DBPR112

Title	Phase I, Open-Label, Multiple Dose, Dose-Finding and Expansion Clinical Study to assess the Safety, Pharmacokinetics, and Efficacy of DBPR112 in Patients with Head and Neck Cancer and EGFR mutated Lung Cancer
Objectives	To determine the maximum tolerated dose (MTD) and the recommended Phase 2 Dose (RP2D); To characterize the pharmacokinetics (PK) of DBPR112 in Asian patients
PIs	Dr. Chia-Chi Lin (NTUH) and Dr. Her-Shyong Shiah (TMUH)
Number of Subjects	Approximately 24 to 30 patients

- DBPR112 received IND approval from U.S. FDA (on Apr, 08, 2016) and Taiwan FDA (on Aug, 23, 2016).
- Phase I clinical trial will be initiated in June, 2017.

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Cell Lines Growth Inhibitory Profiling

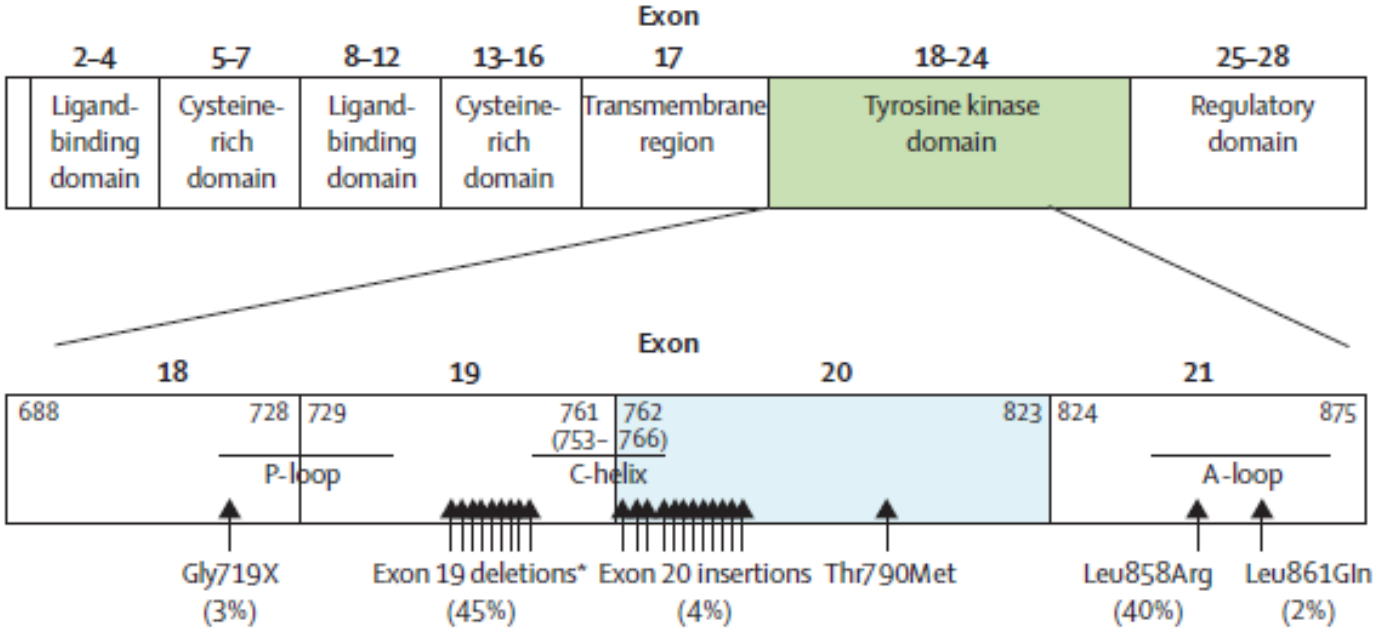
Cell line	Site primary	EGFR status	DBPR112 CC_{50} (nM)	Afatinib CC_{50} (nM)
HCC827	lung	E746_A750 *del*	++++	++++
H3255	lung	L858R	++++	++++
H1975	lung	L858R/T790M	++	++
Ca9-22-Der1	H&N	Wild type	+++	+++
FaDu	H&N	Wild type	+++	+++
HSC3	H&N	Wild type	++	+++
KYSE-270	Esophagus	Wild type	++	++
Cell line	**Site primary**	**HER2 status**	**DBPR112 CC_{50} (nM)**	**Afatinib CC_{50} (nM)**
SK-BR-3	breast	Wild type	++	+++
BT-474	breast	Wild type	++	+++
H1781	lung	HER2 exon20ins	+++	+++

++++	+++	++	+	
CC_{50} < 10 nM	10 nM < CC_{50} < 100 nM	100 nM < CC_{50} < 500 nM	CC_{50} > 500 nM	

- DBPR112 showed significant inhibition of the proliferation of lung, head & neck, breast and esophageal cancer cell lines.

