NDA 208542 – Rociletinib

FDA Presentation

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Major Issues/Uncertainties

Efficacy

- Rociletinib is active but may not be better than available therapy

Safety

- Serious and life-threatening adverse reactions; true incidence unknown (single-arm study)
- Variable exposure to toxic metabolites (NAT2)

Dose

- Applicant's proposed 625 mg dose not supported
- High rate of dose modifications
- Limited data at doses <500 mg

Outline

- Introduction
  - Available therapy for NSCLC
  - Regulatory history and review issues
- Results
  - Clinical pharmacology
  - Efficacy
  - Safety
- Summary

INTRODUCTION

Rociletinib

Mechanism of Action: Irreversibly binds and inhibits signaling through mutated forms of EGFR:

- Exon 21 L858R substitution
- Exon 19 deletion
- T790M resistance mutation

Proposed Indication

For the 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.

This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Non-Small Cell Lung Cancer

- Lung cancer leading cause of cancer death in US (~158,040 in 2015)
  - NSCLC: 85% of lung cancer
  - EGFRm+ NSCLC: 10-15% (US); 30-50% (Asia)
  - EGFR mutations: exon 19 del (45%); exon 21 (L858R) (40-45%)
- FDA-approved drugs for EGFRm+ NSCLC:
  - EGFR TKIs: erlotinib, gefitinib, or afatinib
    - Improved outcomes compared to chemotherapy

Acquired Resistance to EGFR TKIs

- Treatment with EGFR TKIs → acquired resistance
  - T790M mutation: 50-60% of patients
    - Approved EGFR-TKIs are ineffective
    - Patients treated with 2nd-line therapy for NSCLC

Available Therapy for 2nd-Line Metastatic NSCLC

Product	Comparator	ORR (95% CI)	OS advantage?
Docetaxel	BSC	6% (1, 15) docetaxel N/A BSC	Yes
	Vinorelbine/ Ifosfamide	6% (2, 11) docetaxel 1% (0, 5) vinorelbine/ifosfamide	No
Pemetrexed (NSQ)	Docetaxel	13% (8, 18) pemetrexed 10% (5, 15) docetaxel	Yes (NSQ)
Ramucirumab + docetaxel	Docetaxel	23% (20, 26) ramucirumab + docetaxel 14% (11, 17) docetaxel	Yes
Nivolumab	Docetaxel	19% (15, 24) nivolumab 12% (9, 17) docetaxel mDoR: 17 months nivolumab mDoR: 6 months docetaxel	Yes

BSC=best supportive care; N/A=not available; ORR=objective response rate; OS=overall survival; CI=confidence interval; NSQ=non-squamous; mDoR=median Duration of Response

Other Drugs for EGFR Mutant NSCLC

Osimertinib (Tagrisso)

- **Indication**: Treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy.

Efficacy Parameter	Study 1 %(N=201)	Study 2 %(N=210)	Pooled %(N=411)
CR	0	1	0.5
PR	57	60	59
ORR 95% CI	57 (50, 64)	61 (54, 68)	59 (54, 64)

Osimertinib - Common Adverse Reactions

Preferred Term	%(N=411)	
Adverse Reaction	**All Grades**	**Grades 3-4**
Diarrhea	42	1
Rash	41	<1
Dry skin	31	0
Nail toxicity	25	0
Eye disorders*	18	<1

*Includes dry eye, vision blurred, keratitis, cataract, eye irritation, blepharitis, eye pain, lacrimation increased, vitreous floaters. Other ocular toxicities occurred in <1% of patients.

- **Incidence Grade ≥3 toxicities:**
  - Pneumonia: 2.2%
  - Venous thromboembolism: 2.4%

Osimertinib - Other Adverse Reactions

- ILD/Pneumonitis: 3.3%
- Cardiomyopathy: 1.4%
- QTc prolongation
  - >500 ms: 0.2%
  - ΔQTc >60 ms: 2.7%

Rociletinib Regulatory Milestones

Date	Milestones
12/20/2011	Clinical development program initiated
05/14/2013	Orphan Drug Designation
05/19/2014	Breakthrough Therapy Designation N=33 (ORR: 54.5%)
07/17/2014	End of Phase 2 meeting
06/09/2015	Pre-NDA meeting
06/24/2015	Rolling submission of NDA initiated with request for Accelerated Approval
11/09/2015	Mid-Cycle: Application to be referred to ODAC
12/14/2015	Major amendment → PDUFA goal date 6/28/2016
03/21/2016	Late-Cycle meeting

Request for Accelerated Approval

- Efficacy studies
  - CO-1686-008 (TIGER-X)
  - CO-1686-019 (TIGER-2)
- Efficacy endpoint
  - Investigator-assessed objective response rate (ORR)
- Proposed dose
  - Submission: 500 mg BID
  - Post-submission: 625 mg BID

Accelerated Approval

- Condition is serious & life-threatening
- Treatment provides improvement over available therapy
  - Available therapy: therapy that is specified in the approved labeling of regulated products indicated for the condition
- Studies may use a surrogate reasonably likely to predict clinical benefit
- Requires confirmation of clinical benefit
  - Post-marketing trials usually underway at time of approval
  - Applicant will carry out studies with due diligence

Clinical Studies

- CO-1686-008 (TIGER-X)
  - Treatment: rociletinib free base and rociletinib HBr
  - Efficacy endpoints: RECIST v1.1
    - Phase 1: ORR & DoR (investigator)
    - Phase 2: ORR & DoR (1º→investigator; 2º→IRR)
- CO-1686-019 (TIGER-2)
  - Treatment: rociletinib HBr
  - Efficacy endpoints: RECIST v1.1
    - 1º→ ORR by IRR
    - 2º→ DoR by IRR; ORR & DoR by investigator

Confirmatory Study: CO-1686-020 (TIGER-3)

- **Design:** Phase 3, open-label, multi-center, randomized
- **Treatment Arms:** rociletinib vs. single-agent chemotherapy
- **Population**: ±T790M, post-EGFR TKI & platinum doublet
- **1º Endpoint**: invPFS (RECIST)
- **Sample/randomization**: 900 pts; 1:1:1 (500/625/chemo)
- **Enrollment**: N=117 (07 March 2016)

