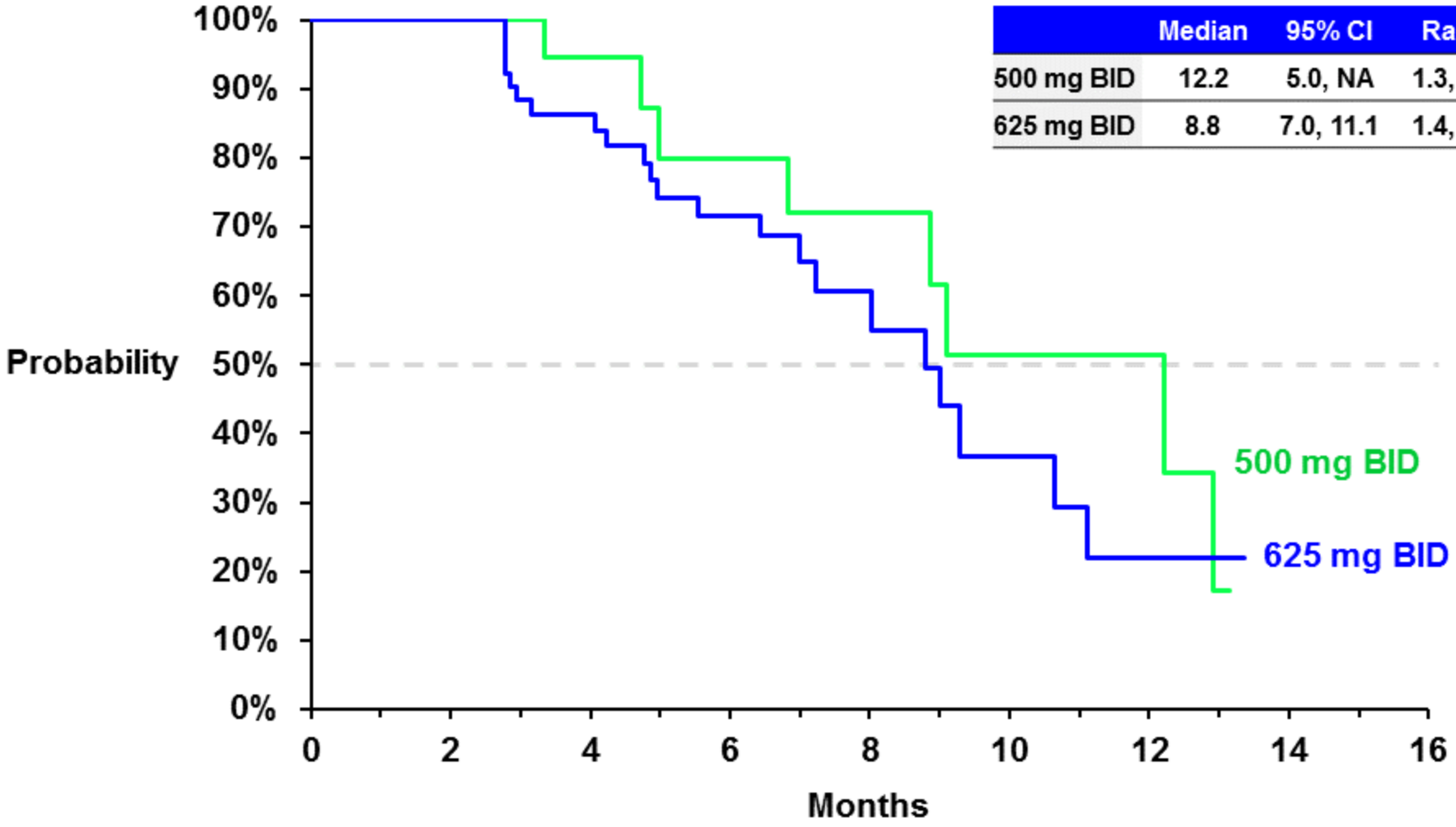
- Starting dose of 625mg BID (n=170)
  - N=93 had a dose reduction
  - **ORR IRR** (95% CI) = **42%** (32-53)
  - **DoR** (95% CI) = **8.8 months** (6.4-NA)
- Starting dose of 500mg BID (n=79)
  - N=31 had a dose reduction
  - **ORR IRR** (95% CI) = **23%** (10-41%)
  - **DoR** (95% CI) = **11.0 months** (6.8–12.9)