DBPR112 Pre-clinical data

EGFR Mutations in Lung Cancers

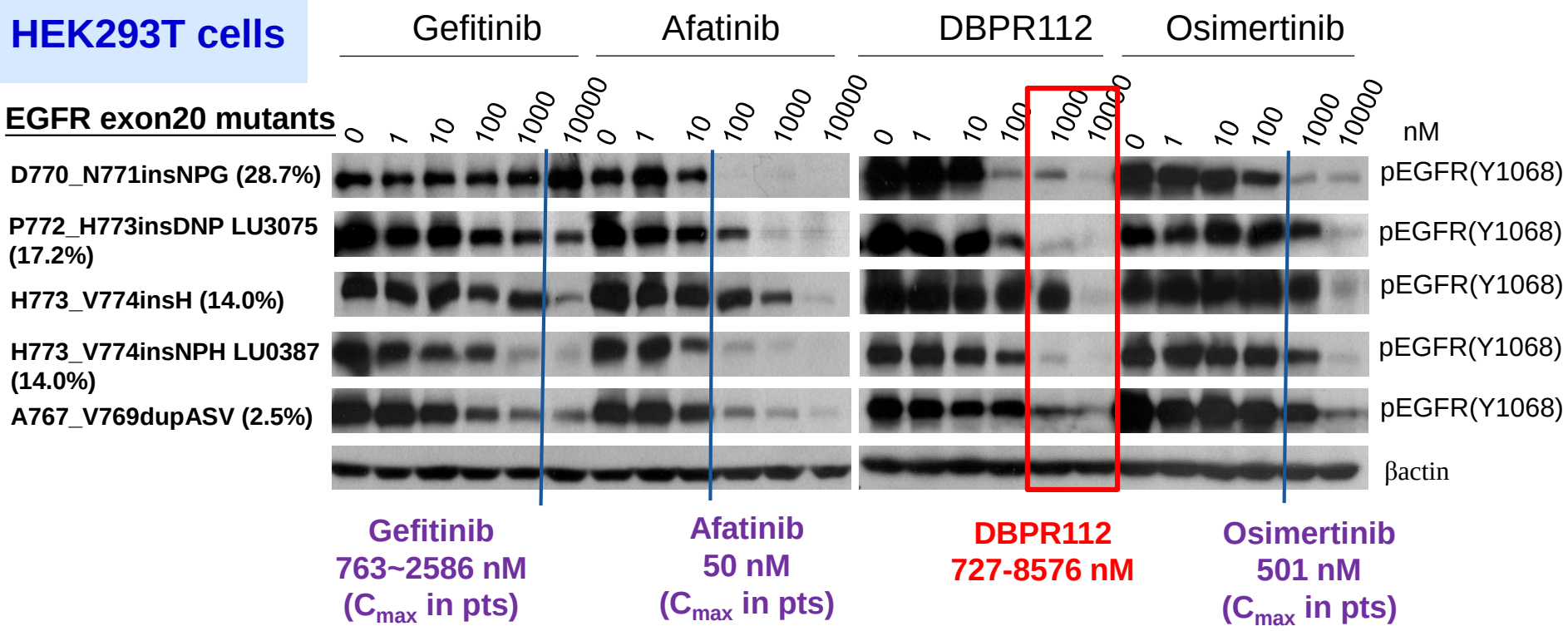


- ***EGFR* exon 20 insertion mutations may account for 4% of all *EGFR* mutations.**
- **Most prevalent EGFR exon 20 insertion mutated proteins are resistant to clinically achievable doses of EGFR-TKIs.**

DBPR112 Pre-clinical data

Compounds	Enzymatic assay, IC_{50} (nM)
	$EGFR^{insNPG}$
DBPR112	3 ± 2
Afatinib	6 ± 3
Gefitinib	138 ± 88

