Hutchison Medi Pharma

R&D briefing
Hutchison MediPharma

Friday, 17 October 2014

9:30am to 1pm

The Andaz Hotel
40 Liverpool Street
London, EC2M 7QN
United Kingdom

CHI-MED

HUTCHISON CHINA MEDITECH LTD

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Agenda

	Topic	Speaker
09:30	**HMP Introduction**	Mr Christian Hogg, Chief Executive Officer
09:40	**HMPL-004 Update**	Mr Christian Hogg
09:45	**Next Generation Kinase Inhibitors for the Treatment of Cancer**	Dr Andrew Mortlock, Vice President of Oncology Projects, AstraZeneca
10:15	**Met & AZD6094 (HMPL-504/volitinib)**	Dr Weiguo Su, Chief Scientific Officer & Dr Ye Hua, Senior Vice President of Clinical Development & Regulatory Affairs
10:45	**EGF and EGFR**	Dr Weiguo Su & Dr Ye Hua
11:05	*Coffee Break*	
11:15	**VEGF and VEGFR**	Dr Weiguo Su & Dr Ye Hua
11:40	**Syk & PI3Kδ**	Dr Weiguo Su
12:05	**Preparing for Commercialisation**	Mr Christian Hogg
12:15	**Wrap-Up / Q&A**	
12:30	*Buffet Lunch*	

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HMP introduction

HMP highlights

The premier novel drug R&D Company in China

Rich and unique pipeline in oncology and immunology

Strategic collaborations with Large pharma & healthcare companies

Strong R&D leadership

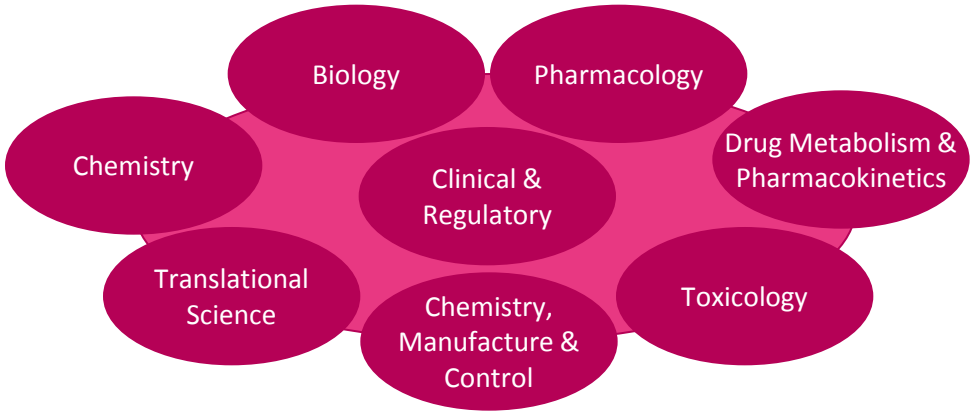
Hutchison Medi Pharma

A world class operation based in China, with a global outlook on drug R&D

Focused on the discovery & development of innovative medicines for patients globally in oncology & immunology

- Established in 2002
- Dedicated state-of-the-art R&D facility in Shanghai
  - GMP facilities in Suzhou
- ~250 well-trained scientists & staff (2013: ~200)
- 7 clinical programs + 4 pre-clinical candidates

Core R&D Platform



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Strong leadership team with global R&D experience

POSITION	EXPERIENCE
CHRISTIAN HOGG, MBA Chief Executive Officer	P&G Procter & Gamble; CHI-MED
WEIGUO SU, PHD EVP, Chief Scientific Officer	Pfizer
YE HUA, MD, MPH SVP, Clinical & Regulatory	Abbott A Promise for Life; Novartis; Celgene
ZHENPING WU, PHD, MBA SVP, Pharmaceutical Sciences	Pfizer; Phenomix
MAY WANG, PHD SVP, Business Dev. / Strategic Alliances	Lilly
MARK LEE, MBA VP, Corporate Finance & Development	Credit Suisse
YANG SAI, PHD VP, Drug Metabolism & PK	Neurocrine Biosciences
WEIGUO QING, PHD VP, Oncology	Roche; Abbott A Promise for Life
XIONG LI, PHD VP, Immunology	Pfizer; GSK GlaxoSmithKline

- Management team comprised mainly of returnees with average 20 years in multinational pharma & biotech
- All scientific leadership have participated in the discovery & development of blockbusters, e.g.