Major Disagreements with Applicant

- Applicant's proposed dose
  - Approach to the review
    - Defining the primary efficacy population
    - Defining the primary efficacy endpoint
- Interpretation of efficacy results
  - Application of protocol-specified criteria
    - RECIST v1.1

Applicant Dose Recommendation

- **July 2015:** 500 mg BID is the proposed dose
- **Jan 2016**: 625 mg BID is the proposed dose
  - Point estimate for ORR numerically higher
- **Feb 2016**: FDA: PK data do not support 625 mg
- **Mar 2016**: TIGER-3 amended to evaluate 625 mg

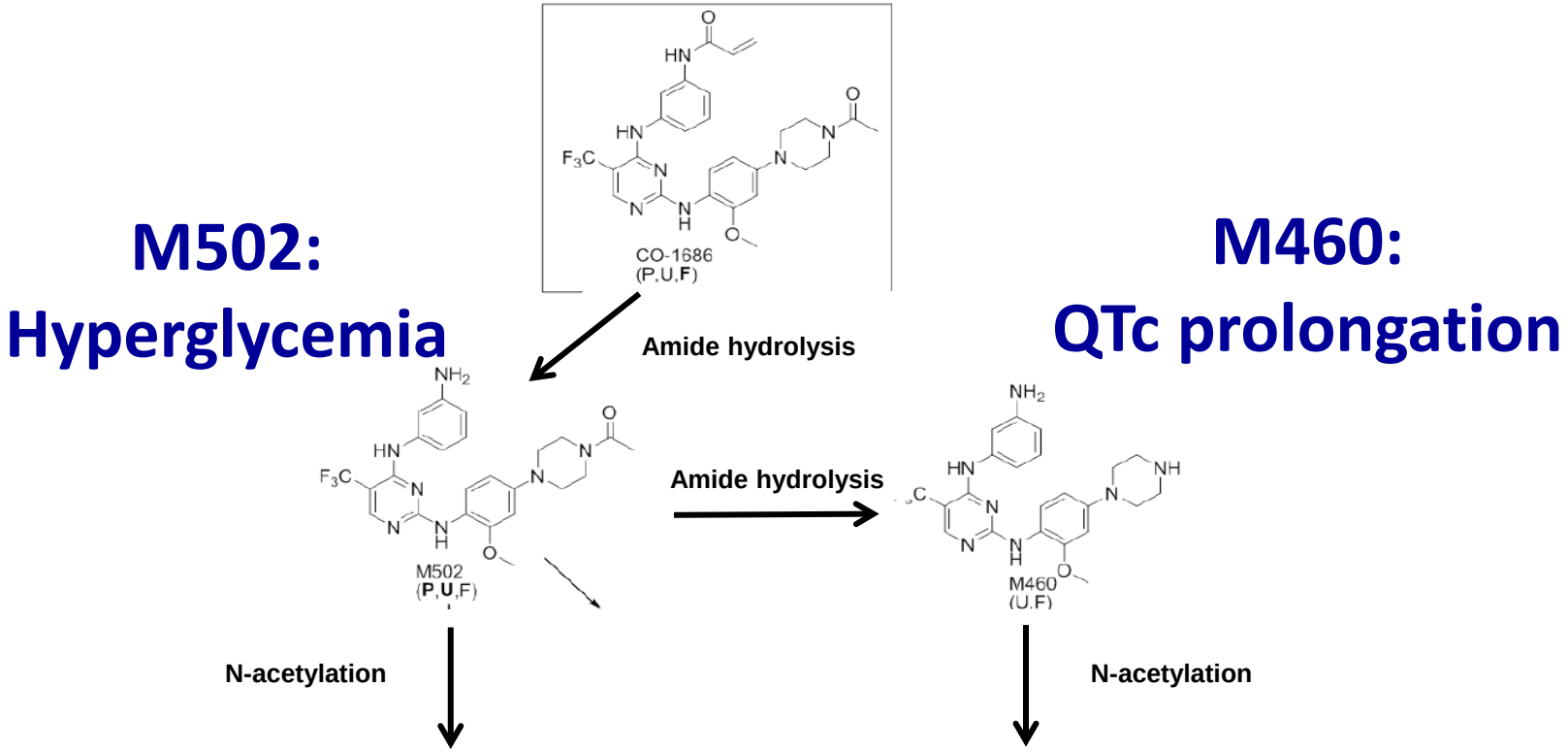
WHAT IS THE APPROPRIATE DOSE OF ROCILETINIB?

Rociletinib PK Highlights

- Rociletinib PK at steady-state
  - Highly variable exposure (up to 79% CV)
  - No accumulation (3.7 hours half-life)
- Practically insoluble (<0.1 mg/mL) when pH >2
- Food effect: high-fat meal increases AUC by 54%
  - Taken with food
- Metabolism
  - Mainly by amide hydrolysis and N-acetylation

Rociletinib Biotransformation Pathway

Rociletinib: Efficacy



M502: Hyperglycemia

M460: QTc prolongation

$T_{1/2}$ (M502): 20 hours
$T_{1/2}$ (M460): 51 hours

Source: Modified from IR-33 (date: 01/25/2016).

Mechanism of Action

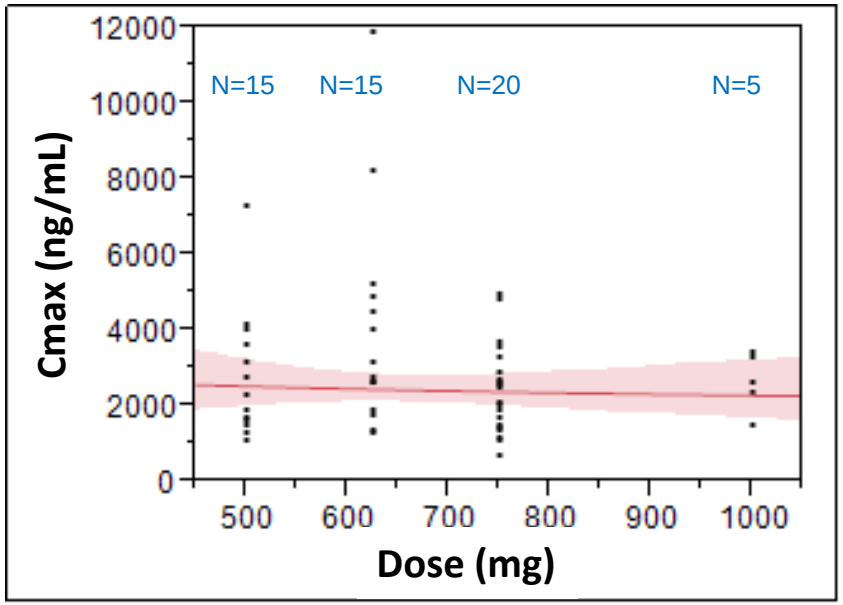
- Efficacy: Rociletinib
- Safety: M460 (QTc prolongation); M502 (Hyperglycemia)