HEK293T cells

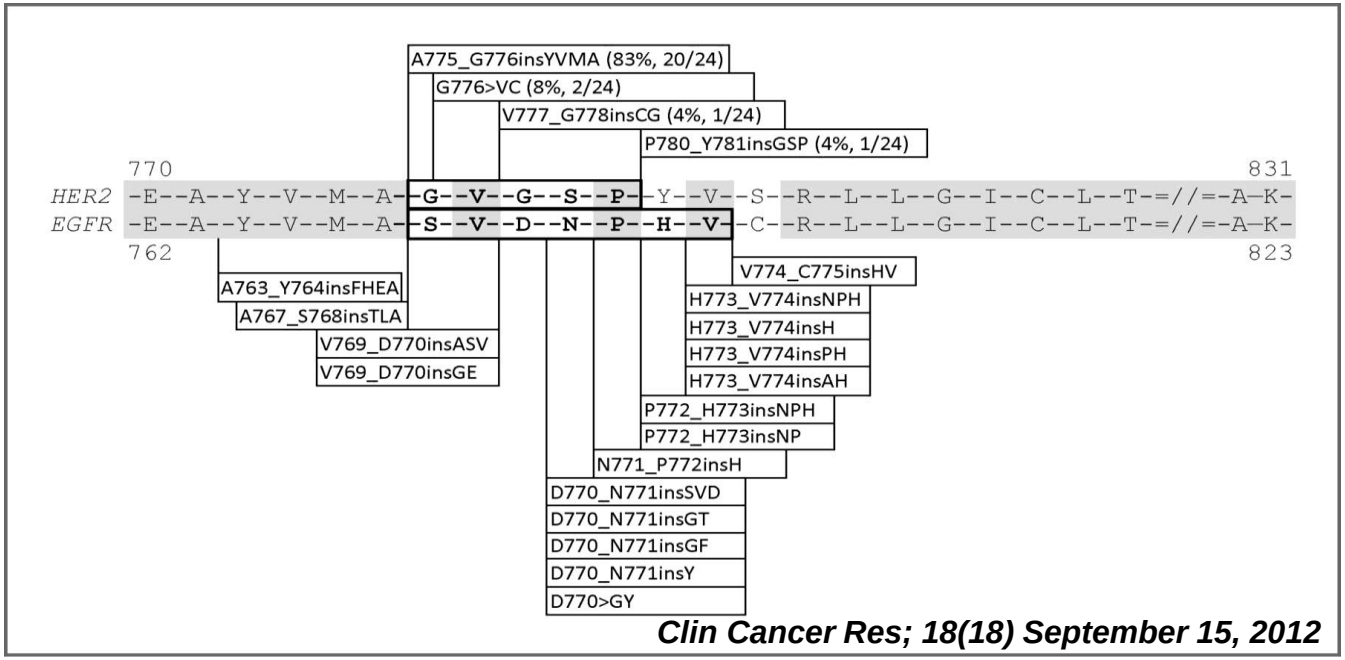


DBPR112 Pre-clinical data

ErbB2 insertion mutation

ErbB2(HER2) mutations occurs with a frequency of approximately 2 to 4% of lung adenocarcinoma from a Chinese population and are more common in Asians, never smokers, women and adenocarcinomas." (J Thorac Oncol 2012;7:85-9)

