Discovery and early development of HMPL-504/AZD6094 (Volitinib)

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105th Annual Meeting of the American Association for Cancer Research
San Diego, California
April 6, 2014

Disclosure

- I am an employee and shareholder of Hutchison MediPharma.
- I will not discuss off label use of any products.

Acknowledgments

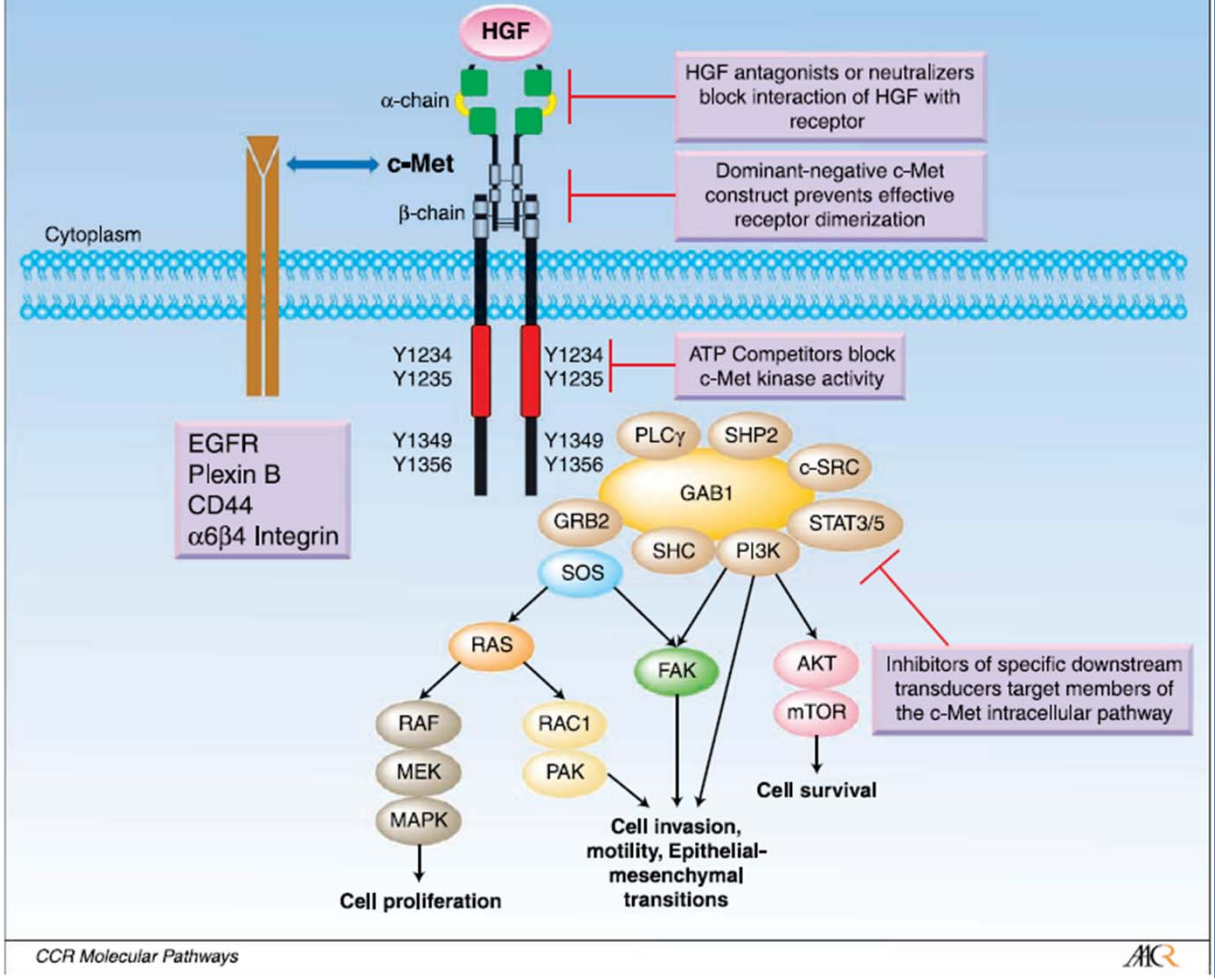
Hutchison MediPharma

Weiguo Su, Guangxiu Dai, Jia Hong, Weiguo Qing, Yongxin Ren, Yumin Cui, Feng Zhou, Longxian Jiao, Shiming Fan, Yi Gu, Jian Wang, Hongcan Ren, Yang Sai, Na Li, James Yan, May Wang, Hua Mu, Charlie Qi

AstraZeneca

Celina D'Cruz, Paul Gavine, Alwin Schuller, Melanie Frigault, Edwin Clark

Background of c-Met signaling pathway

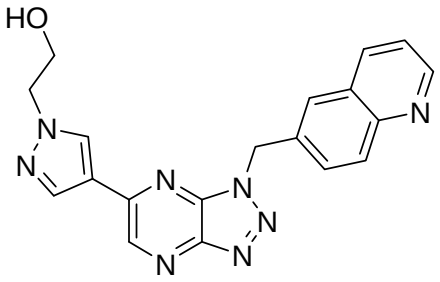


Joseph Paul Eder, et al, Novel Therapeutic Inhibitors of the c-Met Signaling Pathway in Cancer, Clin Cancer Res 2009;15(7)

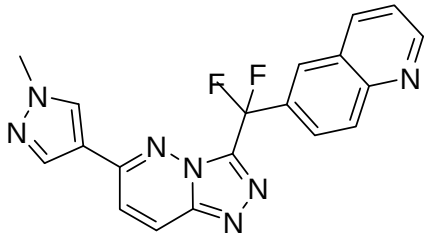
- Aberrant HGF/Met pathway activation leads to uncontrolled tumor cell growth, invasion and survival.
- Four different mechanisms of Met pathway activation:
  - Met gene amplification
  - HGF/Met over-expression
  - Mutations
  - Cross talk with other receptors
- Aberrant HGF/Met axis activation has been detected in multiple major tumor types, including lung, stomach, RCC, CRC and HCC.

Chemistry SAR leading to the discovery of HMPL-504

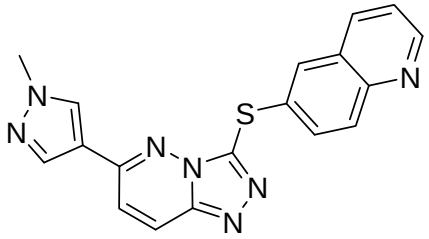
Small molecule c-Met inhibitors



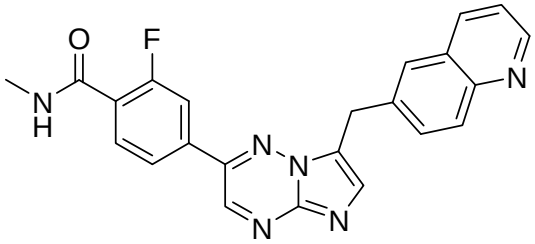
PF-04217903[a]



JNJ-38877605[b]



SGX-523[c]



INC-280[d]

a. Zou H, et al, 99th Annual Meeting for American Association for Cancer Research (AACR); 12 – 16 April 2008; San Diego, USA
b. Perera T, et al, 99th Annual Meeting for American Association for Cancer Research (AACR); 12 – 16 April 2008; San Diego, USA
c. Bounaud et al, WO 2008/051808 A2
d. Liu X, et al, 99th Annual Meeting for American Association for Cancer Research (AACR); 12 – 16 April 2008; San Diego, USA

