Novel EGFR TKI Theliatinib: An Open Label, Dose Escalation Phase I Clinical Trial

2014-309-00CH1

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EGFR: highly active in multiple tumor types

Tumor Types	Wild-type: Gene Amplification	Wild-type: Over Expression	Mutations
NSCLC	29%	62%	*15-40% (EGFR TKIs)*
Esophagus	8-30%	30-90%	12% (esophageal adenocarcinoma)
Stomach	29%	44-52%	<5%
Glioblastoma	36-51%	54-66%	27-54% (EGFR variant III)
Colorectal	4.5%	*53% (mAbs)*	8%
Head and neck	10-30%	*66-84% (mAbs)*	42% (EGFR variant III)

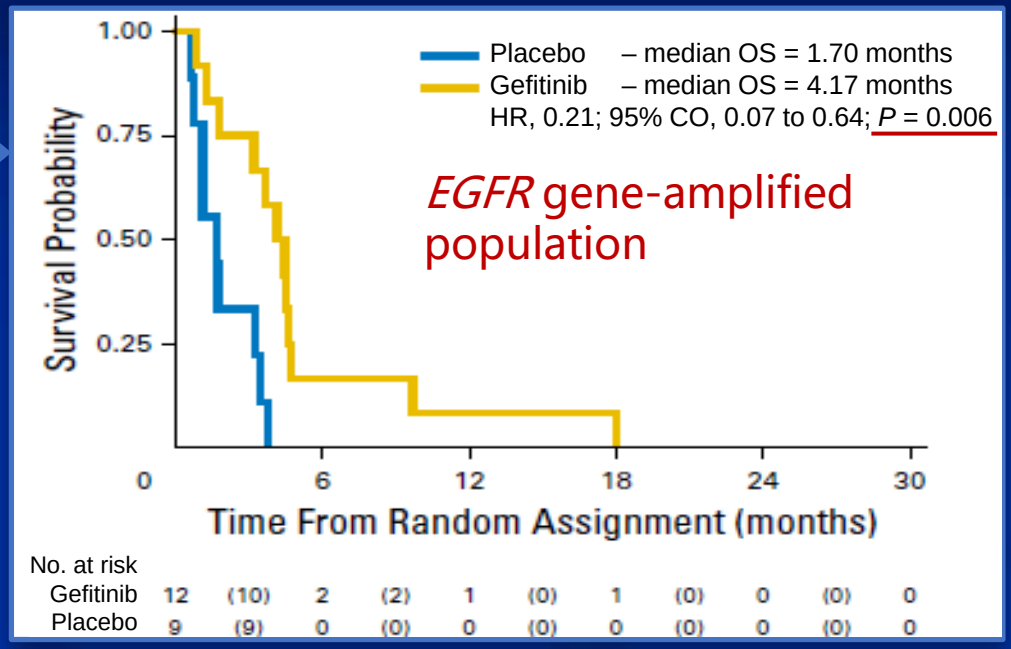
- EGFR inhibitors have had success in the treatment of EGFR-mutant lung cancer
- However, there are multiple tumor types harboring EGFR gene amplification and over-expression; those using EGFR as a target are still at the exploratory stage

[ref]: Chen W et al, CA Cancer J Clin 2016;66:115-132.

Example: Is EGFR a feasible target in esophageal cancer (EC)?

Subgroup Analysis	Treatment	Overall Survival (OS)
EGFR gene-amplified (21, 7.2%)	gefitinib	HR=0.21, p=0.006
	placebo	
EGFR FISH+ (59, 20.2%)	gefitinib	HR=0.59, p=0.05
	placebo	
EGFR FISH– (233, 79.8%)	gefitinib	HR=0.90, p=0.46
	placebo	

Petty RD *etc.*, J Clin Oncol. 2017; 35(20):2279-2287



- **In EGFR gene-amplified and EGFR FISH+ patients, gefitinib group OS was significantly increased, particularly in gene-amplified patients**
- **However, <10% of patients are EGFR gene-amplified; consider exploring other screening methods? E.g. high EGFR protein expression**