HUMIRA adalimumab; INCIVEK (telaprevir) 375 mg Tablets; Revlimid (lenalidomide) capsules; SUTENT capsules sunitinib malate; ZITHROMAX azithromycin; ZOMETA zoledronic acid for injection

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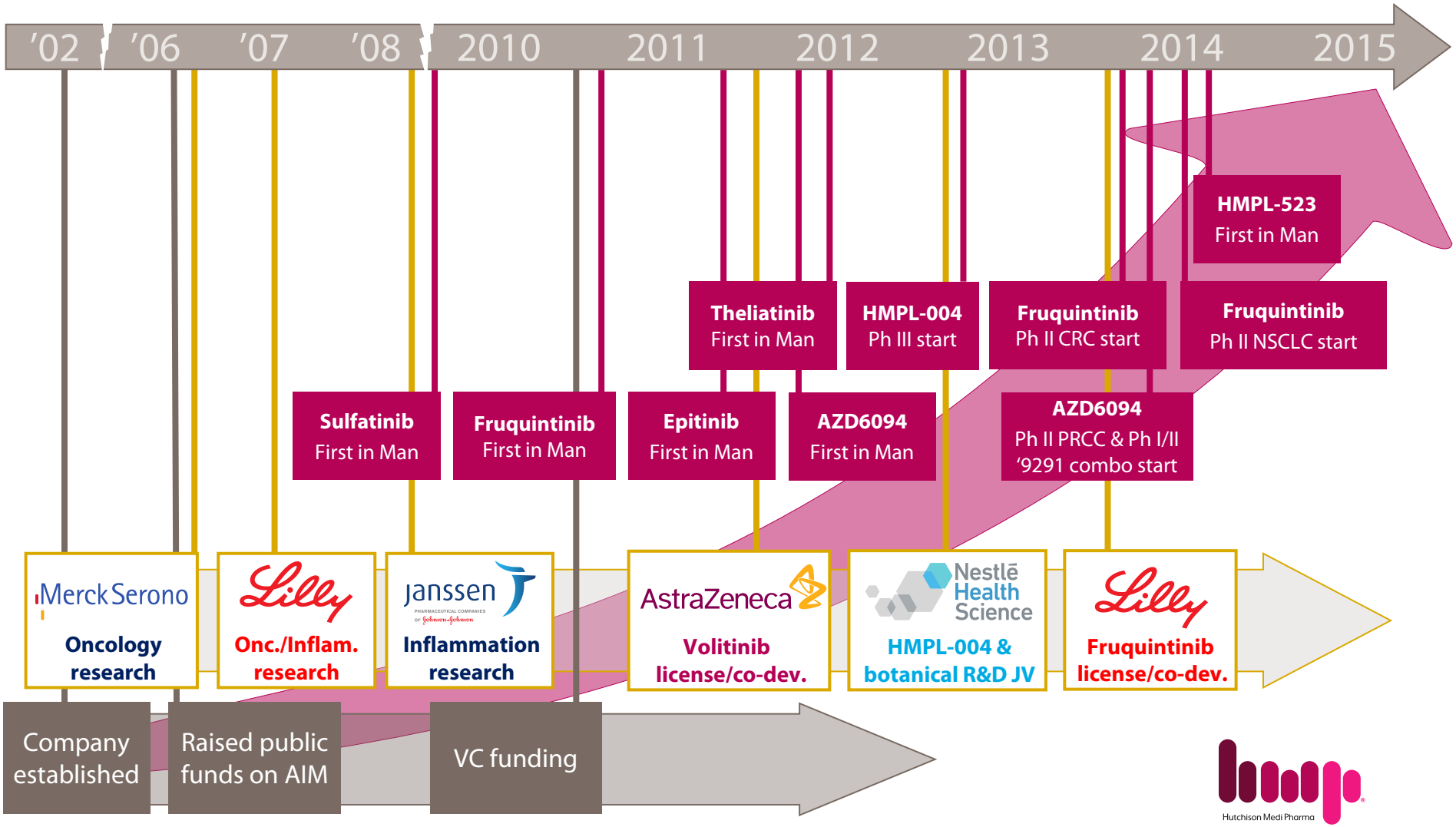
A proven track record of productivity & innovation