Chemistry goals

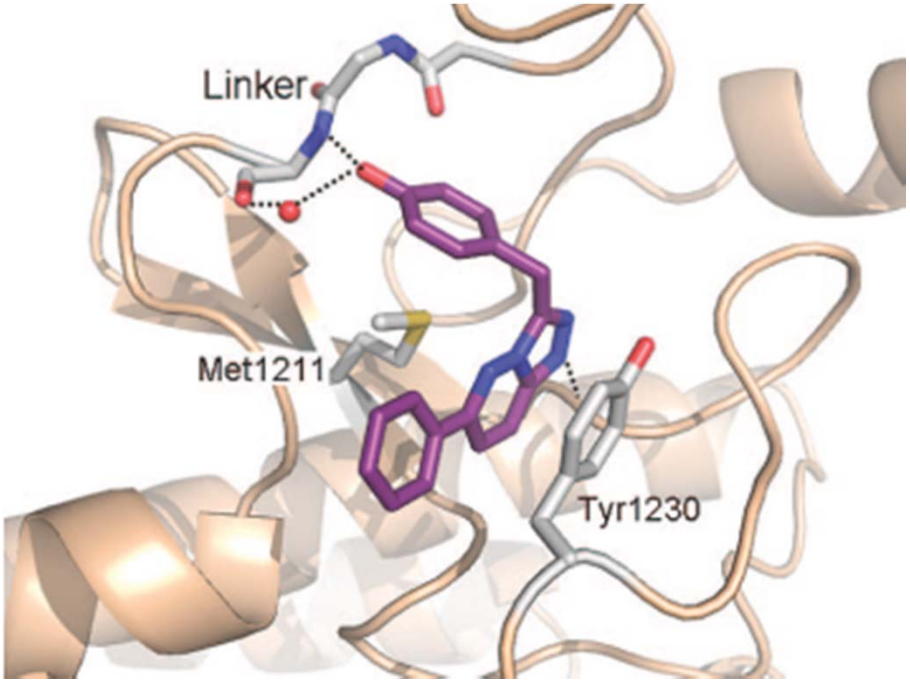
- The predominant metabolite in human, 2-quinolinone, has dramatically reduced solubility and appeared to crystallize in the kidney resulting in obstructive toxicity*

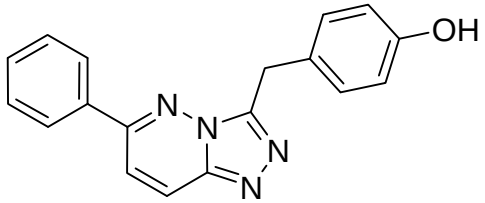
- Remove the possibility of the lactam metabolite formation while retaining good potency and selectivity

- Modify physicochemical properties to optimize solubility and pharmacokinetic properties

*Diamond, S.; et. al.: Species-specific metabolism of SGX523 by aldehyde oxidase, *Drug Metabolism and Disposition* **2010**, *38*, 1277-85

Binding mode of a selective c-Met inhibitor



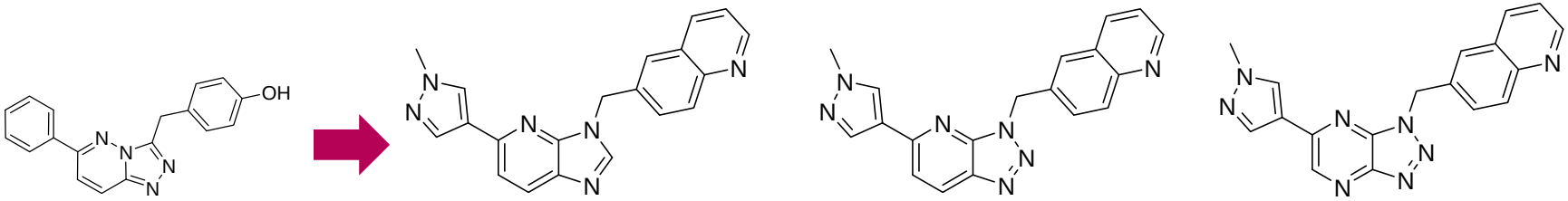


Enzyme c-Met IC_{50} = 0.120 µM

1. A bent "U-shaped" conformation with the inhibitor wrapped around Met1211
2. A hydrogen bond between the backbone NH of Met1160 and the oxygen of the phenol, the hinge binder
3. A hydrogen bonding interaction between N-1 of the inhibitor and the backbone NH of Asp1222
4. A π-stacking interaction between the triazolopyridazine core and Tyr1230

Albrecht, B.K.; et. al.:: . Discovery and optimization of triazolopyridazines as potent and selective inhibitors of the c-Met kinase. *J. Med. Chem.* **2008**, *51*, 2879-82.

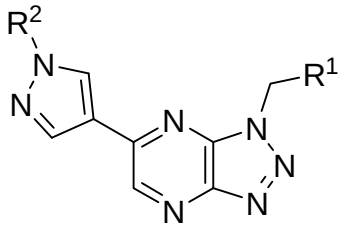
Modifications on the cores

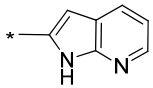
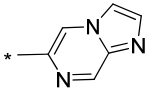
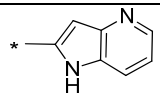
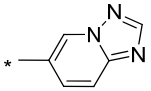
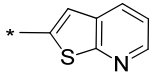
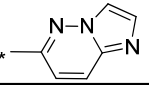
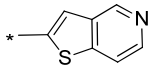
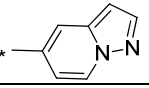
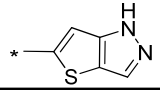
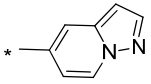
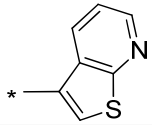
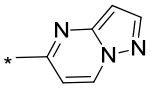
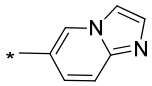
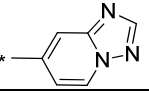
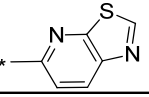


	1	2	3
ClogP	2.43	2.16	1.22
Enzyme c-Met IC_{50} (μM)	0.460	0.012	0.005
p-c-Met IC_{50} in H441 (μM)	-	0.093	0.006

1. A hydrogen bond between the backbone NH of Met1160 and the nitrogen of the quinoline, the hinge binder, is reserved in the SAR exploration.
2. The π-stacking interaction between the core and Tyr1230 is critical to the affinity. The electron-deficient core is favored.
3. Triazolopyrazine is the optimal core that is potent in both enzymatic and cellular assays.

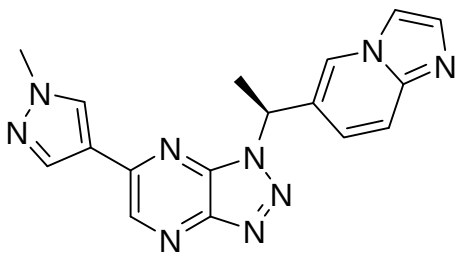
Modifications on the hinges



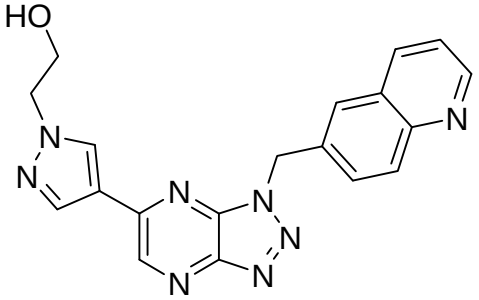
	R¹	R²	c-Met enzyme IC_{50} (μM)	p-Met IC_{50} in H441 (μM)		R¹	R²	c-Met enzyme IC_{50} (μM)	p-Met IC_{50} in H441 (μM)
4		CH_2CH_2OH	0.227	--	**11**		Me	0.13	--
5		Me	71.8% @ 1 μM	--	**12**		Me	0.026	0.077
6		Me	0.194	--	**13**		Me	0.024	0.063
7		Me	0.011	0.061	**14**		Me	0.019	0.020
8		Me	0.006	0.019	**15**		$-CH_2CH_2OH$	0.005	0.007
9		Me	0.378	--	**16**		Me	0.142	--
10		Me	0.006	0.011	**17**		Me	0.359	--
					18		Me	0.106	--

- A series of hinge pieces with a hydrogen bond acceptor have been evaluated in the SAR.
- Compound **10** displayed excellent potency.