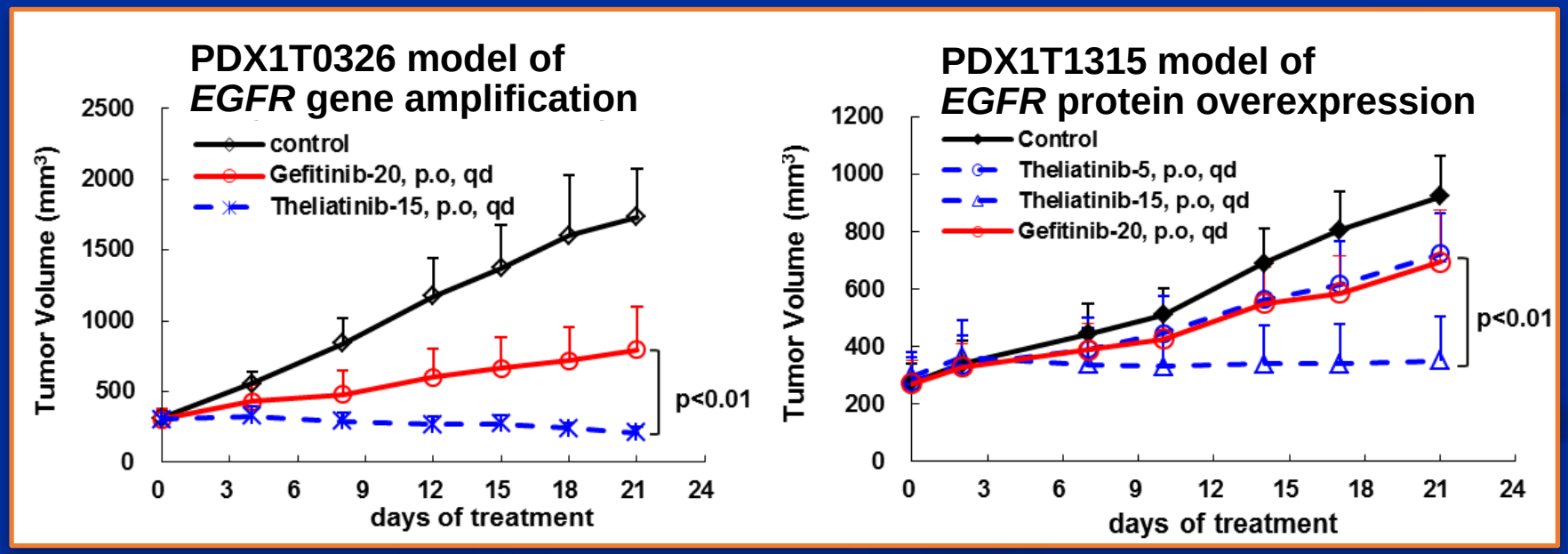
Identifying the benefiting population, and finding a more potent EGFR TKI, will be keys to clinical trial success

Theliatinib: a novel, potent EGFR-TKI

- **EGFR kinase affinity:**

Inhibition activity to wild-type EGFR	Ki (nM)
Theliatinib	0.05
Gefitinib	0.35
Erlotinib	0.38

- **Esophageal cancer PDX model anti-tumor activity: good activity on *EGFR* gene-amplification and over-expression models**



Ren Y et al, Oncotarget. 2017; 8(31):50832-50844.

Phase I Study Design

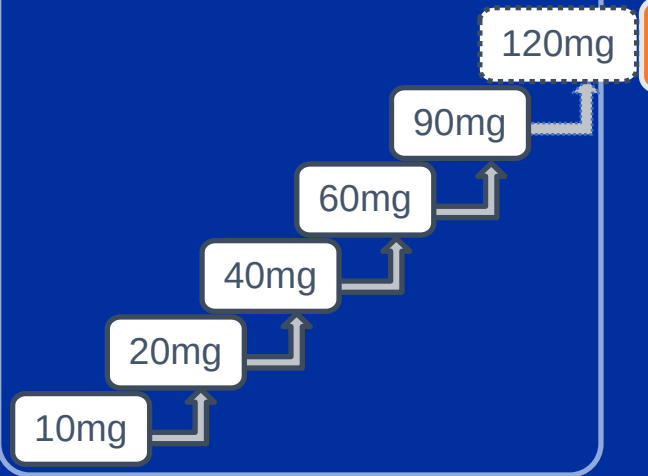
2010-309-00CH1 (Terminated)

10-90mg continuous dosing

Safety good, tolerated

No DLT

MTD not determined



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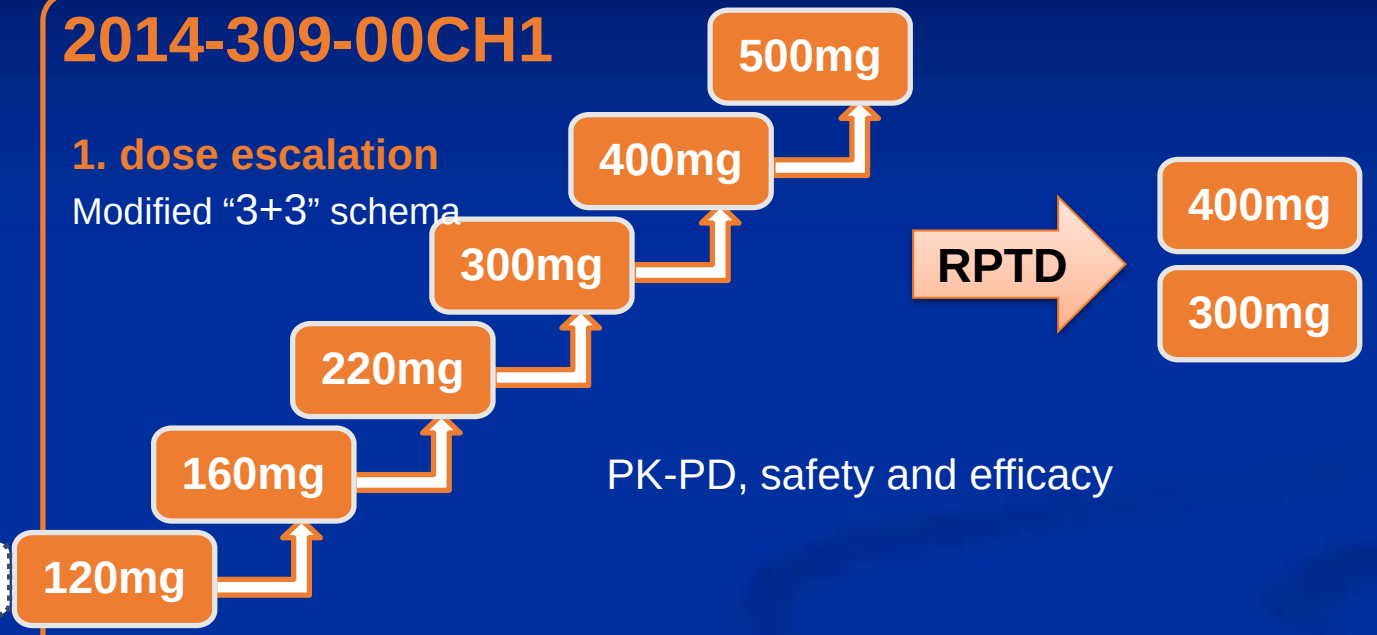