Metformin Use in Studies -008 and -019 (Efficacy Population)

Studies -008 and -019		500mg BID N=79	625mg BID N=170	750mg BID N=76	Overall N=325
Metformin initiated on study	n **ORR IRR** (95% CI)	29 **24%** (10-44)	73 **40%** (29-52)	39 **39%** (23-55)	141 **36%** (28-45)
Metformin not initiated on study	n **ORR IRR** (95% CI)	50 **22%** (12-36)	97 **27%** (18-37)	37 **27%** (14-44)	184 **26%** (19-33)

NDA Population Update: DoR by IRR

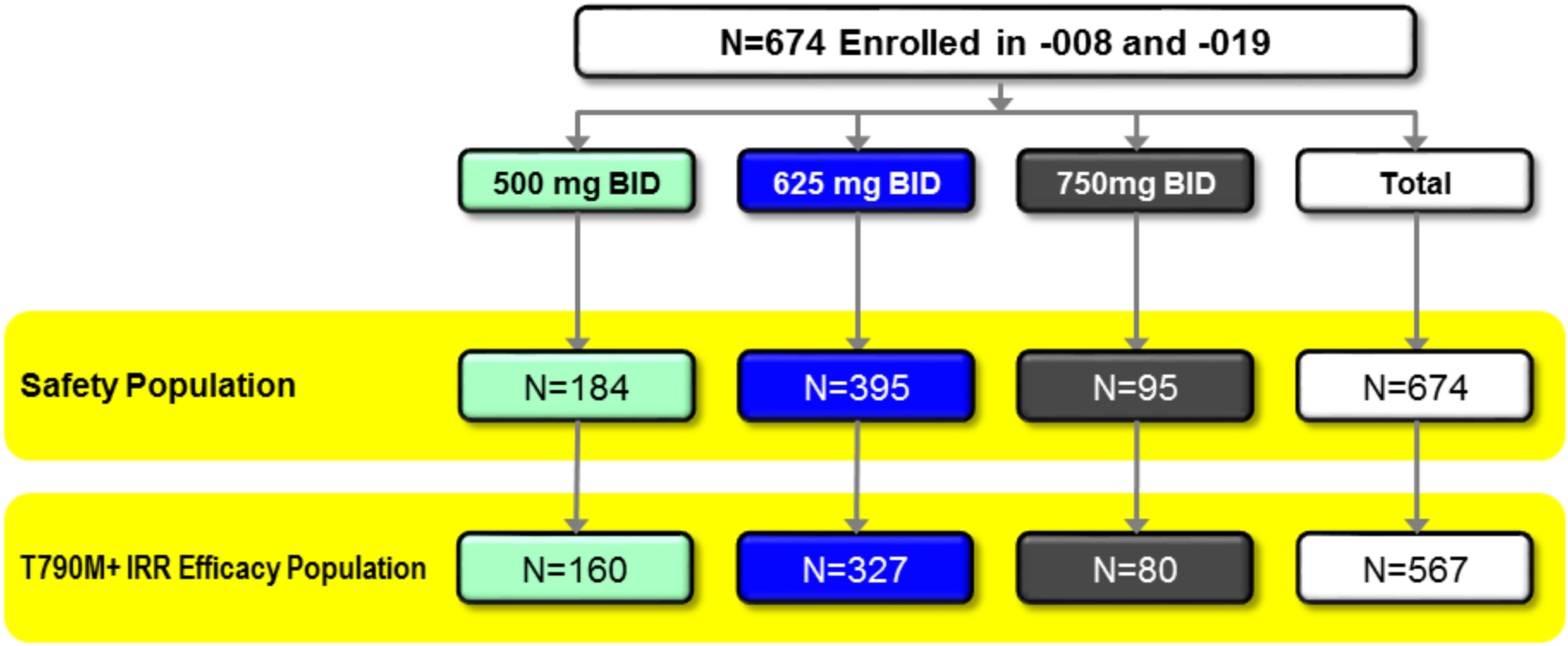
	Median	95% CI	Range
500 mg BID	12.2	5.0, NA	1.3, 13.2
625 mg BID	8.8	7.0, 11.1	1.4, 13.4



As of 18 September 2015

Expanded Dataset Patient Enrollment (Studies -008 and -019) N=674

Enrollment cut off for all patients = July 1, 2015
Visit cut off for all patients = September 18, 2015



As of 18 September 2015