Discovery of HMPL-504



HMPL-504

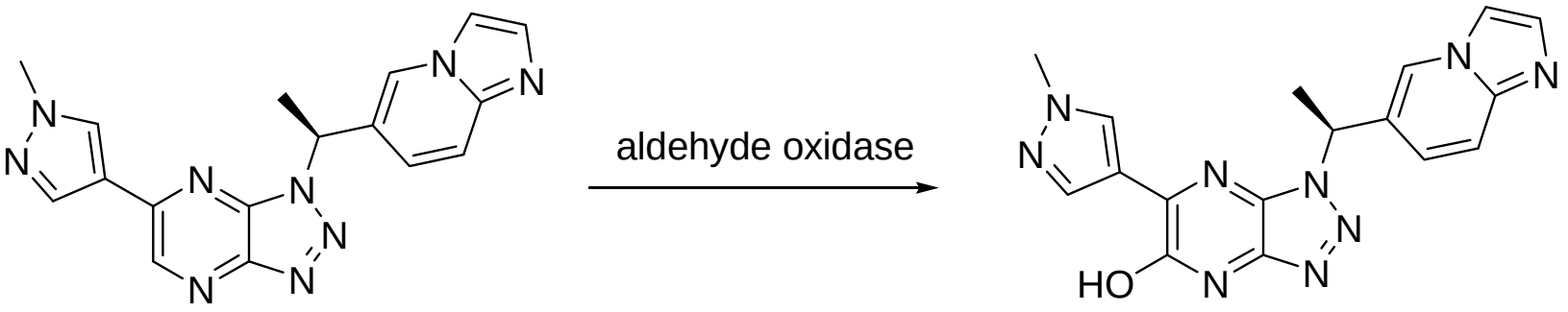


PF-04217903

	HMPL-504	PF-04217903
c-Met kinase IC_{50} (μM)	0.0046	0.006
p-c-Met in H441 cells IC_{50} (μM)	0.003	0.006
HGF dependent H441 proliferation IC_{50} (μM)	0.006	0.022
solubility pH7.4	24.9 μg/mL	0.11 μg/mL

- HMPL-504 has been identified as a highly potent c-Met inhibitor with favorable solubility.
- The (*S*)-Me in HMPL-504 is beneficial in that it increases the cellular potency and metabolic stability.

HMPL-504 and its aldehyde oxidase metabolism



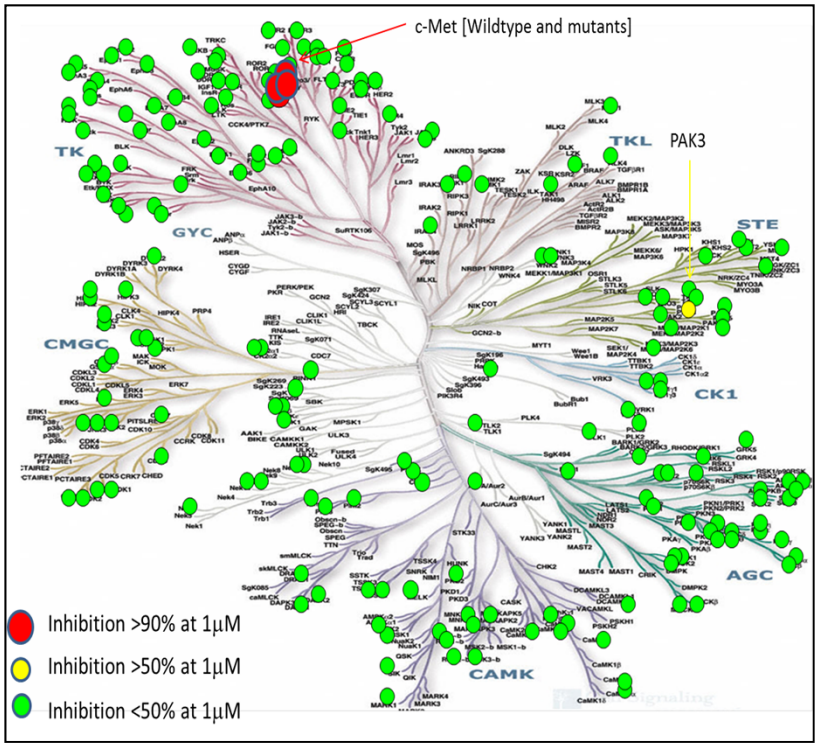
HMPL-504 **HMPL-504-AO**

HMPL-504's metabolism pathway by the aldehyde oxidase is different from SGX523's.

- The extent of the AO-mediated metabolism of HMPL-504 is much lower than that of SGX523.
- HMPL-504 and the AO-mediated metabolite HMPL-504-AO are both quite soluble (24.9 µg/mL and 1.33 mg/mL in pH7.4 aqueous buffer), and therefore HMPL-504 present a less risk in terms of the renal toxicity encountered by SGX523.

In vitro biological profile of HMPL-504/AZD6094

Biochemical activity and kinase selectivity of HMPL-504



Kinase	IC_{50} (nM) / Inhibition (%) at 1μM
c-Met[WT]	4.6[a]
c-Met [M1268T]	5[b]
c-Met[D1246N]	481[b]
c-Met[Y1248C]	596[a]
c-Met [Y1248H]	244[b]
PAK3	51%[c]
Other 268 kinases	<50%[c]

a：the IC_{50} was determined by TranscreenerTM KINASE Assay
b, c: The data were generated by UBI.

- HMPL-504 is a potent and ATP-competitive inhibitor of c-Met
- HMPL-504 showed high selectivity against 274 kinases

Inhibition of c-Met phosphorylation by HMPL-504

Inhibition of c-Met phosphorylation	Cell line	IC_{50} (μM)	Tumor type
HGF-independent	NCI-H1993	0.006	Lung
	MKN-45	0.002	Gastric
HGF-dependent	U87MG	0.001	GBM
	H69	0.002	Lung

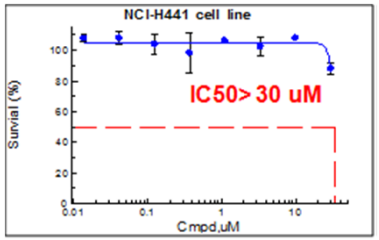
- Potent activity in inhibiting Met phosphorylation in a variety of tumor types with high level of Met (ligand-dependent or independent)

Inhibition of cell survival

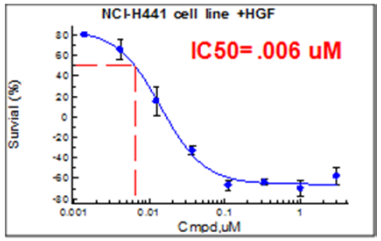
Cell line	tumor origin	c-Met status	IC_{50} (μM)	
			HGF (-)	HGF (+)
EBC-1	Lung	Amp	0.002	ND
H1993	Lung	Amp	0.010	ND
SNU-5	gastric	Amp	0.003	ND
MKN-45	gastric	Amp	0.004	ND
Hs746T	gastric	Amp	0.005	ND
H441	Lung	OE	>30	0.006
U87MG	glioblastoma	OE	>30	0.007
H69	Lung	OE	>30	0.016
H596	Lung	OE	>30	0.009
MDA-MB-468	Breast	Low	>30	>30
Other 57 lines	—	Non-Amp	>30	ND

* Abbreviation: Amp, gene amplification; OE, over-expression;