Compound (% of the total radioactivity in plasma)	IC50 (nM)			
	Efficacy	Hyperglycemia		QTc Prolongation
	T790M EGFR	INSR	IGF1R	hERG
Rociletinib (14%)	**5**	477	166	>1000
M460 (3%)	901	**52**	**27**	**50**
M502 (69%)	>1000	**57**	**23**	>1000

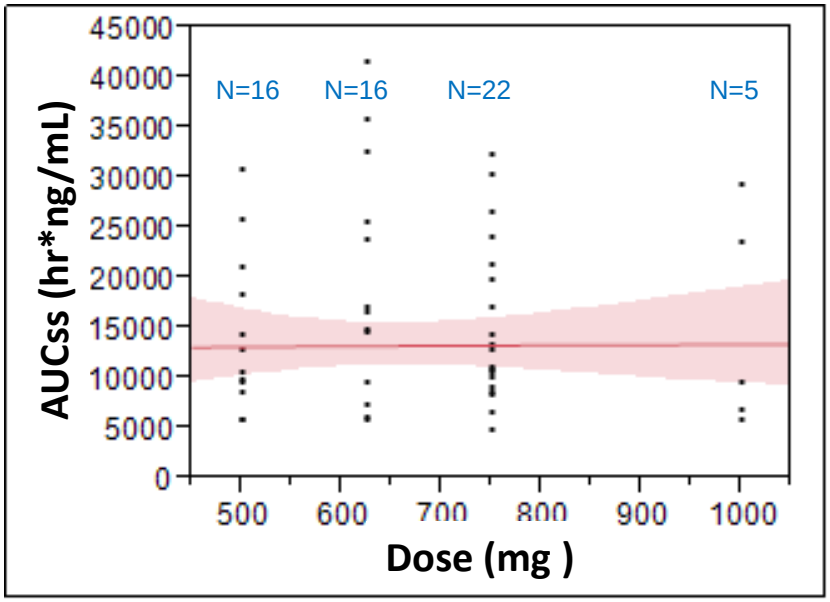
EGFR=epidermal growth factor receptor; IGF1R=insulin-like growth factor 1 receptor
INSR=insulin receptor; hERG=human ether-a-go-go-related gene

Intensive PK: Similar Rociletinib Exposure from 500 to 1000 mg BID

slope -0.15 [-0.74, 0.45] (P=0.69)

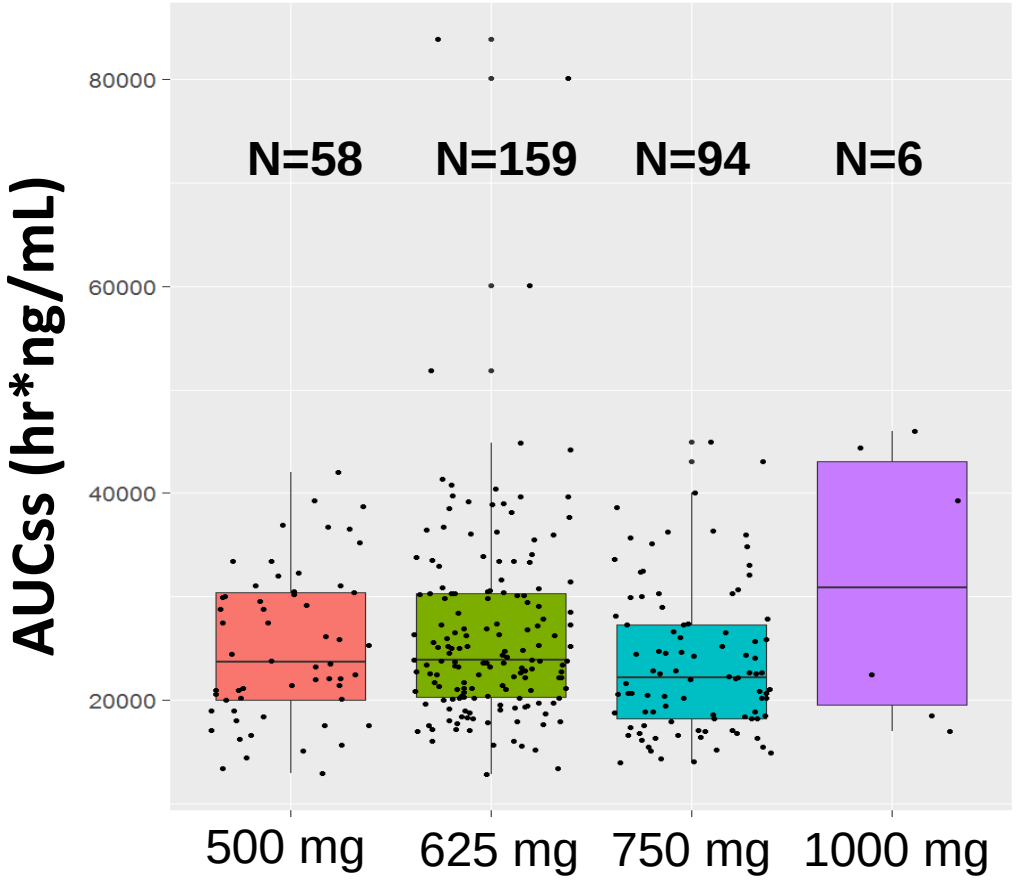


slope 0.028 [-0.59, 0.65] (P=0.94)



