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CK-101 (RX518), a Third Generation Mutant-Selective Inhibitor of EGFR in NSCLC: Results of an Ongoing Phase I/II Trial

Melissa Johnson[1], Janet Karlix[1], Howard A. Burris III[1], Suzanne F. Jones[1], Dean Harris[2], Kenneth O'Byrne[3], Virote Sriuranpong[4], Chaiyut Charoentum[5], Naiyarat Prasongsook[6], Wittawat Jitpewngam[7], Kosin Wirasorn[8], Judy Sing-Zan Wang[9], Saiama N. Waqar[10], James Oliviero[11], Leonid Gorelik[11], Xiangping Qian[12]

[1]Sarah Cannon Research Institute, Nashville, TN; [2]Canterbury District Health Board, Christchurch/New Zealand; [3]Princess Alexandra Hospital, Brisbane, QLD/Australia; [4]King Chulalongkorn Memorial Hospital, Bangkok, Thailand; [5]Chiang Mai University, Chiang Mai, Thailand; [6]Phramongkutklao Hospital, Bangkok, Thailand; [7]Naresuan University Hospital, Phitsanulok, Thailand; [8]Khon Kaen University, Khon Kaen, Thailand; [9]Florida Cancer Specialists/SCRI; [10]Washington University School of Medicine; [11]Checkpoint Therapeutics, Inc., New York, NY; [12]NeuPharma, Inc., Foster City, CA.

- **Research—all compensation to institution**

BerGenBio
Lilly
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Mirati Therapeutics
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CK-101 (RX518)

Novel, oral, third-generation, irreversible tyrosine kinase inhibitor targeting mutant EGFR

Inhibition of Cancer Cell Proliferation (IC_{50}, nM)[1]

Cell Line	EGFR Mutation	CK-101	osimertinib	afatinib
NCI-H1975	L858R/T790M	5	2	23
HCC827	Exon 19 del	10	3	1
A431	WT	689	280	34

- Selectively inhibits both EGFR-TKI-sensitizing mutations and T790M resistance mutation
- Minimal activity on wild-type EGFR
  - *In vitro*, CK-101 was over 100-fold less potent against wild-type EGFR than against L858R/T790M double mutation

[1] Qian et al. AACR 2017, abstract #2078

Ongoing First-In-Human Study

- **Key inclusion criteria:**
  - Measurable disease at baseline
  - ECOG performance status of 0 to 1
  - Dose escalation: Any solid tumor where targeted EGFR deemed reasonable.
  - Dose expansion: Metastatic or unresectable locally advanced NSCLC:
    - TKI Naïve: EGFRm+ without prior exposure to TKI therapy. No limit on number of prior lines of systemic therapy (i.e., chemo, radiation); or
    - TKI Failure: T790M+ with disease progression on previous 1st or 2nd generation EGFR-TKI therapy. No limit on number of prior lines of systemic therapy (i.e., TKIs, chemo, radiation).
- **Key exclusion criteria:**
  - Prior history of ILD or clinically-important cardiac abnormalities
  - Brain metastasis, unless asymptomatic, stable and not requiring steroids

Baseline Characteristics: Dose Escalation

Dose Escalation: US Enrollment		N=18
Age, years	Median (range)	56 (30-81)
Gender	Male/Female, n (%)	11/7 (61/39)
Race	Asian/Non-Asian, n (%)	2/16 (11/89)
ECOG Performance Status	0/1, n (%)	4/14 (22/78)
Enrolled Tumor Types, n (%)	• Colon	5 (28)
	• NSCLC-EGFR WT	3 (17)
	• NSCLC-EGFRm+	2 (11)
	• Sarcoma	2 (11)
	• Bladder	1 (6)
	• Breast	1 (6)
	• Glioblastoma	1 (6)
	• HNSCC	1 (6)
	• Pancreatic	1 (6)
	• Uterine	1 (6)
Lines of Prior Therapies	Median (range)	4 (0-15)