(-) HGF



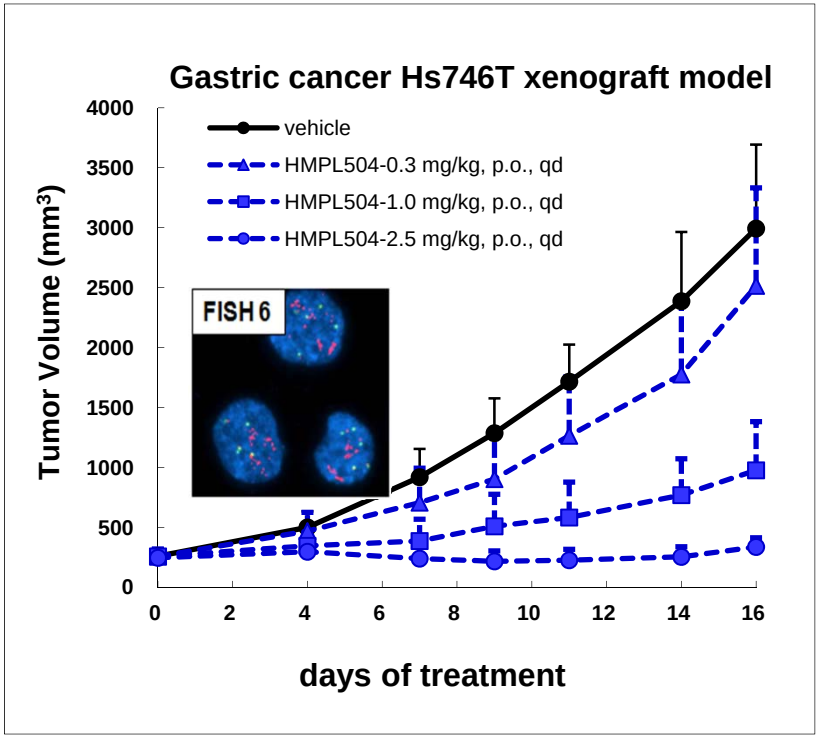
(+) HGF

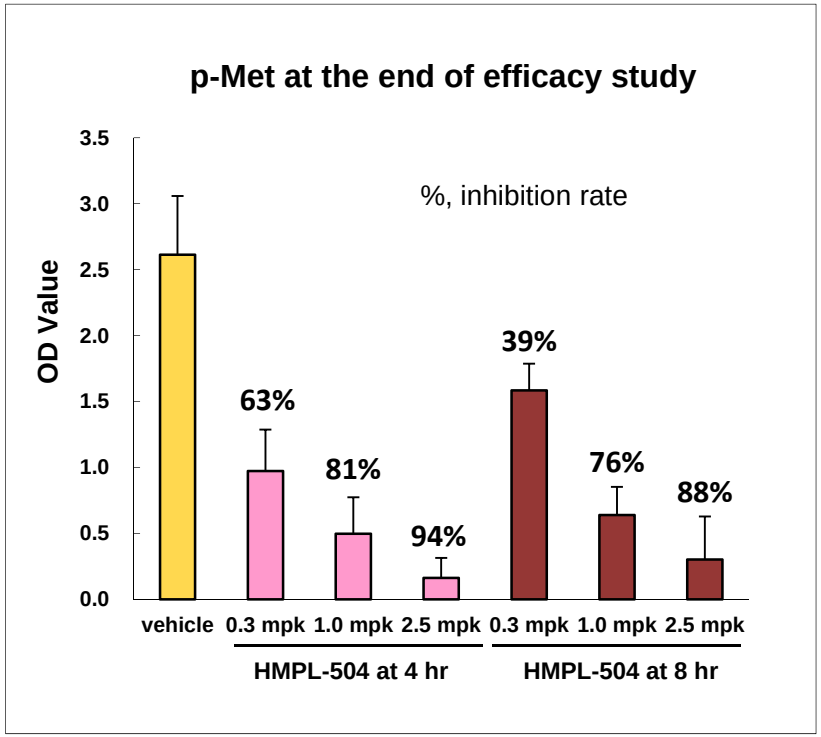


- Potent activity against tumor cell lines with Met amplification in the absence of HGF, indicating HGF-independent Met activation in these cells
- Potent activity in tumor cell lines with Met OE, but only in the presence of HGF, indicating HGF-dependent Met activation
- No activity in tumor cell lines with low Met expression/amplification, suggesting strong kinase selectivity of HMPL-504

In vivo anti-tumor activity of HMPL-504/AZD6094

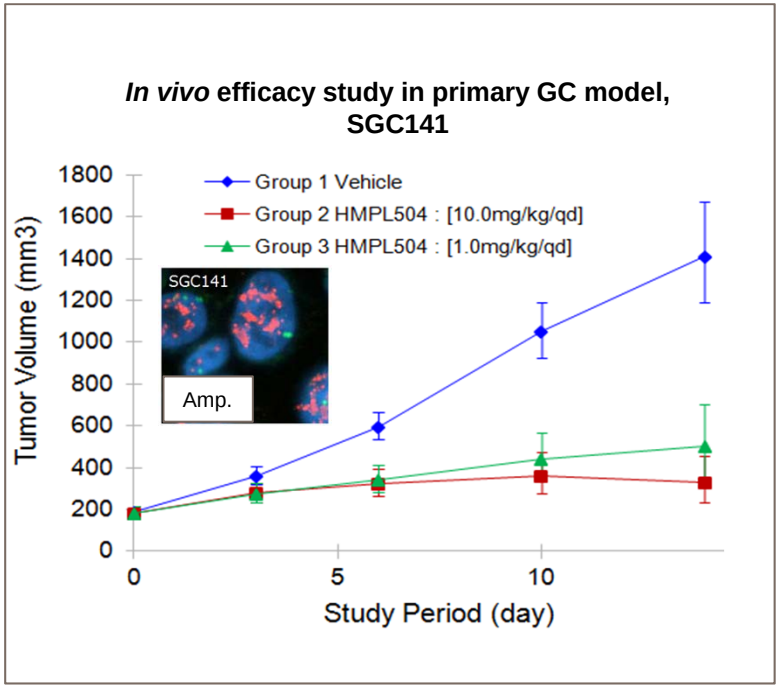
In vivo efficacy in gastric cancer with Met gene amplification

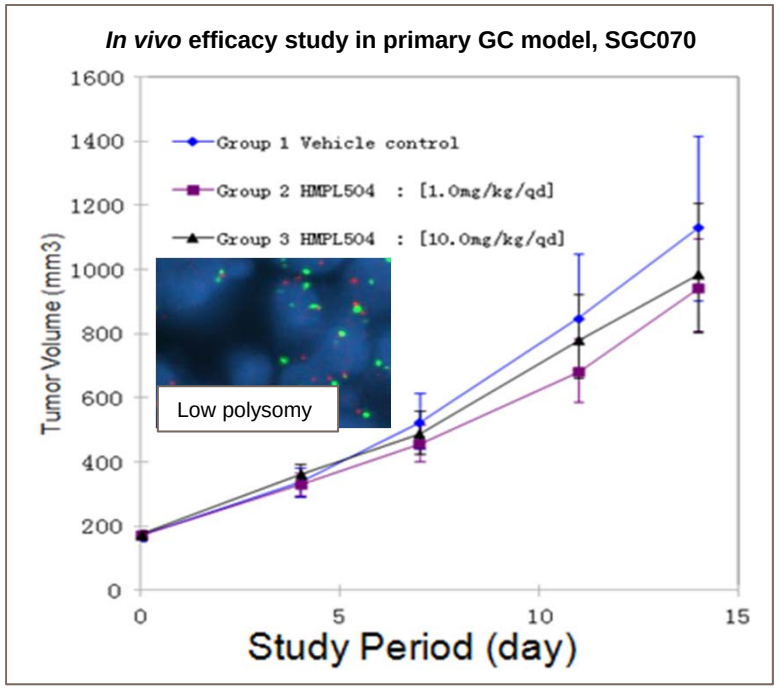




- Potent activity in the Hs746T model with dose response
- Anti-tumor efficacy correlated well with the target inhibition