1. dose escalation

Modified "3+3" schema

PK-PD, safety and efficacy

2. dose expansion

Target population: EGFR+ esophageal cancer (EC)

Sample size: Simon Optimal two-stage design

P0: ORR ≤ 8%

P1: ORR ≥ 25%

2014-309-00CH1 Study Objectives

Primary endpoint		• Determine theliatinib tolerability and safety in advanced solid tumor patients, MTD and/or RPTD for Phase II
Secondary endpoint	Dose escalation	• Evaluate theliatinib single dose and continuous dosing PK/PD profile in humans • Evaluate theliatinib metabolites' profiles
	Dose expansion	• Evaluate theliatinib primary anti-tumor activity, safety and PK in EC patients with EGFR protein-overexpression or gene-amplification positive
Exploratory		• Explore EGFR pathway relevant proteins' expression/gene mutation, and their relevance to tumor response, safety and possible drug resistance mechanism • Explore dose exposure-efficacy relationship

Main inclusion/exclusion criteria

Inclusion Criteria

Dose escalation:

- PS: 0-2
- Metastatic solid tumors
- Failed standard treatments
- >300mg/day cohort must have EGFR positive* esophageal cancer (EC), head & neck cancer or NSCLC

Dose expansion:

- PS: 0-1
- EGFR+ EC patient, confirmed by central lab
- ≤2 systemic chemotherapy
- ≤1 concurrent radiotherapy and chemotherapy
- Measurable target lesions

Exclusion Criteria

- Obvious abnormality in routine blood, liver and kidney, blood coagulation function
- Poor blood pressure control
- Before theliatinib first administration:
  - systemic anti-tumor treatment, radiotherapy, chemotherapy, immunology, biological or hormone therapy, or clinical trials drug therapy in the past 3 weeks;
  - Chinese medicine anti-tumor treatment in the prior week;
  - TKI treatment in the prior week:
- Previous treatment with EGFR antibodies or EGFR-TKI (not applicable to dose escalation)
- Toxicity from previous treatment not recovered; inability to take medication orally, dysphagia; CNS metastatic disease; Uncontrolled active infections

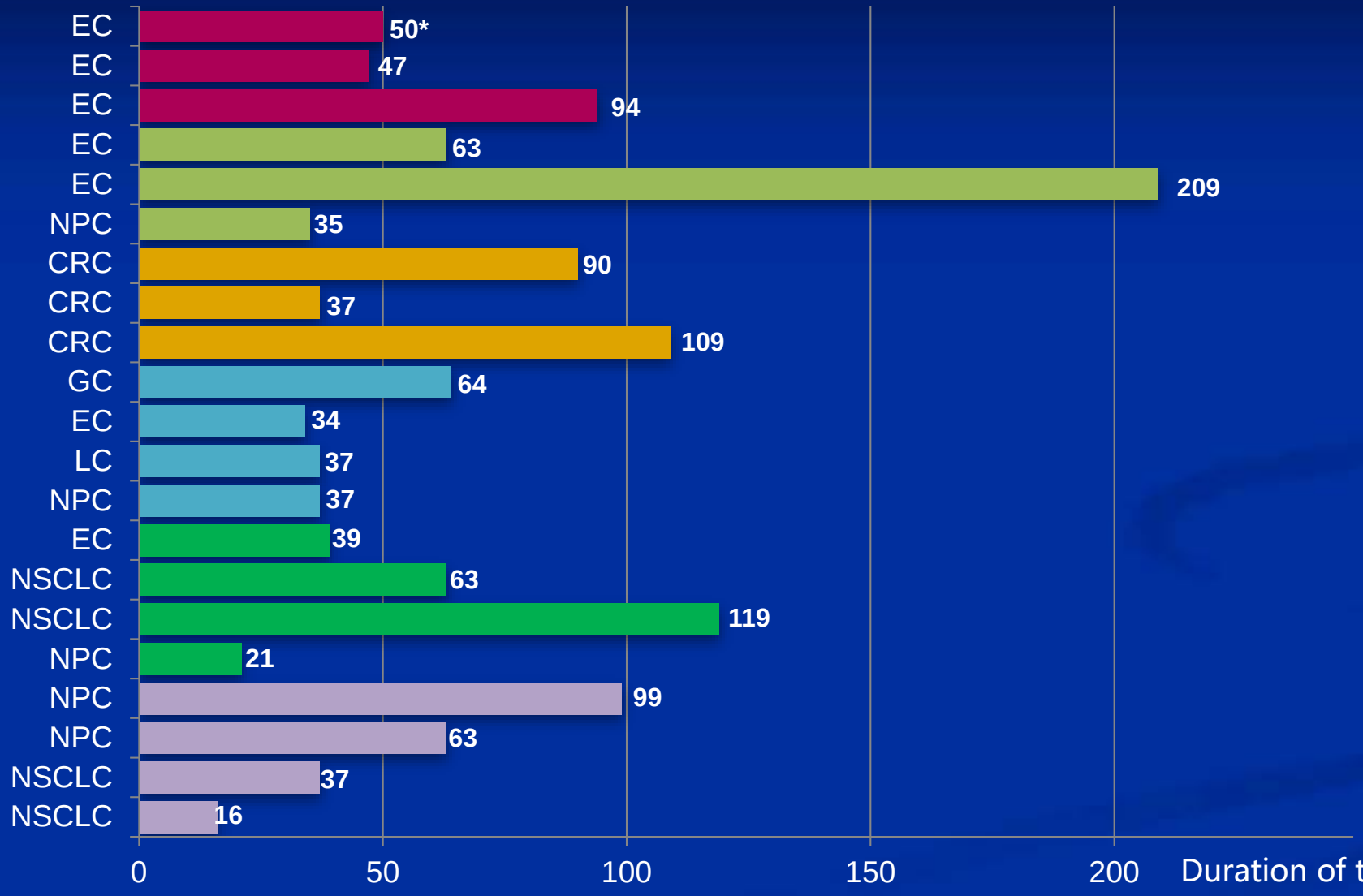
* IHC EGFR H-score≥250 或 ≥75% Tumor Cell 3+