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HMP's 3-legged innovative R&D strategy

- **Small molecule drugs against *novel* targets**
  - With best in class or first in class potential
  - Co-development with global partners
  - Landmark AstraZeneca partnership for selective c-Met inhibitor Volitinib
- **Small molecule drugs against *validated* targets**
  - Targets proven in the global market, but unmet needs in China market
  - Identifying global potential through rapid China POC
  - Encouraging phase I results with selective VEGFR inhibitor Fruquintinib
- **Botanical drugs against multiple targets**
  - Platform specifically created to follow FDA's Botanical Drug Guidance (2004)
  - New source for drugs
  - JV with Nestlé, including HMPL-004 in phase III globally for inflammatory bowel disease

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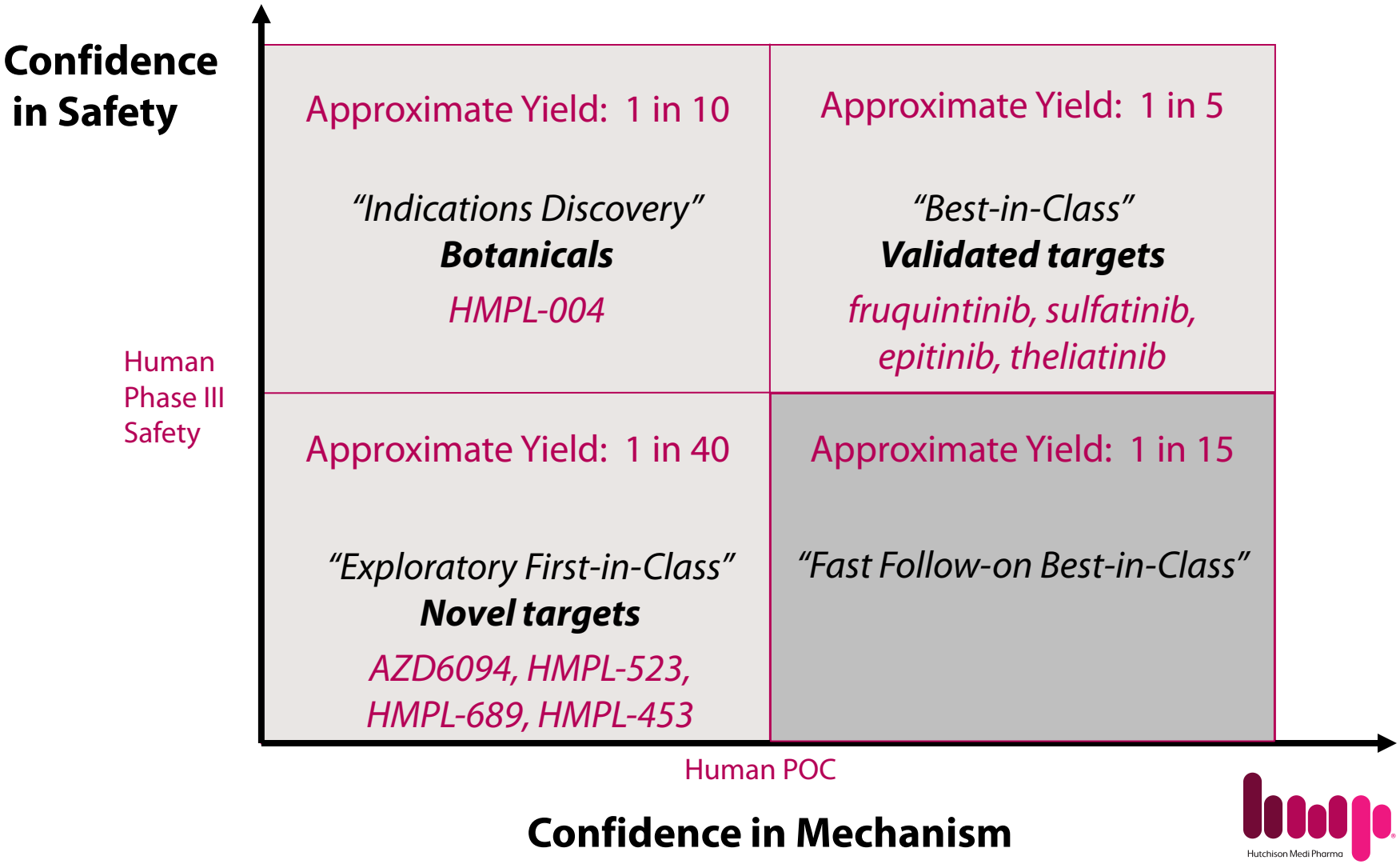
China's leading oncology & immunology pipeline