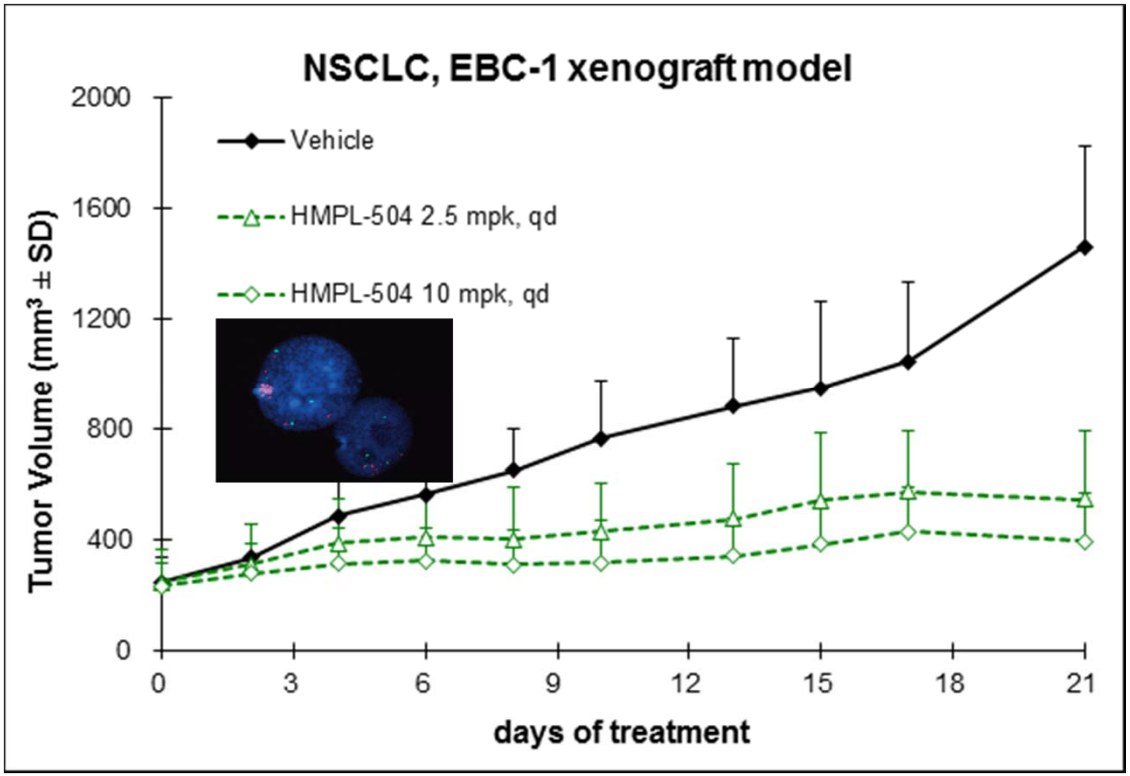
In vivo efficacy in gastric PDX models





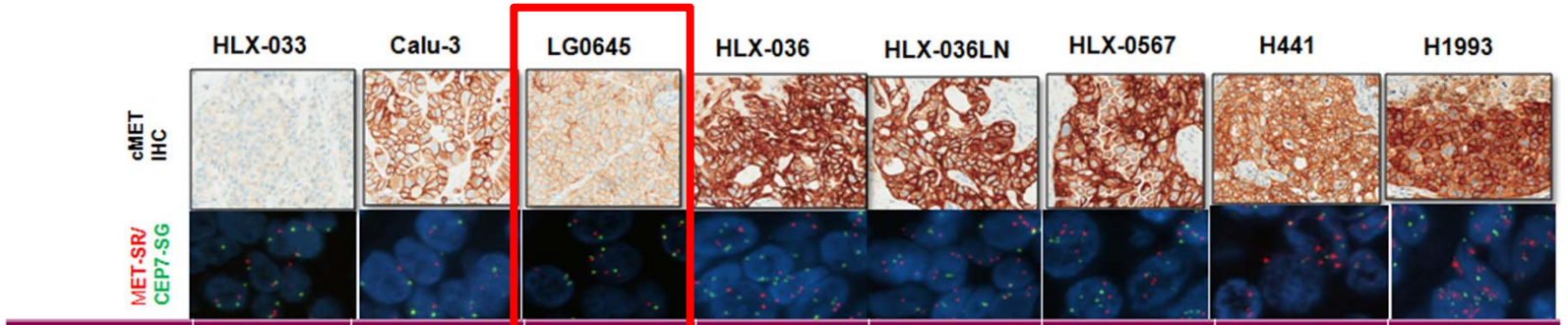
- Anti-tumor efficacy correlated with Met gene amplification/Met overexpression with high levels of p-Met

In vivo efficacy of HMPL-504 in NSCLC with Met amplification



FISH: Cancer Res., 70(19), 7580 (2010)

In vivo efficacy in lung cancer



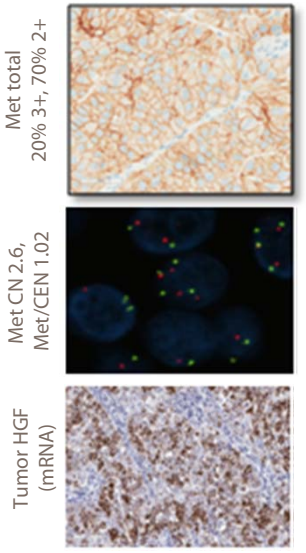
	HLX-033	Calu3	LG-0645	HLXF-036	HLXF-036LN	LG-0567	NCI-441	NCI-H1993
IHC	-ve	20% 3+, 80% 2+	20% 3+, 70% 2+	60% 3+, 30% 2+	90% 3+, 10% 2+	50% 3+, 30% 2+	90% 3+	80% 3+
Avg. CN	2.2	2.1	2.6	3.3	3.7	4.0	4.0	>50
Gene/CEP	1.1	0.84	1.02	0.95	1.33	1.2	<2	>10
KRAS	MT	WT	WT	WT	WT	MT	MT	WT
EGFR	WT	WT	WT	WT	WT	WT	WT (OE)	WT(OE)
HGF expression	Med	Recomb. HGF	Med/H	Low	Low	V.Low	Coimplant	Ligand Indep
HMPL-504 TGI%		22%	41%		154%	70%	77%	65%