Baseline Characteristics: EGFRm+ Dose Expansion

Dose Expansion (AUS, NZ, THAI enrollment)		N=19
Age, years	Median (range)	60 (29-75)
Gender	Male/Female, n (%)	8/11 (42/58)
Race	Asian/Non-Asian, n (%)	17/2 (89/11)
ECOG Performance Status	0/1, n (%)	2/17 (11/89)
Activating Mutations	Ex19del/L858R/other, n (%)	15/3/1 (79/16/5)
TKI Naïve Subset	n (%)	10 (53)
	1L/2L, n	8/2
TKI Failure (T790M+) Subset	n (%)	9 (47)
	2L/≥3L, n	5/4
Prior EGFR-TKIs[1]	• erlotinib, n (%) • gefitinib, n (%) • erlotinib & afatinib, n (%)	5 (56) 3 (33) 1 (11)
CNS Metastases at Baseline	n (%)	5 (26)

[1] Patients may have had multiple other previous systemic therapies (i.e, chemotherapy, radiation) in addition to TKI therap(ies).

Dosing Cohorts

Group	CK-101 Dosing Cohort						Total N
	100 mg QD	200 mg QD	400 mg QD	800 mg QD	1200 mg QD	400 mg BID	
All patients	**2**	**1**	**1**	**2**	**1**	**30**	**37**
Dose Escalation	**2**	**1**	**1**	**2**	**1**	**11**	**18**
Dose Expansion						**19**	**19**
• TKI Naïve[1] (EGFRm+ NSCLC)						10	10
• TKI Failure[2] (T790M+ NSCLC)						9	9

[1] TKI Naïve = No prior EGFR TKI therapy. Patients may have had multiple previous systemic therapies.

[2] TKI Failure = Progression on 1st or 2nd gen TKI (i.e., erlotinib, gefitinib, afatinib). No prior 3rd gen TKI allowed. Patients may have had multiple previous systemic therapies.

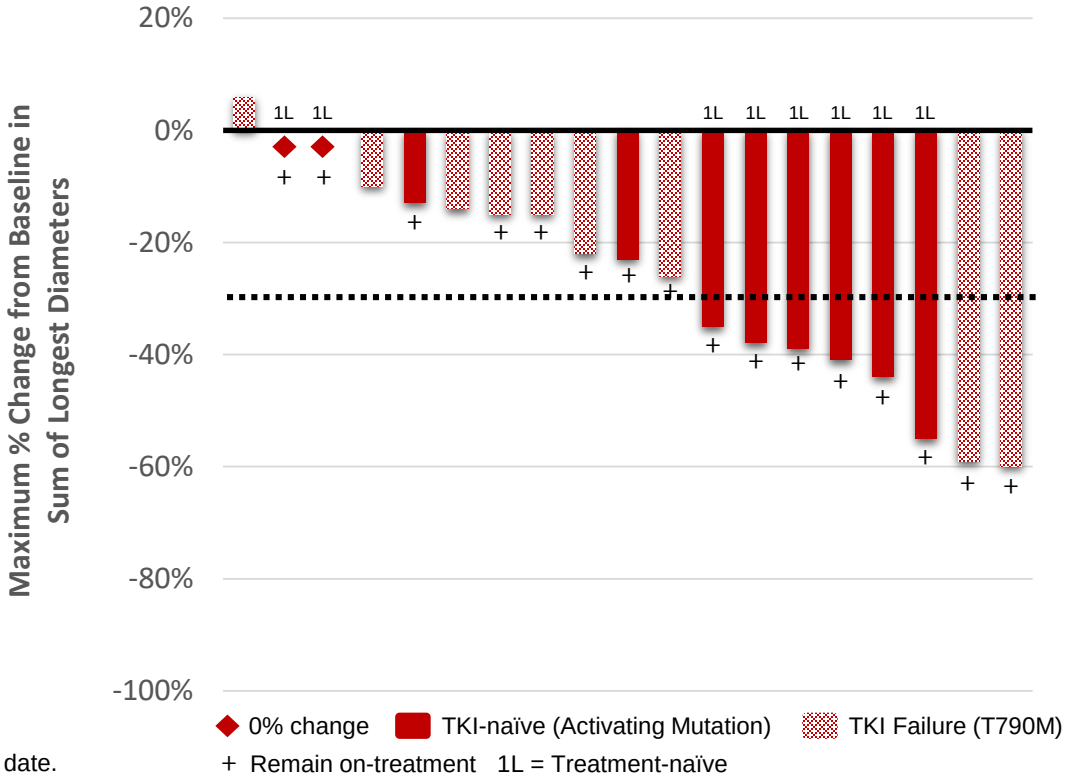
CK-101 Safety Summary

- Most adverse events were Grade 1-2
- No DLTs or treatment-related SAEs
  - MTD has not been defined
- No discontinuations due to a treatment-related AE
- **No events of:**
  - Interstitial lung disease (ILD) or pneumonitis
  - QTc prolongation or cardiomyopathy
  - Nail toxicities
  - Stomatitis
  - Hyperglycemia