Program	Target	Partner	Indication	Preclinical	Phase I	PhIb	Phase II	Phase III
HMPL-004	Anti-TNFα	Nestlé Health Science	Ulcerative Colitis (Mild-Mod.) (8 week Induction -- US/EU)			n/a		
			Ulcerative Colitis (Mild-Mod.) (52 week Maintenance -- US/EU)			n/a		
			Crohn's Disease (8 week Induction -- US)			n/a		
Fruquintinib	VEGF 1/2/3	Lilly	Colorectal Cancer (3rd Line all comers -- China)					
			Non-small cell lung Cancer (3rd Line all comers -- China)			n/a		
Sulfatinib	VEGFR/FGFR		Neuroendocrine Tumours (Pancreatic, lung, gastric -- China)					
Epitinib	EGFRm+		Non-small cell lung cancer (EGFRm+ w/ Brain Mets. -- China)					
Theliatinib	EGFR WT		Esophageal cancer; other solid tumors (China)					
AZD6094 (HMPL-504 / Volitinib)	c-Met	AstraZeneca	Papillary renal cell carcinoma (1st line -- US/Canada/EU)			n/a		
			Non-small cell lung cancer (EGFRm+ combo. w/ AZD9291)					
HMPL-523	Syk		RA, MS, Lupus (potential Lymphoma, CLL) (Australia)					
HMPL-453	FGFR		Solid tumours (Global)					
HMPL-689	PI3Kδ		B cell malignancies (Global)					Oncology
Collaboration	Novel	Janssen	Inflammation (Global)					Immunology

Notes: MS = Multiple Sclerosis; RA = Rheumatoid Arthritis; CLL = Chronic Lymphocytic Leukaemia.