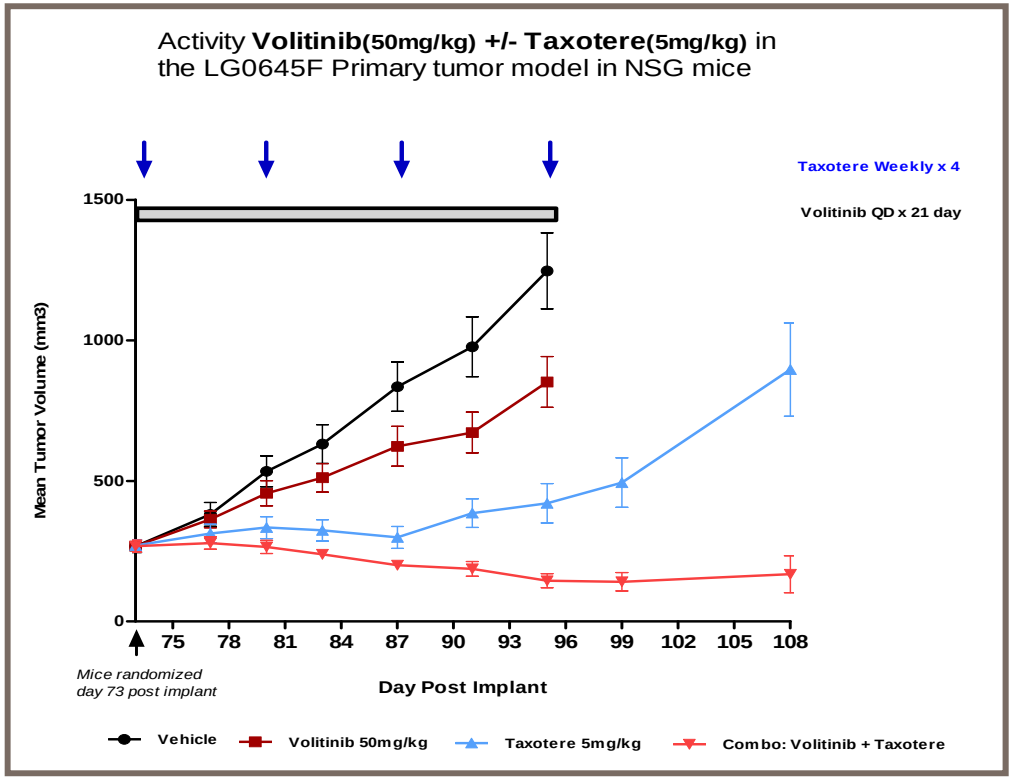
For details: see 2014 AACR Poster #3114

- Met amplification or over expression favors HMPL-504/AZD6094 effect
- Correlation with Met status seemed less clear in lung comparing to gastric
  - Heterogeneity/variation of p-Met levels
  - Activation of compensatory pathways (eg. EGFR, KRAS, etc)

Combination possibly a good choice for less responsive tumors

LG0645 NSCLC:adeno
EGFR WT, KRAS WT





For details: see 2014 AACR Poster #3114

Met amplification in EGFRm+ NSCLC post-TKI treatment

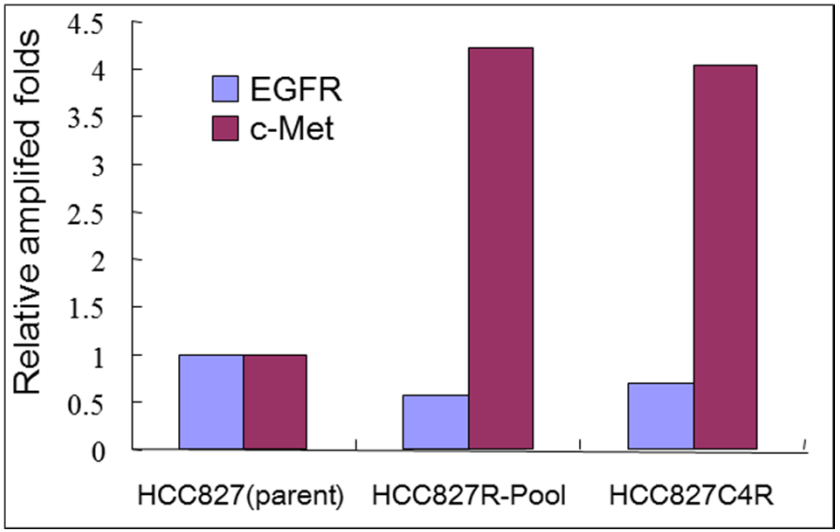
Source	MET Amp (Pre-TKI)	MET Amp (Post-TKI)	MET Amp +T790M co-occurrence (Post-TKI)
Onitsuka	0/8	0/10	0/10
Chen	2/53 (3.77%)	5/29 (17.2%)	2/29 (6.90%)
Bean	2/62 (3.22%)	9/43 (20.9%)	4/43 (9.30%)
Engleman	0/8	4/18 (22.2)	1/18 (5.56%)
Turke	no data	4/27 (14.8%)	2/27 (7.40%)
Costa	no data	0/7	0/7
Jiang	no data	1/6 (16.7%)	0/6

Adapted from Ma et al. J Thoracic Disease (review of clinical data in literature Jan1, 2005-May 31, 2010

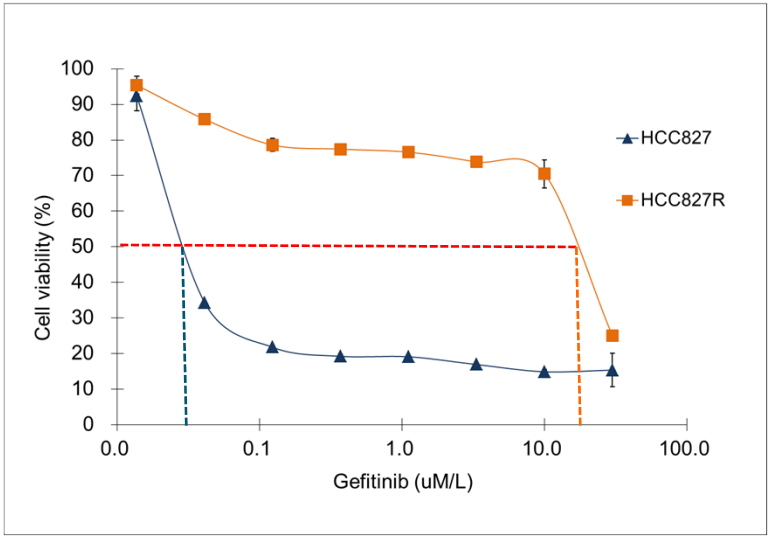
- Met amplification appeared to be low around 3% prior to TKI treatment
- Met amplification detected in roughly 20-30%, including 5-9% with concomitant T790M post TKI treatment