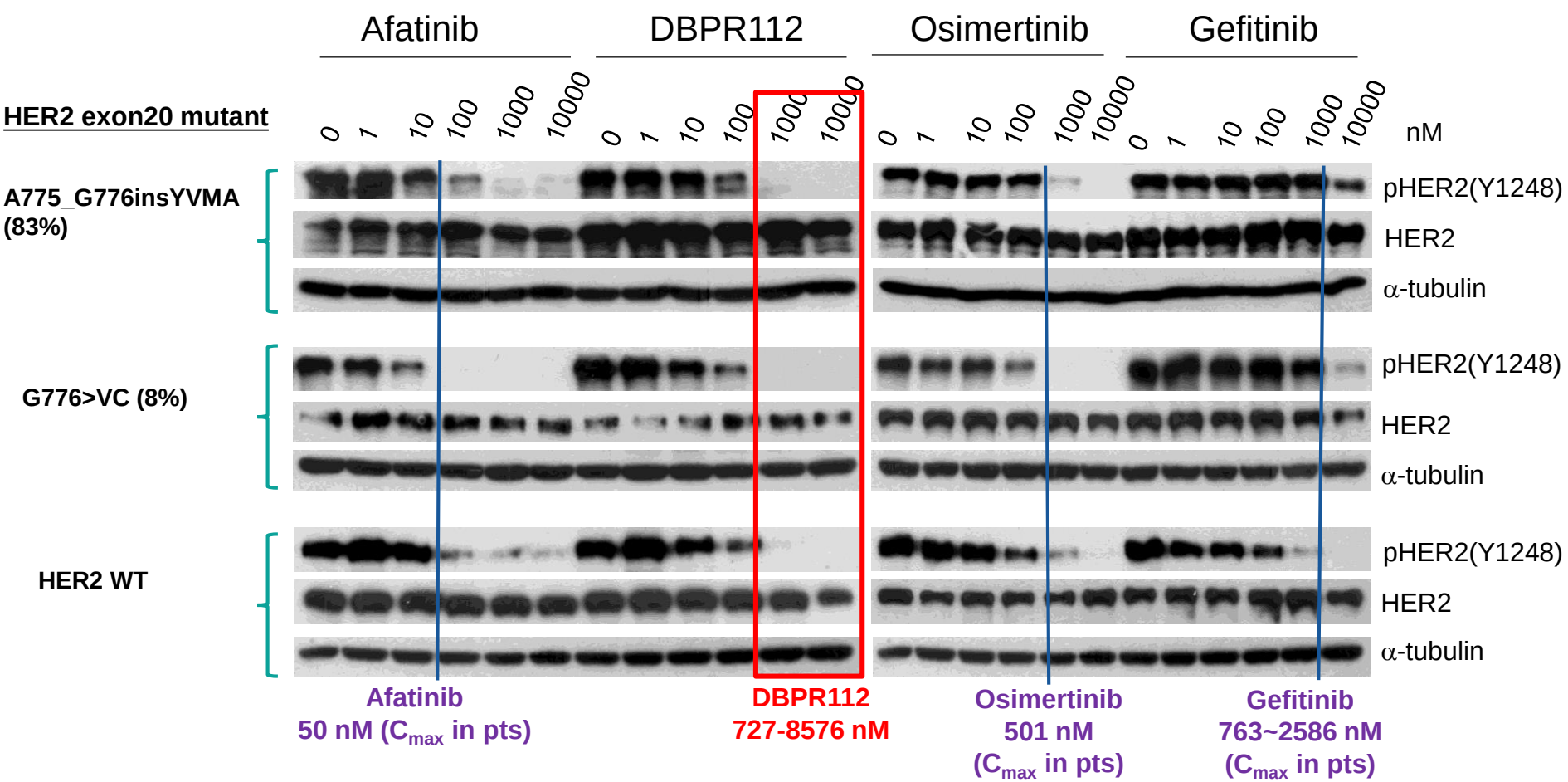
Although, NSCLC patients with HER2 mutation treated with afatinib showed objective responses. (Oncotarget. 2016 Nov 22;7(47):78152-78158.) However, afatinib does not have this indication possibly due to toxicity-limited dosages.