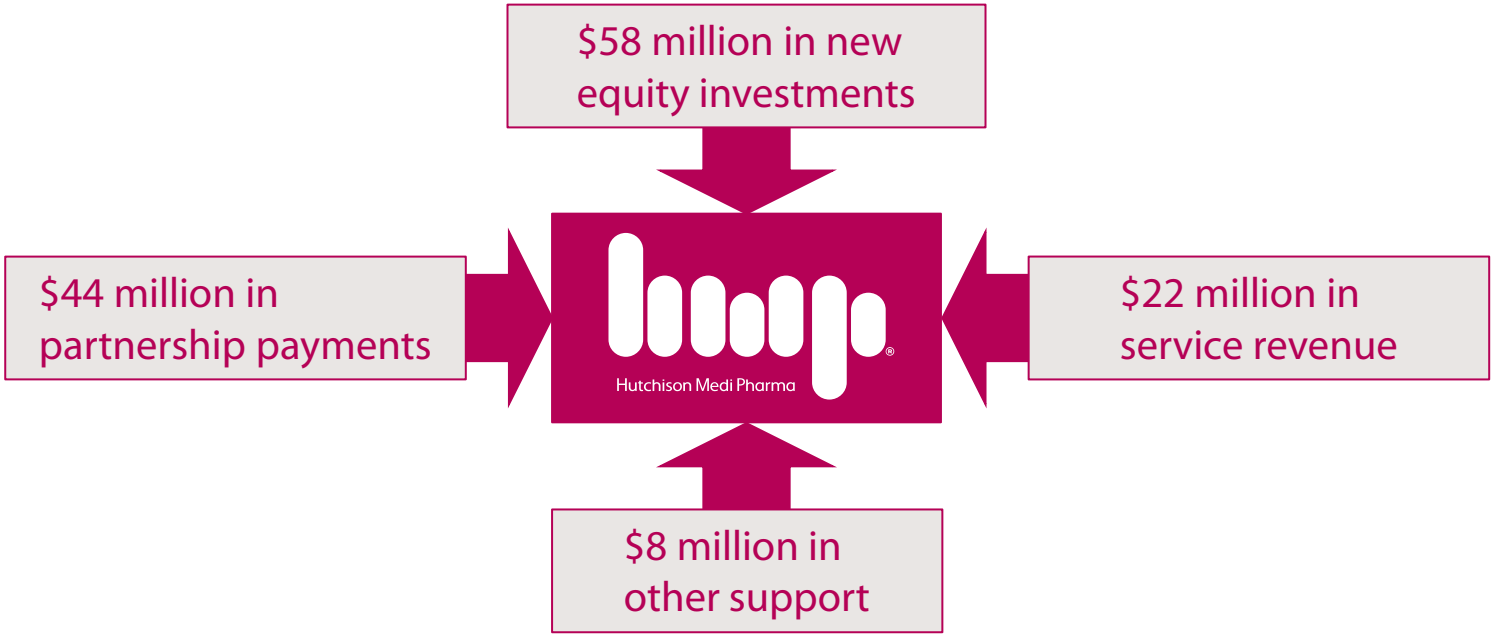
Level of target validation vs. success rate



HMP Group has secured ~US$130 million in external funding and support since 2010

FUNDS FROM EXTERNAL SOURCES, 2010 - H1 2014

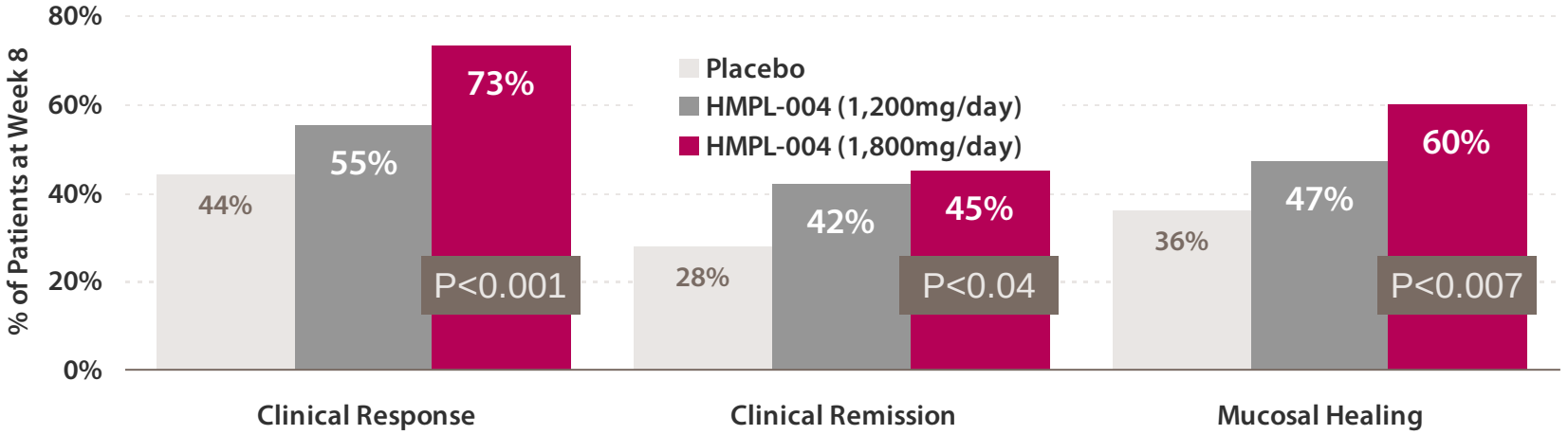
(US$ in millions)