Patient baseline

		Patients N=21 (%)
Age: median (range)		57 (28-64)
Gender	Male	15 (71.43)
	Female	6 (28.57)
ECOG rating	0	5 (23.81)
	1	16 (76.19)
	2	0 (0)
Tumor type	EC	7 (33.33)
	NSCLC	5 (23.81)
	NPC	5 (23.81)
	CRC	3 (14.29)
	GC	1 (4.76)

		Patients N=21 (%)
Pathology type	adenocarcinoma	8 (38.10)
	squamous carcinoma	7 (33.33)
	Others	4 (19.05)
	Not clear	2 (9.52)
Previous treatment	<3	7 (33.33)
	≥3	14 (66.67)
Smoking history	No smoking	10 (47.62)
	Current smoking	8 (38.10)
	Previous smoking	3 (14.29)

Duration of treatment



Dose	N
120mg	4
160mg	4
220mg	4
300mg	3
400mg	3
500mg	3

*1 EC patient is on treatment

Related AEs by dose cohort (incidence ≥10%)

AEPT	120mg N=4 n(%)	160mg N=4 n(%)	220mg N=4 n(%)	300mg N=3 n(%)	400mg N=3 n(%)	500mg N=3 n(%)	Total N=21 n(%)
Rash	2 (50.0)	2 (50.0)	2 (50.0)	2 (66.7)	3 (100.0)	1 (33.3)	12 (57.1)
Diarrhea	1 (25.0)	2 (50.0)	3 (75.0)	2 (66.7)	2 (66.7)	0	10 (47.6)
Hemoglobin decrease	0	0	2 (50.0)	3 (100.0)	1 (33.3)	3 (100.0)	9 (42.9)
Nausea	0	1 (25.0)	2 (50.0)	1 (33.3)	1 (33.3)	2 (66.7)	7 (33.3)
WBC decrease	0	1 (25.0)	1 (25.0)	2 (66.7)	0	2 (66.7)	6 (28.6)
Weight lose	0	1 (25.0)	0	1 (33.3)	2 (66.7)	1 (33.3)	5 (23.8)
Palmar-plantar erythrodysesthesia	0	1 (25.0)	0	2 (66.7)	1 (33.3)	0	4 (19.0)
Platelet decrease	0	1 (25.0)	0	0	1 (33.3)	1 (33.3)	3 (14.3)
Mouth ulcer	0	0	2 (50.0)	0	0	1 (33.3)	3 (14.3)
Vomit	1 (25.0)	0	0	0	0	1 (33.3)	2 (9.5)
Dry skin	1 (25.0)	0	0	1 (33.3)	0	0	2 (9.5)
AST increase	1 (25.0)	0	0	1 (33.3)	0	0	2 (9.5)
Rash	0	0	0	0	2 (66.7)	0	2 (9.5)
Diarrhea	0	0	0	1 (33.3)	0	1 (33.3)	2 (9.5)
Hemoglobin decrease	0	0	0	2 (66.7)	0	0	2 (9.5)
Nausea	1 (25.0)	0	0	1 (33.3)	0	0	2 (9.5)
WBC decrease	0	0	1 (25.0)	0	0	1 (33.3)	2 (9.5)