Clin Cancer Res; 18(18) September 15, 2012

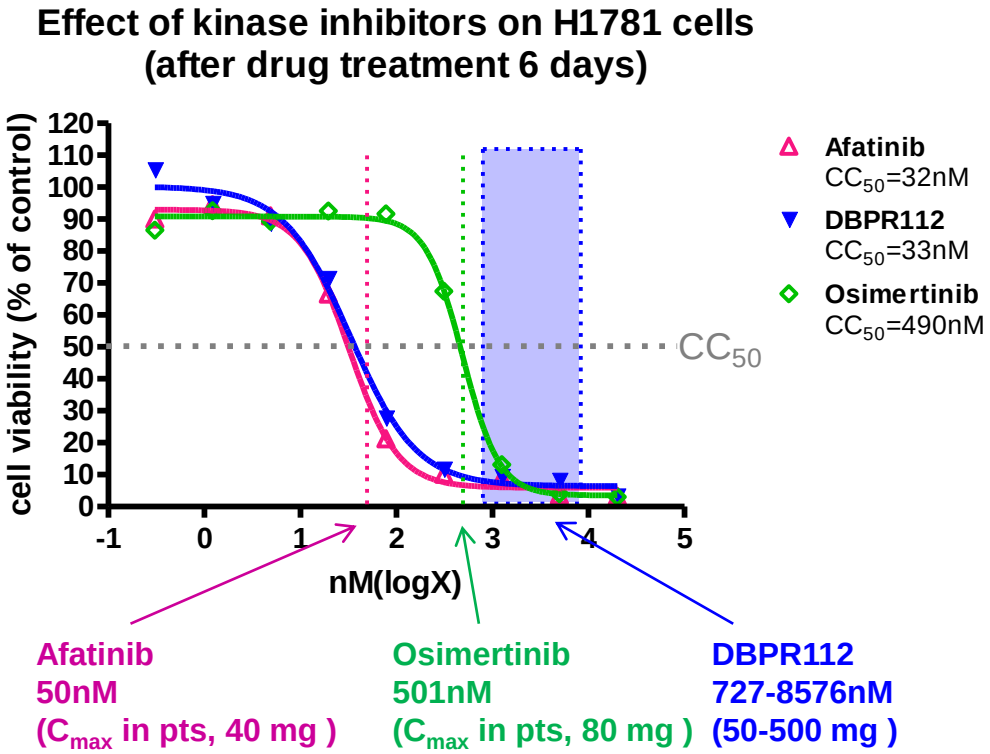
DBPR112 Pre-clinical data

Effect of DBPR112 on p-HER2^{Y1248} in HEK293T cells



Effect of Afatinib, DBPR112 and Osimertinib on H1781 ($HER2^{G776VC}$) cells

DBPR112 Suppresses H1781 (exon20INS-HER2) Proliferation at Achievable Concentrations in Human



H1781	Afatinib	DBPR112	Osimertinib
CC50 (nM)	32	33	490

Differentiation of DBPR112 and Afatinib

DBPR112

Better PK properties!

- EGFR exon20ins
- Her2
- Her2 exon20ins
- H&N Cancer
- Esophageal Cancer
- Breast Cancer

Afatinib

- 1st line user for NSCLC

	Afatinib	DBPR112	
	40 mg	50 mg (FiH Dose)	500 mg (NOAEL HED)
Concentration	50 nM	727 nM ~ 851 nM	4064 nM~8576 nM

Differentiation of DBPR112 and Afatinib

Compounds		EGFR variants				HER2		Clinical Outcome (1st line use)	COST
		WT	L858R	insNPG	L858R/ T790M	WT	exon20 ins		
1st Gen	Gefitinib	++	++	+	-	-	-	OS ▬ PFS ▲	Medium
2nd Gen	Afatinib	++	++	++	++	++	++	OS ▲ PFS ▲	Medium
Better-2nd Gen	**DBPR112**	**++**	**++**	**++/+++**	**++**	**++**	**++/+++**	**OS ▲? PFS ▲?**	**Low-Medium?**
3rd Gen	Osimertinib	+	++	+	+++	+	+	OS ▲? PFS ▲	10k USD/mon

DBPR112 has better PK properties and better tolerance/safety, and is expected to reach much higher drug concentration in patients

DBPR112 has been positioned as an Afatinib-BETTER candidate for 1st line use, and expected to increase OS/PFS with lower costs.

Major Advantages and Differentiation of DBPR112

- Selective and potent inhibition of $EGFR^{wt}$, $EGFR^{L858R}$ and $EGFR^{L858R/T790M}$ mutants
- DBPR112 potently inhibits the insertion mutations (exon20-INS) such as $EGFR^{Asp770\_Asn771insNPG(exon\ 20)}$ and $Her2^{Wild\text{-}type,\ A775\_G776insYVMA,\ or\ G776VC(exon\ 20)}$ which are of unmet needs in NSCLC.
- Overall PK profile (exposure and oral bioavailability) of DBPR112 is significantly better than Afatinib (2nd generation EGFR inhibitor approved as 1st line treatment of EGFR dependent NSCLC).
- In addition to NSCLC with exon20-INS within EGFR or HER2, DBPR112 can be targeted for solid tumors dependent on EGFR or HER2: NSCLC, H/N, Esophagus, Breast (single agent or in combination).
- Since there is no therapy for NSCLC with exon20-INS, DBPR112 would be developed under **fast track** route.