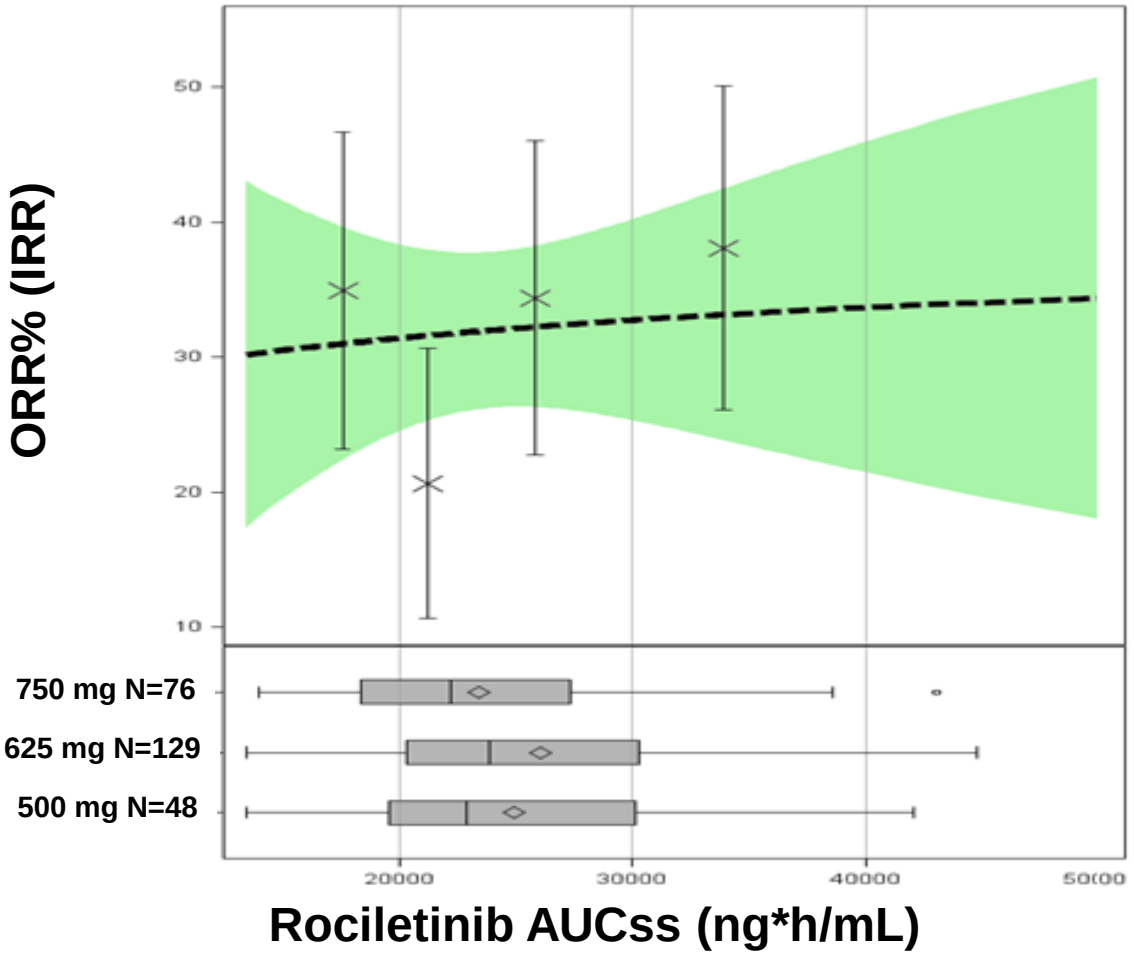
Intensive PK data available from a subset of the patients on Day 15. Non-compartmental analysis (NCA) used to derive steady-state Cmax & AUC.