HCC827C4R created to mimic Met amplification resistance

Gene copy numbers of *Met* in HCC827 resistant cells



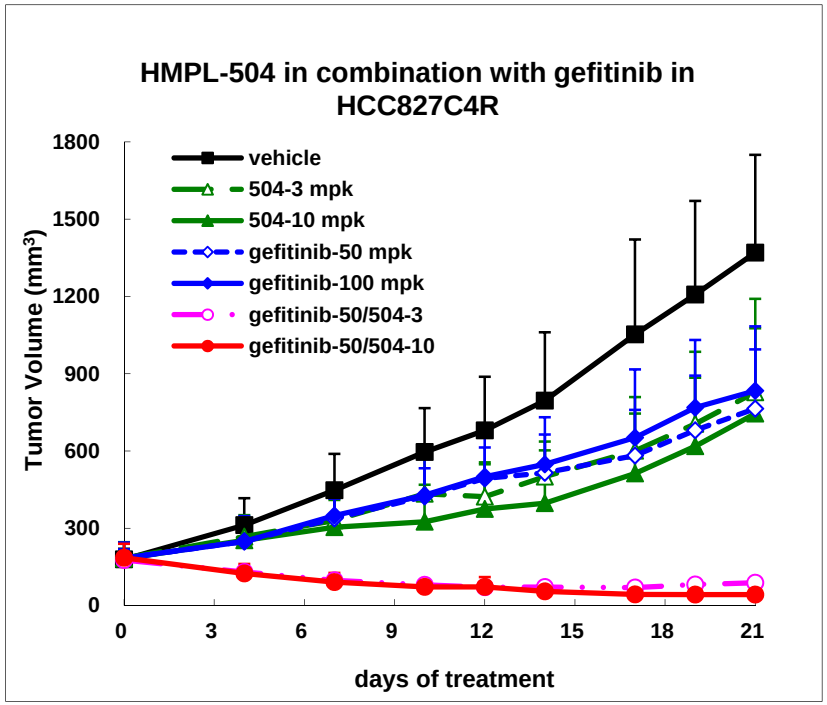
Gefitinib effect on cell viability

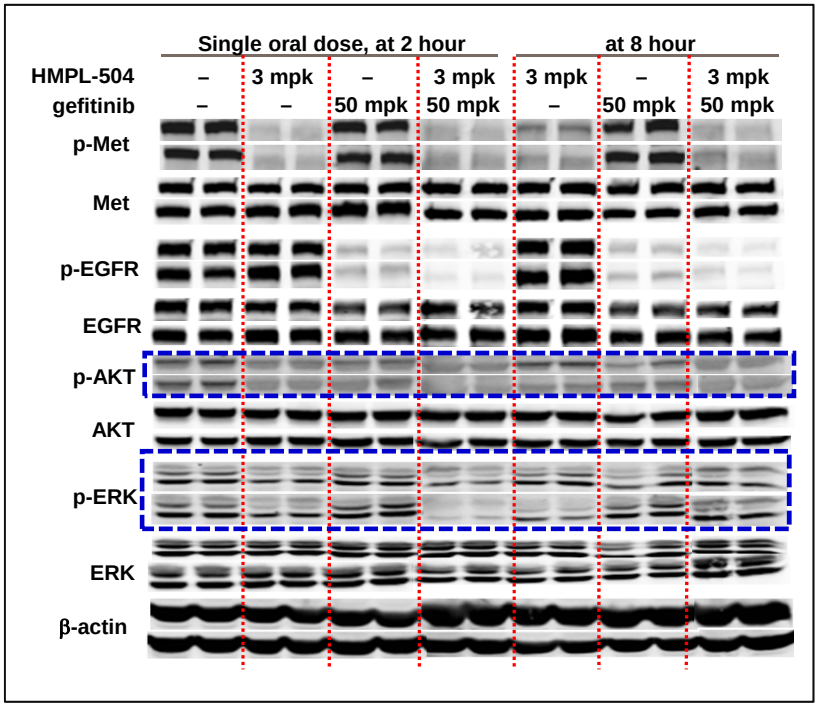


- HCC827 is a NSCLC cell line with exon 19 deletion, highly sensitive to EGFR TKIs
- After multiple passages in the presence of increasing concentrations of TKI, HCC827C4R was selected with 4-fold Met gene copies and resistant to EGFR TKIs

2013 AACR poster #971

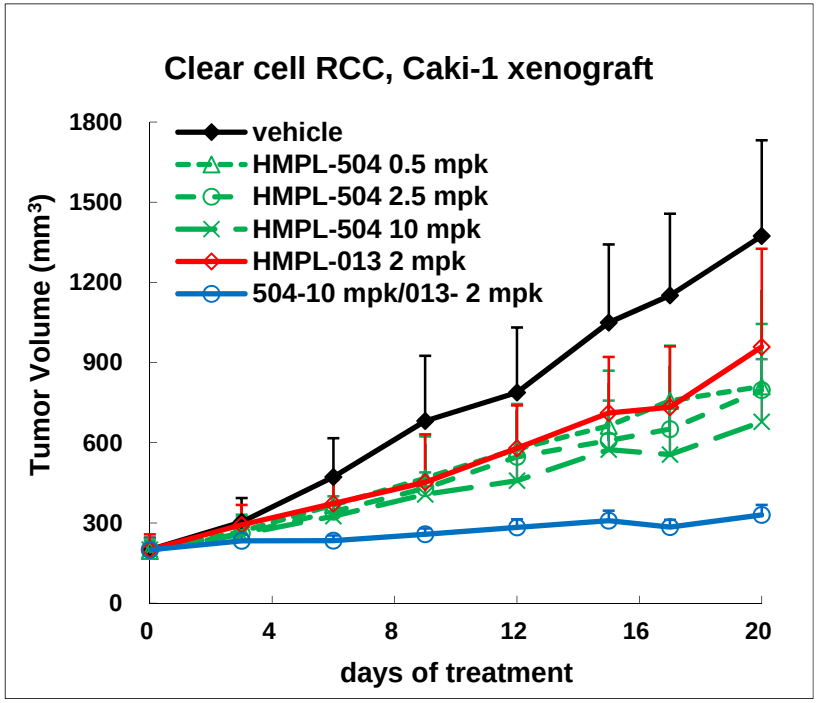
In vivo efficacy of gefitinib in combination with HMPL-504 in HCC827C4R

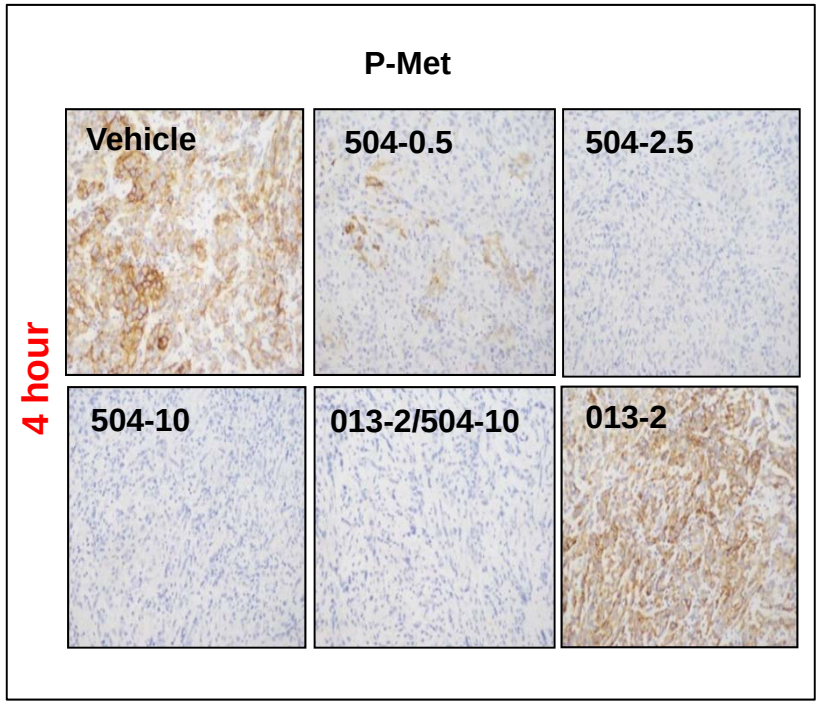




- Mono therapy less effective with poor dose response
- Clear synergistic effect when HMPL-504 is added to the treatment
  - The strong efficacy correlated well with the target inhibition
- Potential for patients who progressed after EGFR TKI treatment (Met+/T790M-)

In vivo efficacy of HMPL-504 in combination with a VEGFR inhibitor HMPL-013 in a Caki-1 ccRCC model

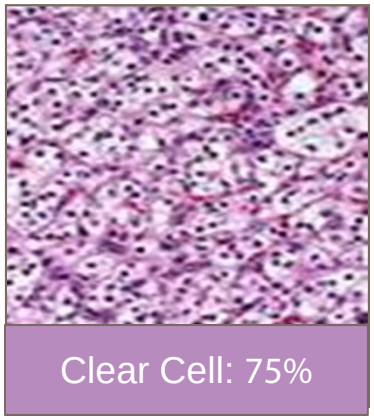




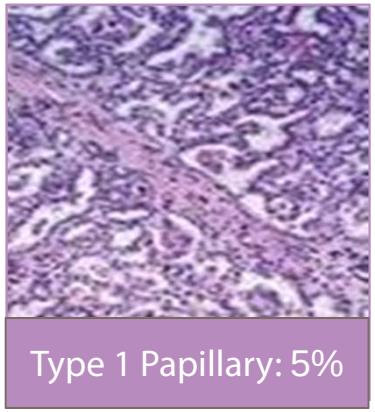
- High level of p-Met in Caki-1
- Neither VEGFR inhibitor HMPL-013 nor c-Met inhibitor HMPL-504 was particularly effective
- Combination of the two produced significant synergy

Papillary renal cell carcinoma (PRCC)