Most Common (≥3 pts) Treatment-Related Adverse Events, n (%)	All Patients Treated (N=37)		
	All Grades	Grade 3	Grade 4
Nausea	6 (16)	-	-
Diarrhea	5 (14)	1 (3)	-
Lacrimation increased	5 (14)	-	-
Vomiting	4 (11)	-	-
ALT increased	3 (8)	1 (3)	-
AST increased	3 (8)	1 (3)	-
Bilirubin increased	3 (8)	2 (5)	-
Dysphonia	3 (8)	-	-
Hypoaesthesia	3 (8)	-	-
Pruritus	3 (8)	1 (3)	-
Rash	3 (8)	2 (5)	-

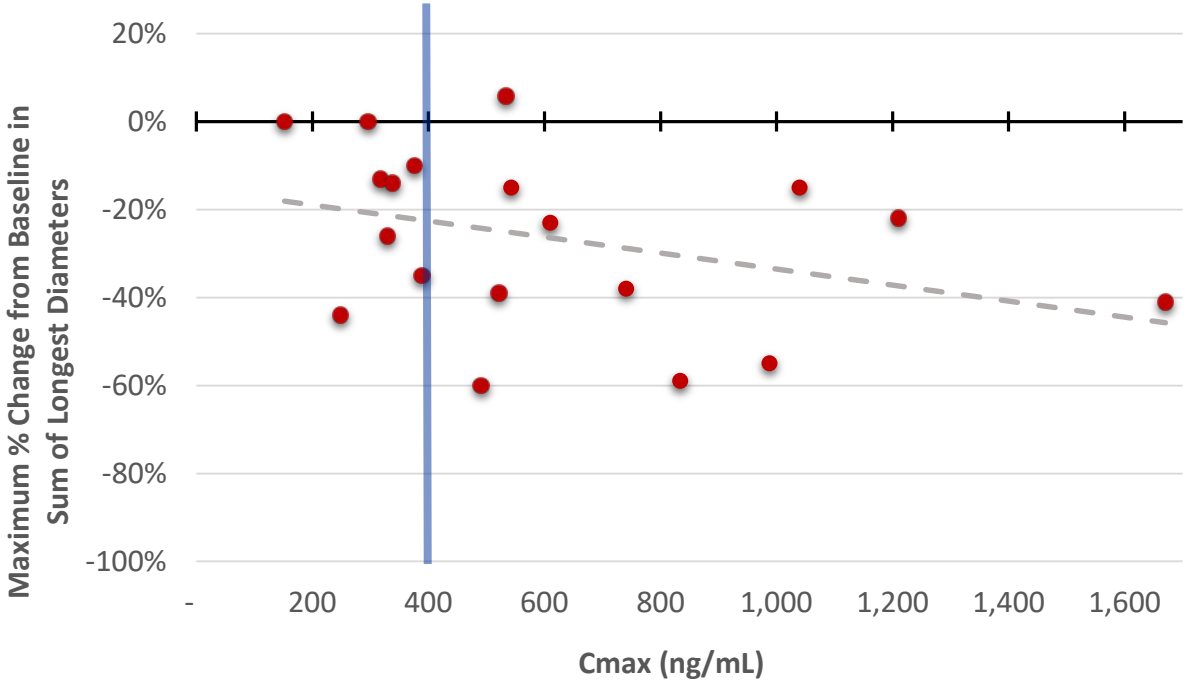
Preliminary Responses of CK-101
EGFR Mutant NSCLC Expansion Cohort: 400mg BID

- 42% ORR (8/19 pts)[1]
  - 75% ORR (6/8 pts) in treatment-naïve pts
- 84% (16/19) pts had target lesion reductions versus baseline
- 3/5 patients with baseline brain metastasis had intracranial disease response
- Median DoR and PFS were not reached



[1] Includes 7 confirmed PRs, 1 pending.
Does not include additional PR (T790M pt) achieved post-data cutoff date.