Population PK: Similar Rociletinib Exposure from 500 to 1000 mg BID



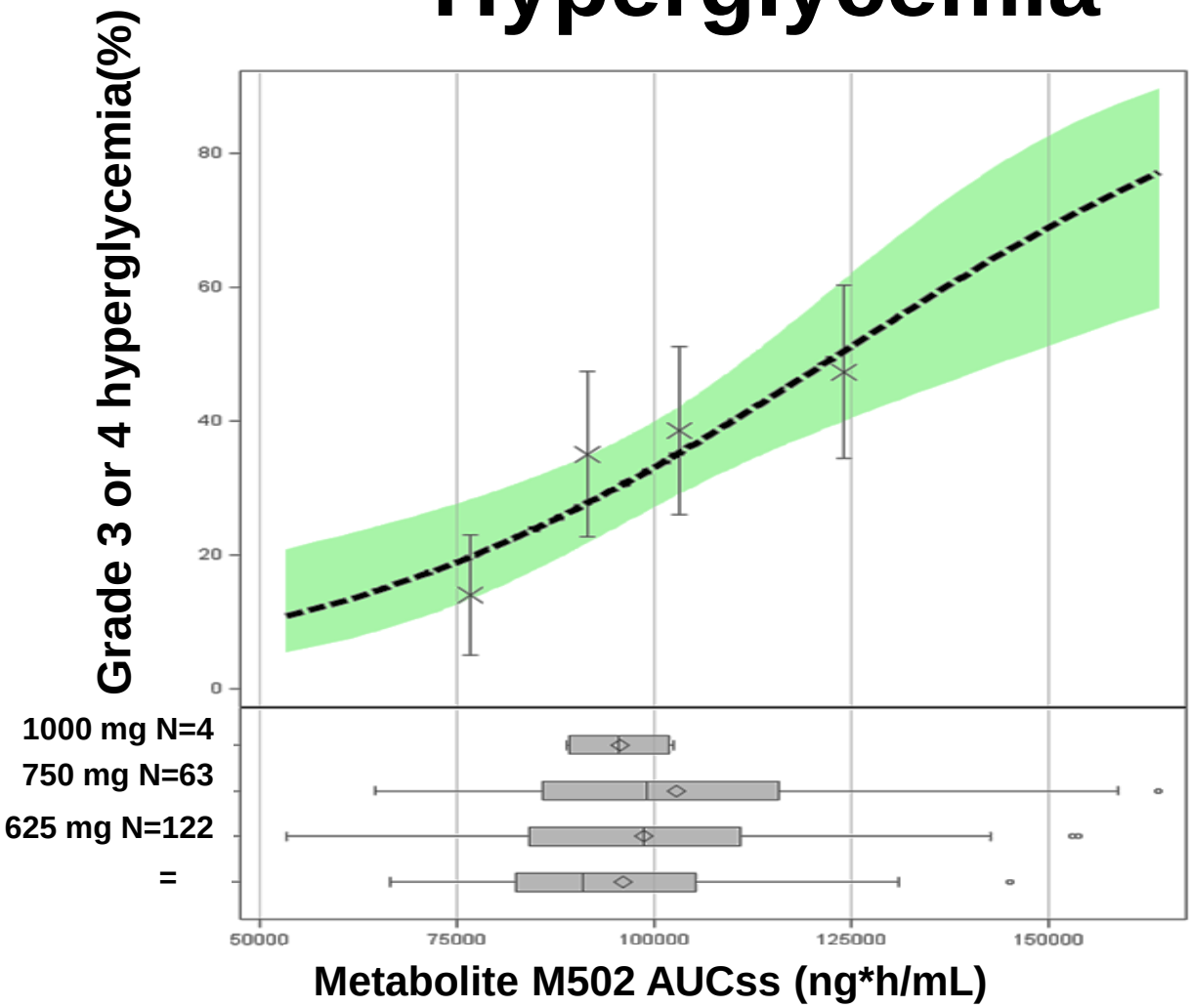
Dose-Exposure is flat

Rociletinib Exposure-Efficacy Relationship



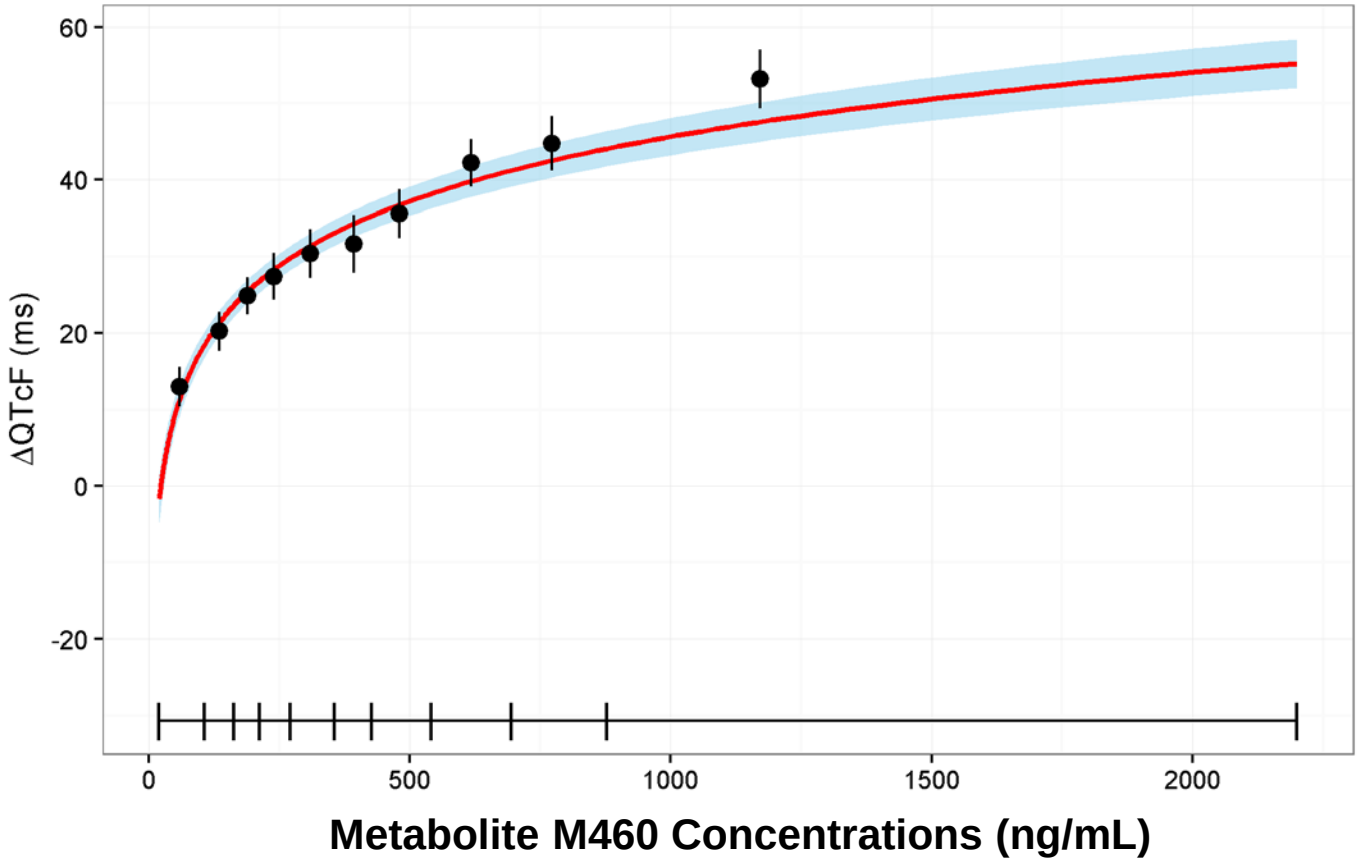
Rociletinib steady-state AUC was derived from population PK analysis

M502 Exposure-Safety Relationship: Hyperglycemia



M502 steady-state AUC was derived from population PK analysis

M460 Exposure-Safety Relationship: QTc Prolongation



M460 concentrations were from observed data

What is the Appropriate Dose of Rociletinib Based on Available Data?

- **Dose-exposure relationship is flat from 500 to 1000 mg BID**
  - FDA pooled data across different dose levels for safety & efficacy
- **Exposure-efficacy relationship is flat**
  - Patients with higher rociletinib exposure are unlikely to have further benefit
- **Exposure-safety relationship is steep**
  - Patients with higher metabolite exposure are at increased risk for QTc prolongation & hyperglycemia

625 mg BID not adequately supported

Primary Efficacy Endpoint

Clinical Pharmacology Data

- Dose-exposure flat across doses 500-1000 mg BID
- Exposure-efficacy flat at across doses 500-1000 mg BID

FDA Approach: Pooling of the efficacy data across several dose groups may provide a reasonable estimate of the true effect of rociletinib on tumor response.