AEs ≥ G3 and SAEs

AEs≥G3

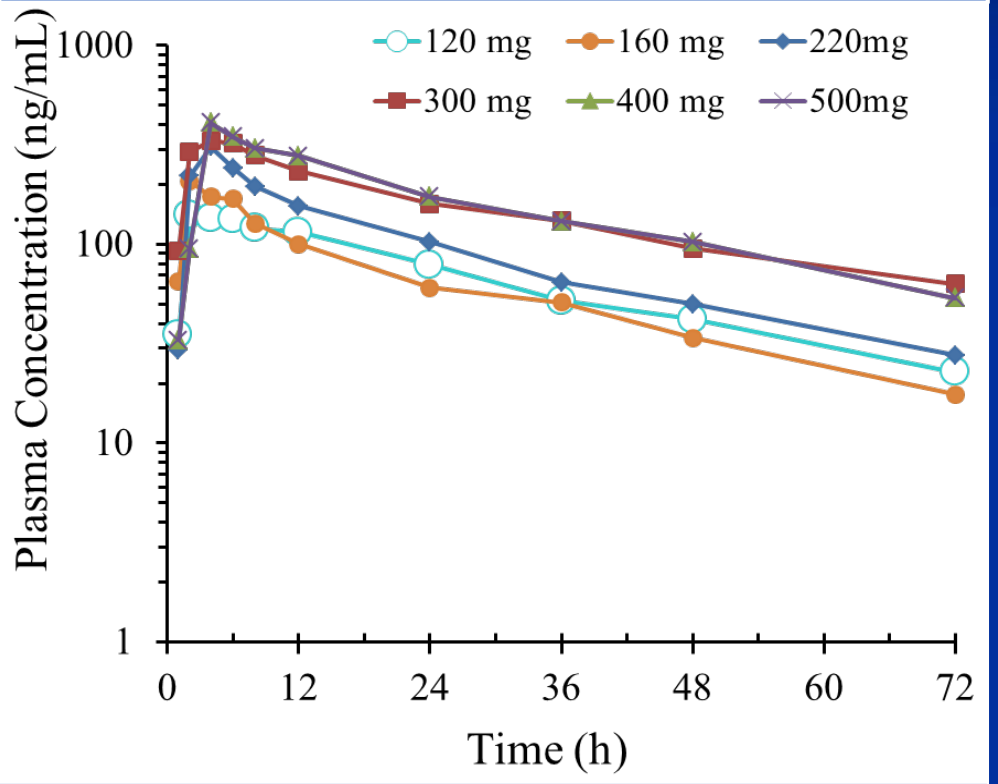
AEPT	CTC Grade 3/4/5	120mg N=4 n(%)	160mg N=4 n(%)	220mg N=4 n(%)	300mg N=3 n(%)	400mg N=3 n(%)	500mg N=3 n(%)	Sum N=21 n(%)
Gastrointestinal bleed	CTC G3	0	0	0	0	1 (33.3)	0	1 (4.8)
WBC decrease	CTC G3	0	0	0	0	0	1 (33.3)	1 (4.8)
Hemoglobin decrease	CTC G4	0	0	0	0	0	1 (33.3)	1 (4.8)
Platelet decrease	CTC G4	0	0	0	0	0	1 (33.3)	1 (4.8)

SAEs

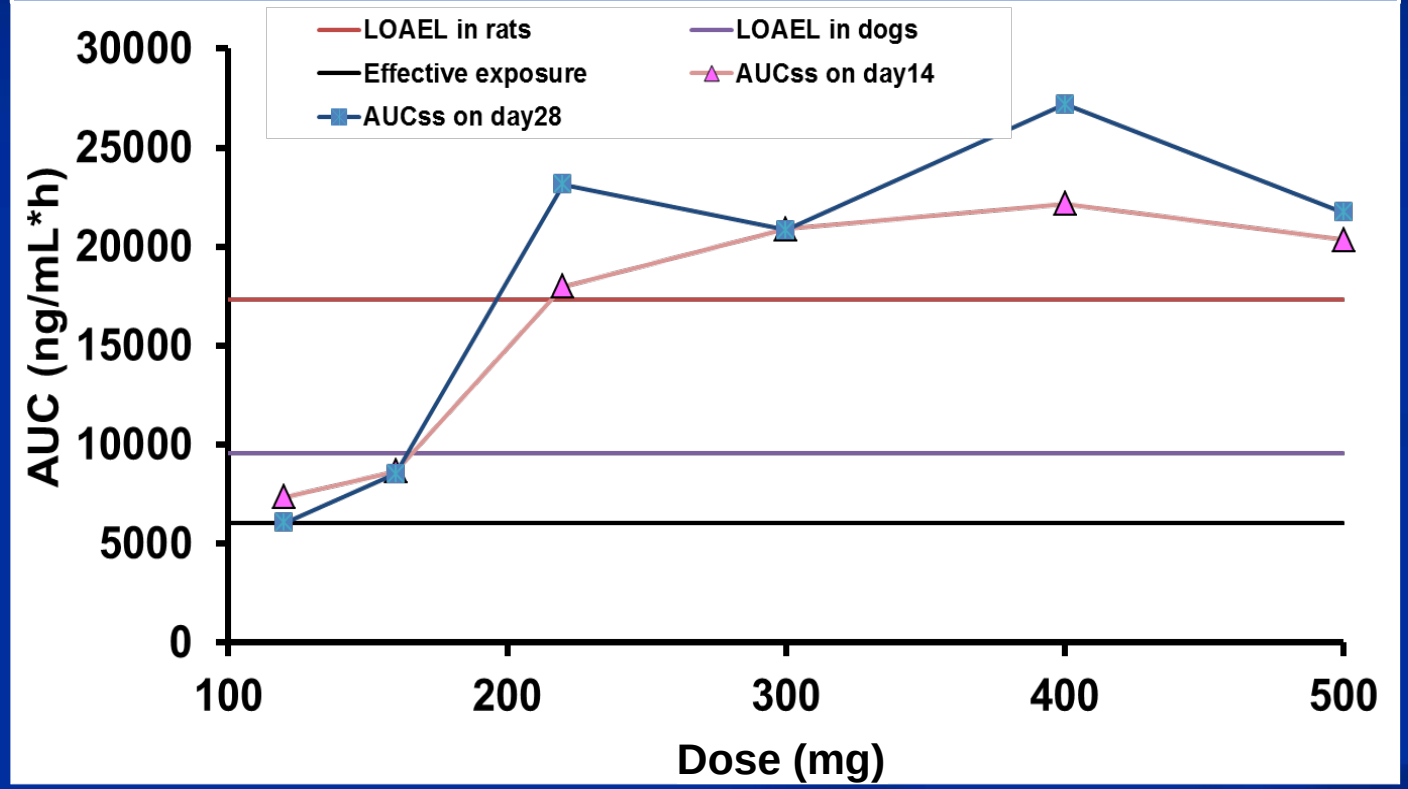
Pt	Dose	First dose	SAE	Onset date	End date	Severity	Dose adjustment	causality	outcome
2008	400	2016/09/23	GI bleed	2016/12/03	2016/12/16	Severe / CTC G3	Drug suspension	Unlikely related	Recovered
2010	500	2017/02/07	Fever	2017/01/29	2017/02/02	Mild / CTC G1	Not	Not related	Recovered
2011	500	2017/02/23	Platelet decrease	2017/04/11	2017/05/25	Life-threatening or disability / CTC G4	Discontinuous	Possibly related	Recovered