Preliminary PK Suggest Response Correlates with Higher Drug Peak Concentrations



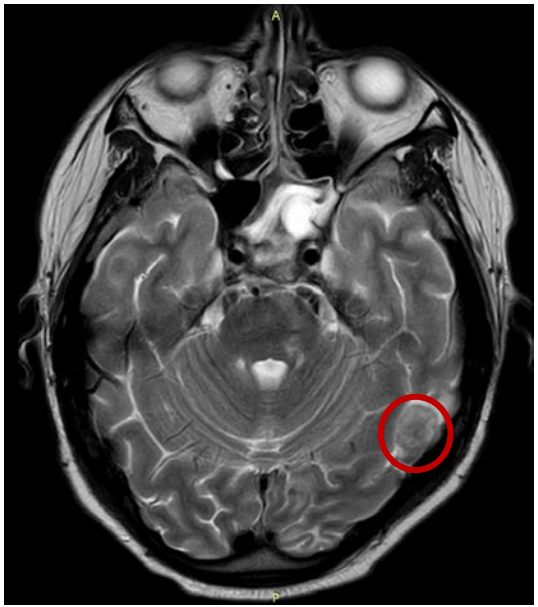
CNS Activity

3/5 patients with baseline brain metastasis had intracranial disease response

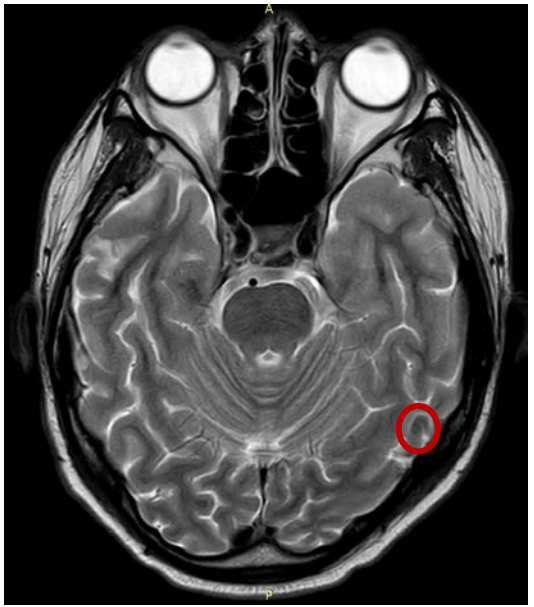
29M, EGFR Ex19del NSCLC, Asian, never smoker

- Dec 2017: Metastatic disease
  - Lung, brain, bone, lymph nodes
- No prior systemic therapies
- Jan 2018: CNS radiation therapy
- Feb 2018: Started CK-101
- Mar 2018: Partial response @ C2
  - Systemic and CNS response ongoing through C9

Baseline
18x15 mm



Cycle 9
9x6 mm



Conclusions

- CK-101 was well-tolerated across multiple dose groups
  - Maximum-tolerated dose not defined (no DLTs or treatment-related SAEs to date)
- CK-101 demonstrates preliminary activity in EGFR mutation-positive NSCLC
  - ORR of 75% (6 of 8) in treatment-naïve patients
- Soft gel capsule dosage form has been introduced to replace hard shell capsule; study ongoing to determine optimal dose, targeting higher serum concentrations
- Phase 3 trial in treatment-naïve EGFRm+ NSCLC planned for 2019

We thank the patients, their families and caregivers, and participating clinical sites

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- Gallipoli Medical Research Foundation

New Zealand
- Auckland Clinical Studies
- Canterbury Regional Cancer & Hematology Service
- Wellington Blood and Cancer Centre

Thailand
- King Chulalongkorn Memorial Hospital
- Maharaj Nakorn Chiang Mai Hospital
- Naresuan University Hospital
- Phramongkutklao Hospital
- Siriraj Hospital
- Srinagarind Hospital

United States
- Tennessee Oncology/Sarah Cannon
- Florida Cancer Specialists/Sarah Cannon
- Hackensack UMC
- University of Oklahoma/Sarah Cannon
- Washington University