FDA Primary Efficacy Population

- **Efficacy**
  - Rociletinib HBr
  - T790M+ (central)
  - Reviewed by IRR

Analysis Population	Rociletinib HBr Dose Cohorts					Total
	-008				-019	
	500	625	750	1000	625	
Efficacy	79	128	76	0	42	**325**
Safety	90	167	95	6	42	**400**

EFFICACY RESULTS

Clovis' Submission to FDA

Objective Response Rate in T790M-positive Patients, by RECIST

	500 mg BID		625 mg BID		750 mg BID	
	IRR	INV	IRR	INV	IRR	INV
	N = 55	N = 76	N = 126	N = 163	N = 64	N = 79
Best Objective Response (%)						
CR	0	0	0.8	0	0	0
PR	38.2	42.1	50.0	46.6	51.6	44.3
SD	47.3	40.8	27.8	28.2	28.1	35.4
PD	14.5	10.5	16.7	20.2	20.3	19.0
Not evaluable[a]	0	6.6	4.8	4.9	0	1.3
ORR (CR + PR)	38.2	42.1	50.8	46.6	51.6	44.3
95 % CI (%)	25.4, 52.3	30.9, 54.0	41.7, 59.8	38.8, 54.6	38.7, 64.2	33.1, 55.9

[a] Patients were considered not evaluable due to early death or discontinuation due to clinical progression before the first restaging scan; these patients were included in the denominator for the ORR calculation

- ORR is likely to increase as more patients reach Cycle 4 and data mature
- ORR (Inv) as of July 30 at 500 mg BID is 47.4%

FDA's Position on Submission

- The objective response rates must be based on confirmed responses only (RECIST v1.1)
- The denominator in IRR assessment must be the Intent-to-Treat population (RECIST v1.1)
- IRR-assessed ORR must be the primary efficacy endpoint (RECIST v1.1)

Results of FDA's Efficacy Analysis

Analysis Value	500 mg (N=79)	625 mg (N=170)	750 mg (N=76)	Pooled* (N=325)
CR	0	0.6%	0	0.3%
PR	22.8%	31.8%	32.9%	29.8%
ORR (95% CI)	22.8% (14.1, 33.6)	32.4% (25.4, 39.9)	32.9% (22.5, 44.6)	30.2% (25.2, 35.5)
Median DoR, mos [95% CI]	9.1 [6.8,12.9]	8.8 [6.4, NR]	7.3 [3.4,7.3]	8.9 [7.2,12.9]

* Patients in 500/625/750 dose groups CI=confidence interval;
DoR=duration of response; ORR=objective response rate; mos=months
NR=not reached

SAFETY OVERVIEW

Incidence of Adverse Reactions

	500 mg %(N=90)	625 mg %(N=209)	750 mg %(N=95)	1000 mg %(N=6)	Pooled %(N=400)
≥1 TEAE	100	99	100	100	100
≥1 SAE	44	46	47	83	47
Fatal SAE (all)	13	17	15	50	16
Fatal SAE (non-PD)	3	1	2	33	2

TEAE=treatment emergent adverse event; SAE=serious adverse event;
PD=progressive disease

Common Adverse Reactions

	500 mg %(N=90)		625 mg %(N=209)		Safety Population %(N=400)	
AE (PT)	All* Grades	Grades 3-4	All* Grades	Grades 3-4	All* Grades	Grades 3-4
Hyperglycemia (SMQ)	54	31	55	32	58	34
Diarrhea	56	0	55	4	55	3
Nausea	46	3	52	3	52	4
Fatigue	42	4	41	5	44	5
Decreased appetite	32	0	34	1	36	1
QT prolonged	33	8	33	10	33	11
Vomiting	29	7	32	2	30	4

*AEs with NCI-CTCAE “missing” excluded; PT= preferred term

Dose Modifications

Dose Modification	Safety Population %(N=400)
Interruptions	56
Reductions	51
Discontinuations	21

Dose Interruptions

	500 mg %(N=90)		625 mg %(N=209)		Safety Population %(N=400)	
Preferred Term	**All Grades**	**Grades 3-4**	**All Grades**	**Grades 3-4**	**All Grades**	**Grades 3-4**
Hyperglycemia*	22	18	19	16	24	19
QT prolonged	9	8	11	7	10	8
Nausea	7	2	11	2	10	2
Vomiting	7	3	6	<1	6	2
Fatigue	3	2	7	2	8	2
Diarrhea	2	0	10	3	7	2

*Hyperglycemia (SMQ)

Dose Reductions

	500 mg %(N=90)		625 mg %(N=209)		Safety Population %(N=400)	
Preferred Term	**All Grades**	**Grades 3-4**	**All Grades**	**Grades 3-4**	**All Grades**	**Grades 3-4**
Hyperglycemia*	19	17	17	13	24	18
QT prolonged	9	6	11	5	11	7
Fatigue	2	1	9	3	9	3
Diarrhea	2	0	7	2	7	2
Nausea	3	1	5	0	6	1
↓Appetite	2	0	6	<1	6	1

*Hyperglycemia (SMQ)

Number of Dose Reductions

Dose	1	2	3	4	5	Total
500 mg %(N=90)	23	13	3	0	0	40
625 mg %(N=209)	26	15	5	1	0	47
750 mg %(N=95)	24	19	18	5	1	66
1000 mg %(N=6)	17	0	50	0	0	67