Pharmacokinetics

PK profiles from 120mg to 500mg



Dose-AUC_{ss} relationship (steady state)



- Single dosing: theliatinib exposure increased as dose increased
- After 300mg, steady-state plasma drug concentration did not increase significantly as dose increased

Efficacy by dose cohort

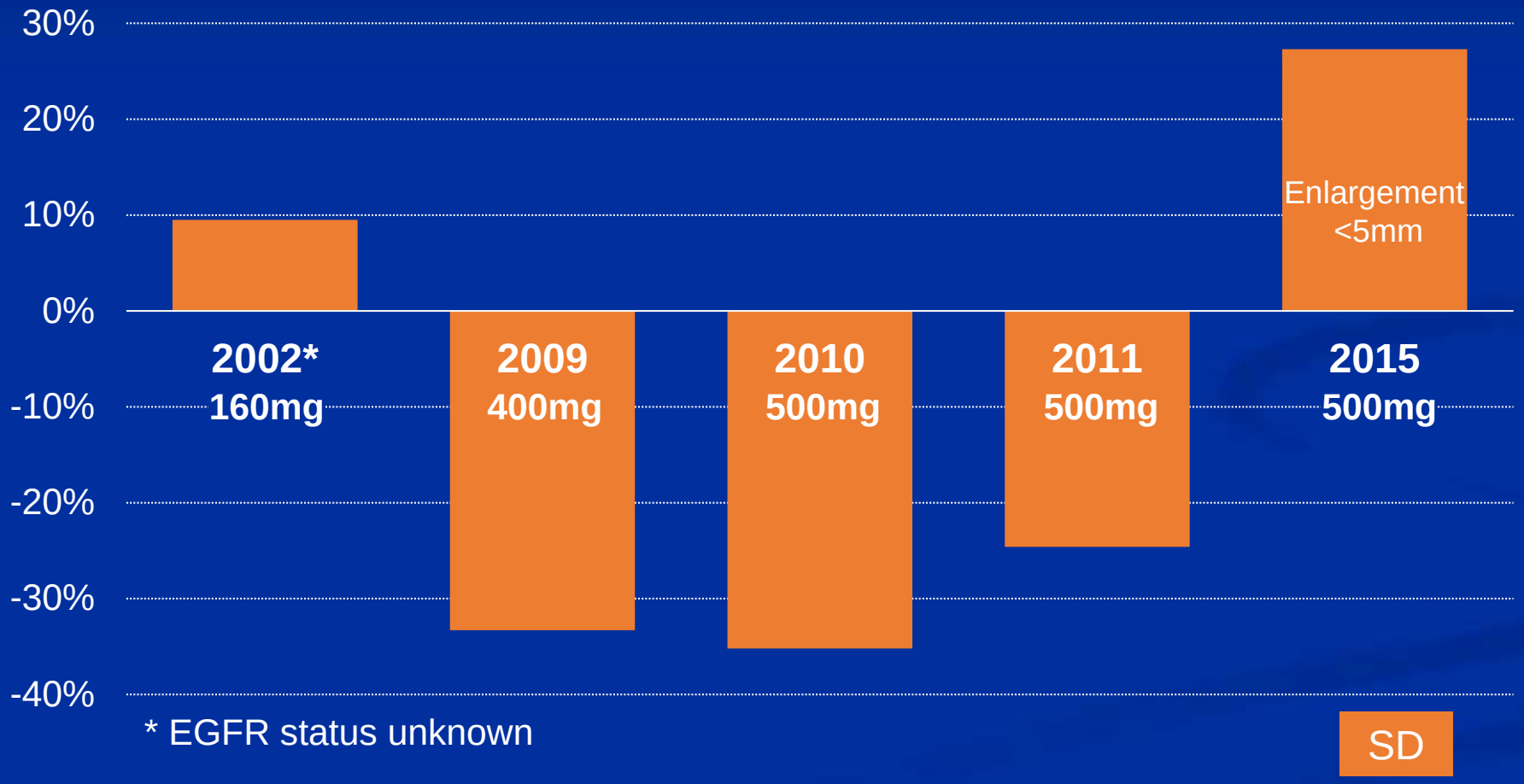
Dose cohort	Subject No.	Tumor type	Best response	
120 mg	1001	NSCLC	NA	
	1002	NSCLC	PD	(PD @ C2D1)
	1003	NPC	PD	(PD @ C3D1)
	1004	NPC	SD	(PD @ C4D1)
160 mg	1006	NPC	PD	(PD @ C1D14)
	1008	NSCLC	SD	(PD @ C5D1)
	1010	NSCLC	PD	(PD @ C3D1)
	2002	EC	NE	(withdraw @ C2D1)
220 mg	1012	NPC	PD	(PD @ C2D1)
	1013	LC	PD	(PD @ C2D1)
	2003	EC	NA	
	2004	GC	PD	(PD @ C3D1)