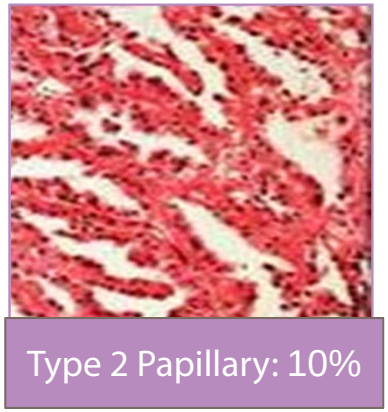
- Subset of kidney cancer (10-15%) with 6-9,000 new cases per year of PRCC in US
- No targeted therapies specifically approved for PRCC. VEGFR/mTOR inhibitors approved as first line for RCC, but ineffective for PRCC
- Two types of PRCC (Type 1 and Type 2, or "non-Type 1") identified pathologically
- Marked by high levels of Met activation
  - High incidence (up to 85%) of chromosome 7 trisomy, where both c-MET and its ligand, HGF, reside
  - c-Met mutations present in all patients with hereditary (HPRCC) and ~10% of sporadic PRCC



Clear Cell: 75%

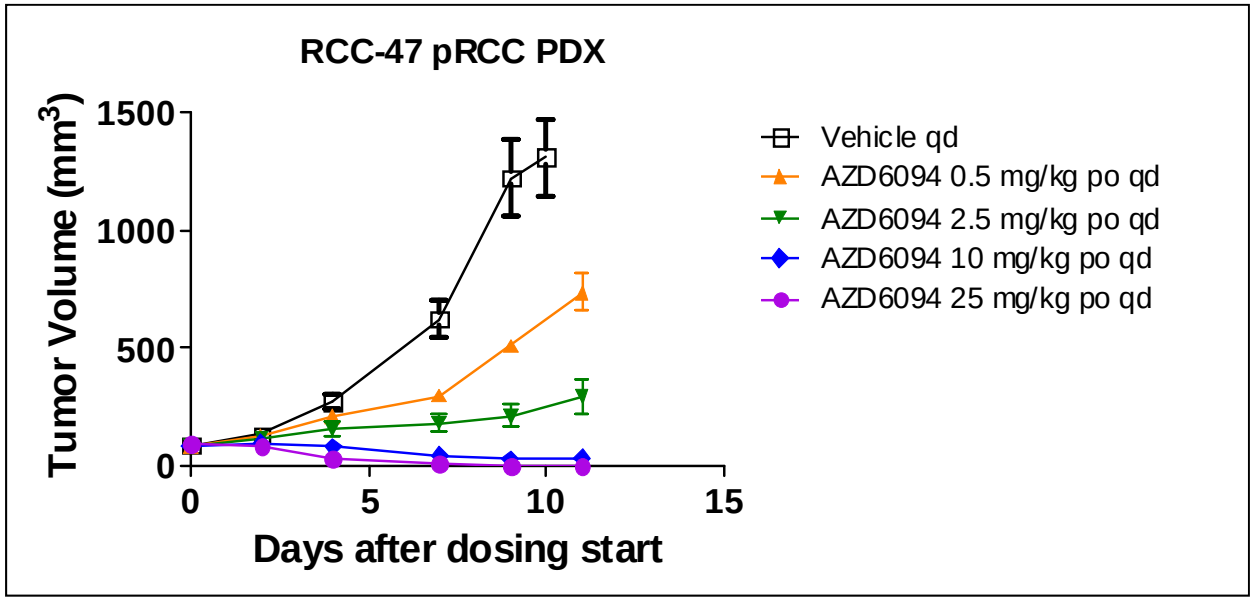


Type 1 Papillary: 5%



Type 2 Papillary: 10%

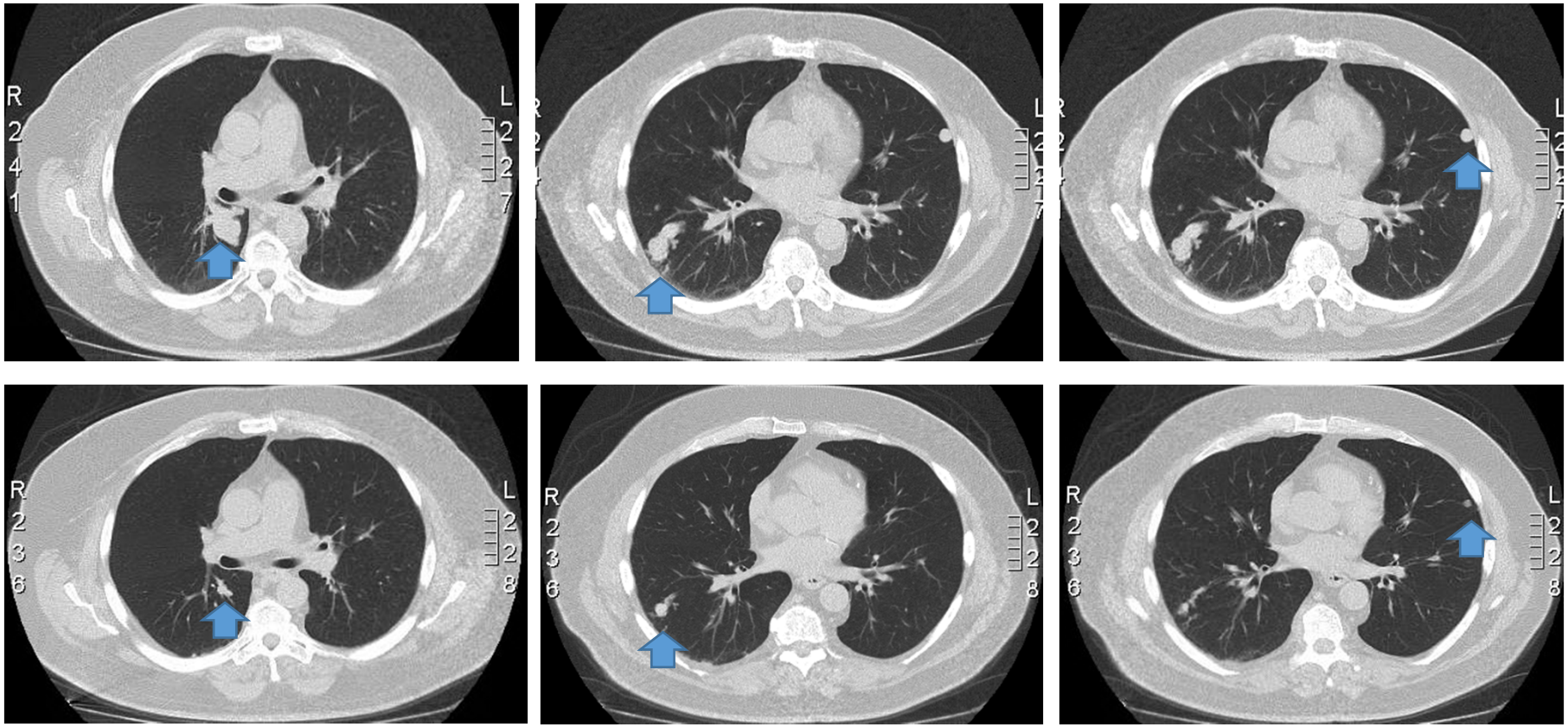
HMPL-504/AZD6094 demonstrated strong activity in a PRCC PDX model



- Potent tumor growth inhibition activity with good dose response

CT scans of a PRCC patient who responded to HMPL-504

Baseline



After 5 months

Summary of HMPL-504/AZD6094 (Volitinib)

- HMPL-504/AZD6094 is a potent and highly selective small molecule c-Met inhibitor
- HMPL-504/AZD6094 demonstrated robust anti-tumor activity *in vivo* against a variety of tumors in which Met is a main driver of growth, such as gastric and lung cancers with Met gene amplification (Patient selection key to success)
- In tumors Met is a partial driver of growth, adding HMPL-504/AZD6094 to the existing therapy could bring additional benefits
- HMPL-504/AZD6094 produced clear single agent activity in early clinical evaluation

Thank you