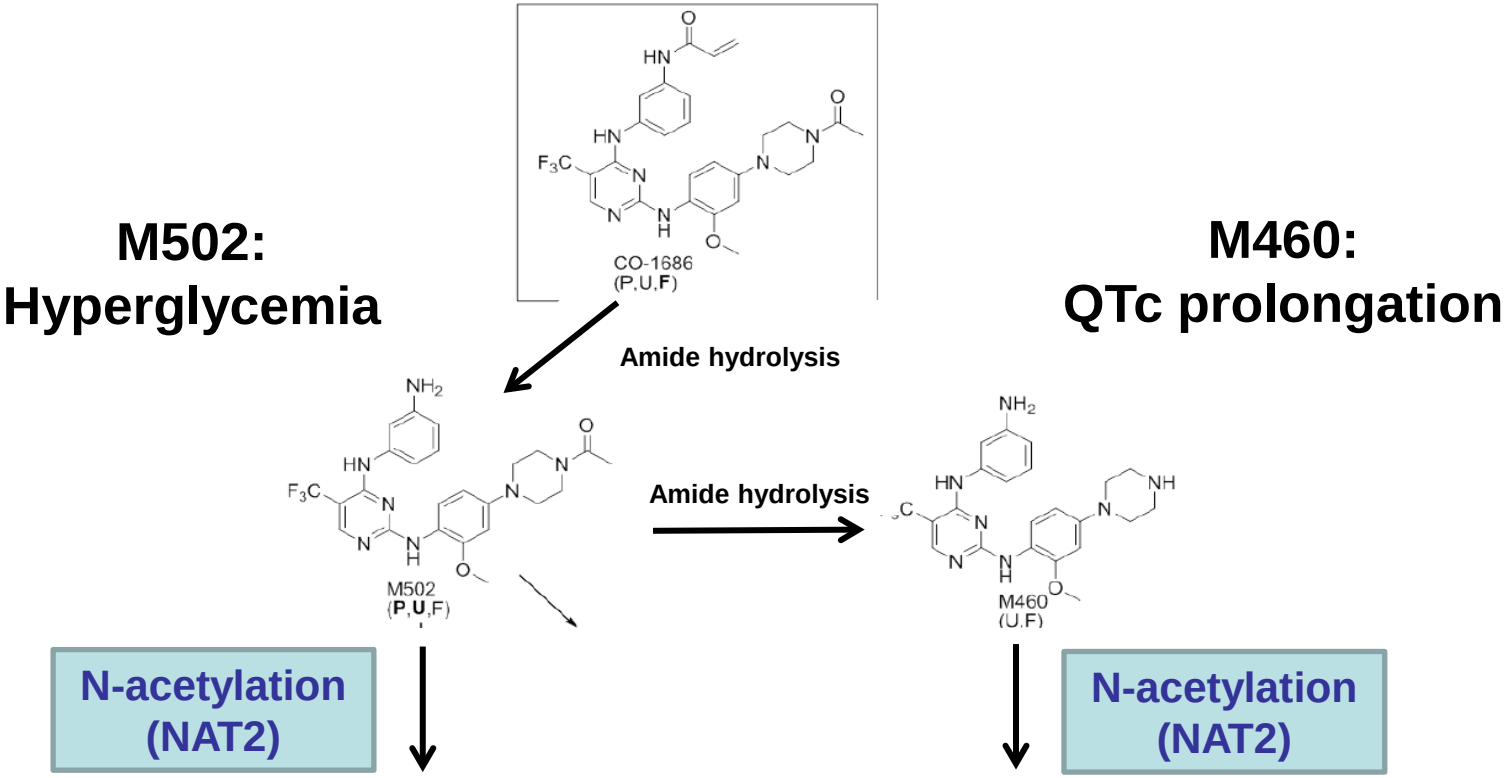
ADVERSE REACTIONS OF SPECIAL INTEREST

Adverse Reactions of Special Interest

- QTc Prolongation
- Cardiac arrhythmias
- Hyperglycemia
- Pancreatitis
- ILD/pneumonitis
- Cataracts

Rociletinib Biotransformation Pathway

Rociletinib: Efficacy

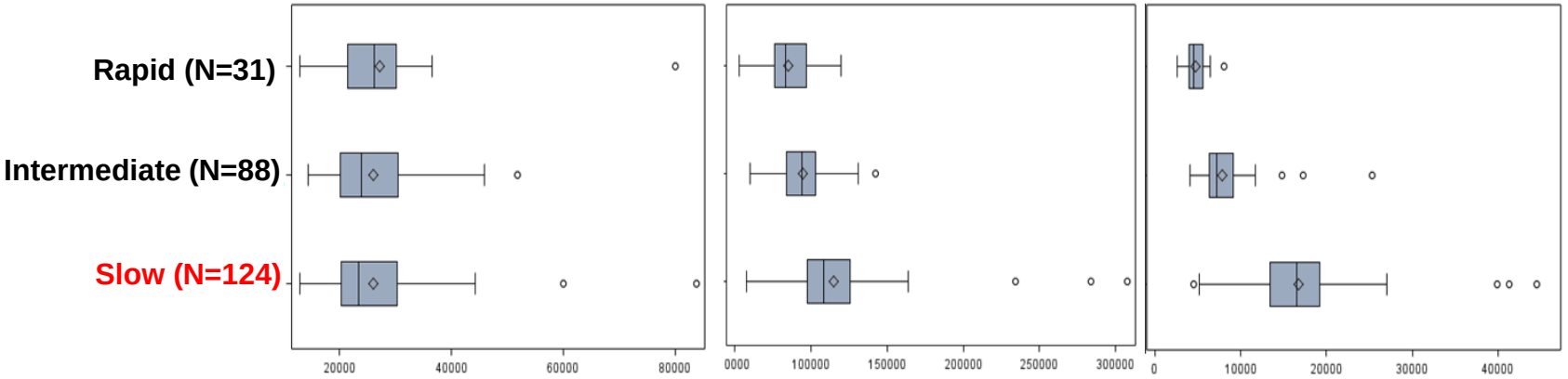


NAT2: N-acetyltransferase 2

Source: Modified from IR-33 (date: 01/25/2016).

40-60% of Whites and
Blacks are slow acetylators.