Dose cohort	Subject No.	Tumor type	Best response	
300 mg	2005	CRC	SD	(PD @ C4)
	2006	CRC	PD	(PD @ C2D1)
	2007	CRC	SD	(PD @ C4D1)
400 mg	1014	NPC	PD	(PD @ C2D1)
	2008	EC	SD	(PD @ C8D1)
	2009	EC	SD	(Withdraw @ C3; PD @ EOT)
500 mg	2010	EC	SD	(PD @ C4D1)
	2011	EC	PD	(PD @ C2D15)
	2015	EC	SD	(ONGOING @ C2)

Note: NPC: Nasopharyngeal carcinoma; EC: esophageal cancer; LC: lung cancer; GC: gastric cancer; CRC: colorectal cancer

Efficacy in esophageal cancer patients – dose escalation phase

Best response of target lesions

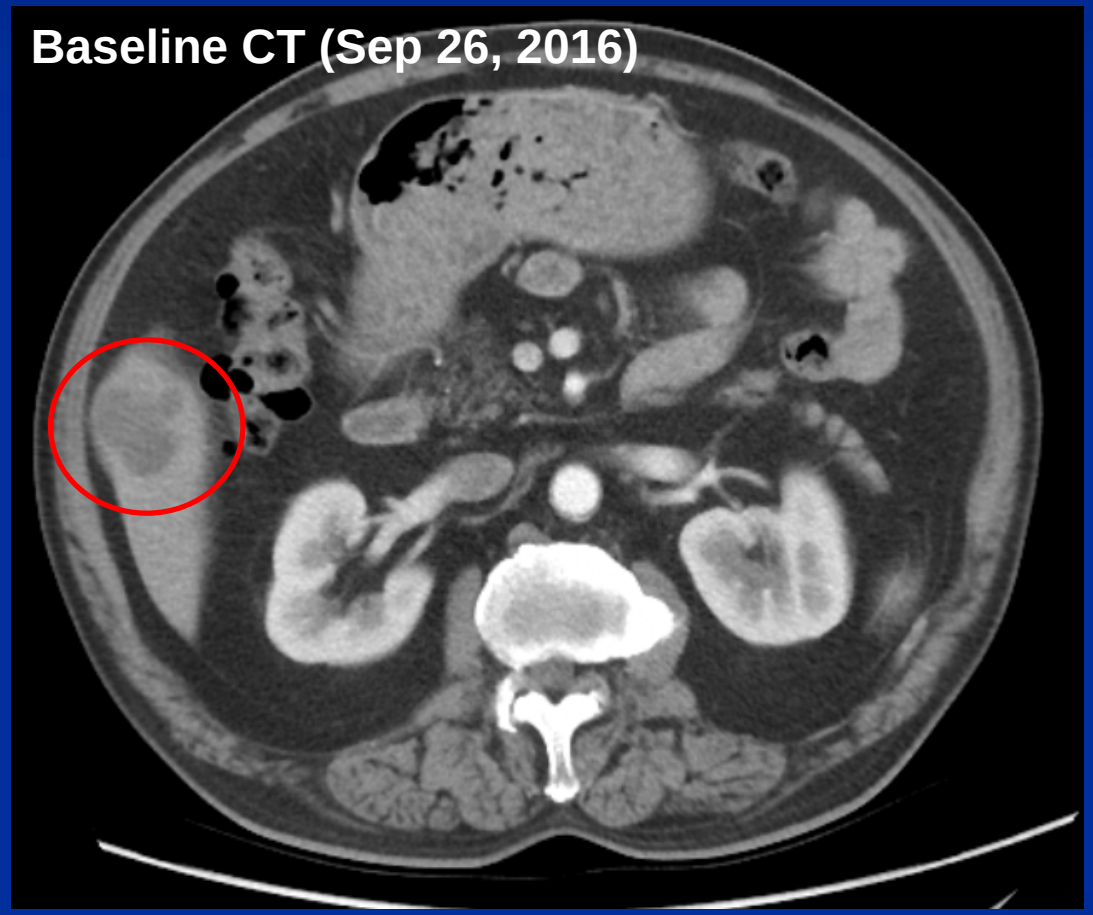


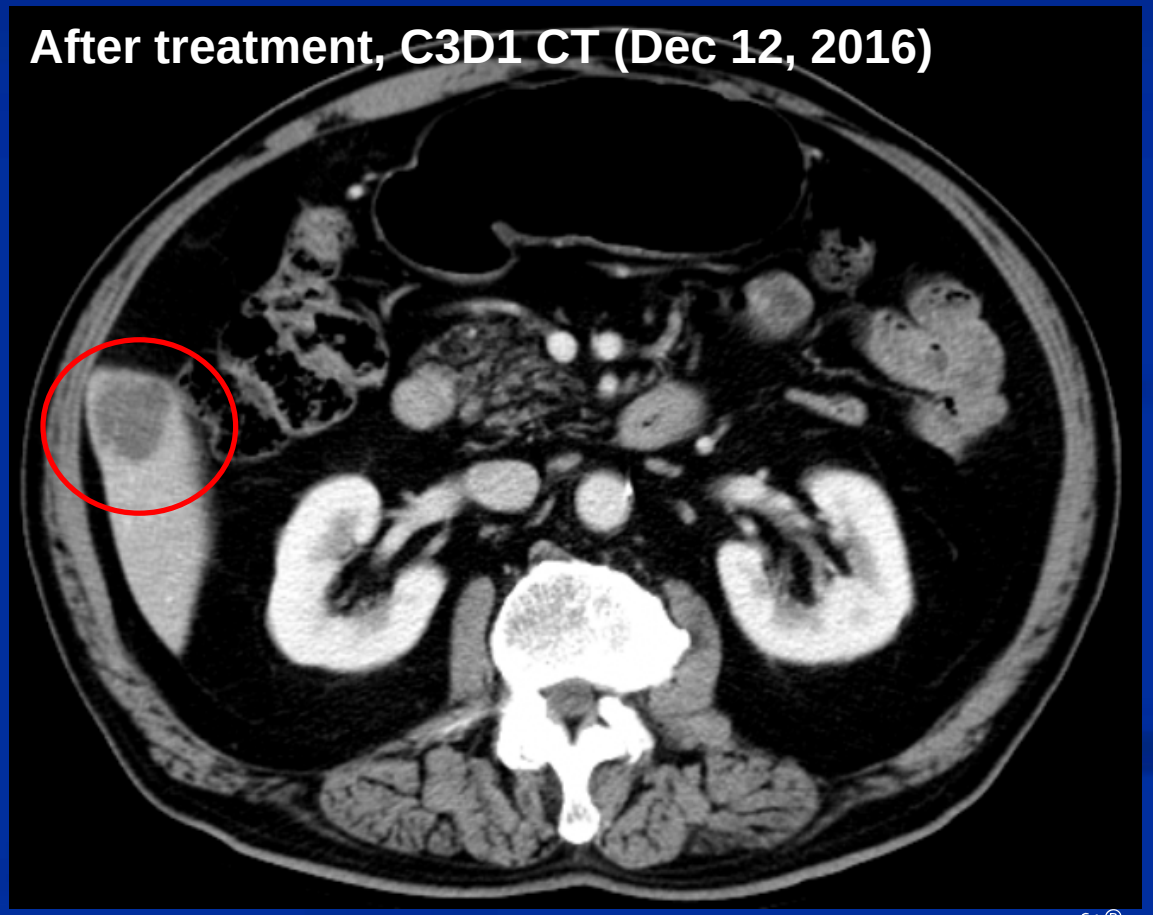
* EGFR status unknown

- 7 EC patients enrolled
- 5 have measurable disease and at least one post treatment tumor assessment
  - 1 withdrawal
  - 1 no measurable disease
  - 1 (#2015) is on treatment, SD on C1

Patient profile (#2009): After 2 weeks' treatment, target lesion (liver metastasis) shrank from 36mm to 23mm diameter

Male, 62, EGFR+ ESCC Stage IV (cT3N0M1); 400mg/d theliatinib treatment





Conclusions

- Theliatinib 120mg~500mg QD single drug, continuous dosing, good safety and well-tolerated, no DLT, MTD not determined
- PK: Drug exposure increased with dose increasing 300 mg and above dose can effectively reach plasma concentration that inhibits EGFR phosphorylation
- Efficacy: 18 evaluable patients:
  SD 8 cases (44.4%)
  PD 10 cases (55.6%)
  12-week DCR 44.4%
- Plan to further explore efficacy and safety of theliatinib at 400mg dose on EGFR highly active esophageal cancer patients

Acknowledgements

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Thank you for your hard work!

Clinical sites	Investigators
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San Yat-sen University Cancer Center	Li Zhang, Hongyun Zhao, Wenfeng Fang, Yang Zhang

We welcome any interested sites to join our study!

Thank you!