Effect of NAT2 Acetylator Status on Exposure



Rociletinib AUCss (Efficacy)

M502 AUCss (Hyperglycemia)

M460 AUCss (QTc Prolongation)

Rociletinib, M502 and M460 exposures were derived from population PK for patients with both PK and NAT2 data

Risk of QTc Prolongation

- QTc prolongation→serious & fatal cardiac arrhythmias
  - Torsades de pointes
- Specific ΔQTc vs. proarrythmia risk not established
  - In general large effects on QTc → ↑risk

- **ICH E14**: Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (May 2005)

Definition: QTcF Prolongation

NCI-CTCAE v4.03

- Grade 1: 450- 480 ms
- Grade 2: 481 - 500 ms
- Grade 3: ≥ 501 msec on ≥ 2 separate ECGs
- Grade 4: ≥ 501 ms and Torsade de pointes or polymorphic Vtach or signs/symptoms of serious arrhythmias, **OR**

  >60 ms change from baseline & Torsade de pointes or polymorphic Vtach or signs/symptoms of serious arrhythmias

QTc Prolongation & Proarrhythmic Potential

- ICH E14: Drugs mean ↑QT/QTc interval >20 ms
  - ↑ likelihood of proarrhythmia
  - May observe arrhythmic events
  - Marked QTc increases
    - QT >500 ms
    - ΔQTc >60 ms
- NCI-CTCAE: Grades 3 or 4
- FDA/QT IRT: ΔQTc >30 ms

Post-Baseline QTc Prolongation

Parameter	500 mg N=90	625 mg N=209	Safety population N=400
QTcF ≥ 450 ms (%)	52	56	63
QTcF ≥501 ms (%)	12	12	13
Mean ΔQTcF, ms	36	36	36
Δ>30 ms (%)	76	72	76
Δ>60 ms (%)	26	33	34

Ventricular Tachyarrhythmias/ Sudden Deaths

Subject	Preferred term	Study Day	Documented QTc Prolongation?	Documented QTcΔ >30 ms?
1	Ventricular tachyarryhtmia	115	Yes	Yes
2	Torsades de pointes	10	No	No
3	Sudden death	4	No	No
4	Sudden death	13	No	No
5	Cardiac arrest, ventricular fibrillation	23	No	Yes

QTc Prolongation by NAT2 Status

	Rapid %(N=35)	Intermediate %(N=111)	Slow %(N=157)
SMQ Cardiac Arrhythmia			
Overall	28.6	32.4	45.2
QTc AE	25.7	26.1	40.8
Post-baseline QTcF by ECG Assessment			
QTcF ≥501ms	2.9	9.0	21.0
ΔQTcF >30ms	77.1	65.8	83.4
ΔQTcF >60ms	22.9	23.4	51.0

QTc prolongation is attributed to M460

Oncology Drugs with QTc Labeling

Drug	Indication	Mean increase in QTcF (msec)	Patients QTcF > 500 msec %	Cases of Torsades/ sudden death
Xegafri (rociletinib)	NSCLC	36	13	Yes
Caprelsa (vandetinib)	MTC	35	4.3	Yes
Tasigna (nilotinib)	CML	10	<1	Yes
Xalkori (crizotinib)	NSCLC	12	2.1	No
Zykadia (ceritinib)	NSCLC	16	1	No
Tagrisso (osimertinib)	NSCLC	16	0.2	No

NCI-CTCAE: Hyperglycemia

- Grade 1: FG >ULN* to 160 mg/dL
- Grade 2: FG >160 mg/dL to 250 mg/dL
- Grade 3: >250 mg/dL to 500 mg/dL; hospitalization
- Grade 4: >500 mg/dL; life-threatening
- Grade 5: death

ULN= upper limit of normal; *Normal FG=70 to 99 mg/dL; impaired fasting glucose=100 to 125 mg/dL (**Source**: https://www.nlm.nih.gov/medlineplus/ency/article/003482.htm)

Hyperglycemia

- **Incidence:** 58% (Grades 3-4: 34%)
- **Dose modifications:** Interruptions:22%; reductions: 22%; discontinuations: 1%
- **Diabetic ketoacidosis**: 3 patients
- **Hospitalization**: 7%
- **Anti-hyperglycemia medications**: 49%
  - Prior history of hyperglycemia: 16%
  - Use of insulin: 23%
  - Prophylactic metformin: 9%

Hyperglycemia by NAT2 Status

	Rapid %(N=35)	Intermediate %(N=111)	Slow %(N=157)
SMQ Hyperglycemia			
Hyperglycemia	34.3	58.6	67.5
Glucose Values (Laboratory Testing)			
Any post baseline glucose >250 mg/dL (Grade 3)	14.3	27.0	40.1
Any post baseline glucose >500mg/dL (Grade 4)	0	0.9	3.2

Hyperglycemia is attributed to M502

Other Adverse Reactions of Special Interest

Pancreatitis

- Incidence**:** 4%; Grades 3-4: 3%
- Hospitalization: 2%

Pneumonitis/ILD

- Incidence: 3%; Grades 3-4: 1%
- Hospitalization: 1%

Cataracts

- Incidence: 10%
  - Surgical intervention (Grade 3): 83%
- Median time to events: 11.1 mos (range 1.4-16.3)

SUMMARY

Efficacy Summary

- Rociletinib
  - ORR: 30.2 %(25.2, 35.5)
  - DoR: 8.9 months (7.2, 12.9)
- Available Therapy
  - Docetaxel+Ramucirumab
    - ORR: 23% (20, 26); OS↑
  - Nivolumab
    - ORR:19% (15, 24); DoR: 17 mos; OS↑

Safety Summary

- **Common adverse reactions:** Hyperglycemia (58%), diarrhea (55%), nausea (52%), QT prolongation (33%), vomiting (30%)
- **Grade ≥3%**
  - Hyperglycemia (34%)
  - QT prolongation (11%)
  - Cataracts (9%)
- **Other SAEs**: pancreatitis, ventricular tachyarrhythmias (including 1 case of Torsades de pointes), 2 sudden deaths
- **Treatment interruptions/dose reductions** (65%)
  - Discontinuation d/t AEs: 21%

Major Issues/Uncertainties

Efficacy

- Rociletinib is active but may not be better than available therapy

Safety

- Serious and life-threatening adverse reactions; true incidence unknown (single-arm study)
- Variable exposure to toxic metabolites (NAT2)

Dose

- Applicant's proposed 625 mg dose not supported
- High rate of dose modifications
- Limited data at doses <500 mg

Questions to the ODAC

- **DISCUSS**: Whether the benefit-risk profile of rociletinib is favorable in the proposed population.

- **VOTE**: Should the results of the randomized clinical trial (TIGER-3) be submitted before FDA makes a regulatory decision on this application?

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FDA BACK-UP SLIDES SHOWN

Exposure-Efficacy Relationship of Rociletinib between AUCss and ORR (INV)