HMPL-004

HMPL-004's successful global Phase IIb UC trial

- **Significantly improved clinical response,** clinical remission, and mucosal healing
- **Excellent safety** profile
- Clearly demonstrated **dose response**



- Randomized, double-blind, placebo-controlled multicenter trial in mild to moderate active UC
- 3 arms: 1,800 mg/day, 1,200 mg/day, & Placebo. 8 weeks treatment.
- 224 patients at 50 centers in US and Europe

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HMPL-004 data review ongoing

- Interim analysis in August
  - Surprised by the result
  - Terminated the Phase III programme
- IBD is a highly complex disease with a very diverse patient population, but it is also a disease indication with very high potential
- We now have over 500 patients of clinical data on HMPL-004
- Deep dive analysis of the data is ongoing
- Working with Nestlé, we will reach a decision if there is a way forward
- We will provide a further update in mid Q1 next year

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Keynote speaker

Dr Andrew Mortlock, Vice President for Oncology Projects, AstraZeneca

Next generation kinase inhibitors for the treatment of cancer

Andrew Mortlock

VP Oncology Projects

AstraZeneca, Cambridge, UK

London, 17 October 2014

AstraZeneca

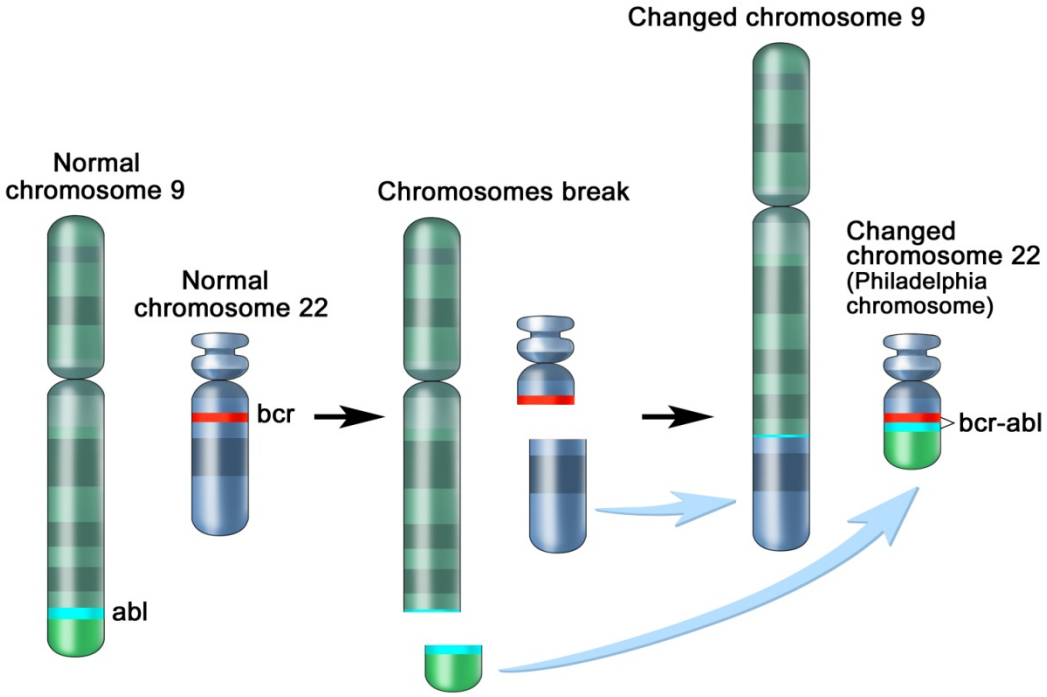
Overview

- **Kinase inhibitors approved by FDA (1998-2013)**
  - Targets and inhibitor types
- **First Generation kinase inhibitors in practice**
  - Do more selective compounds make better drugs?
  - Dose selection and combinations
  - Exploiting oncogene addiction for patient selection
- **Opportunities for next generation inhibitors**
  - (ALK – LDK378 / Ceritinib)
  - EGFR – AD9291
  - cMet – AZD6094 (Volitinib)
- **Future directions**

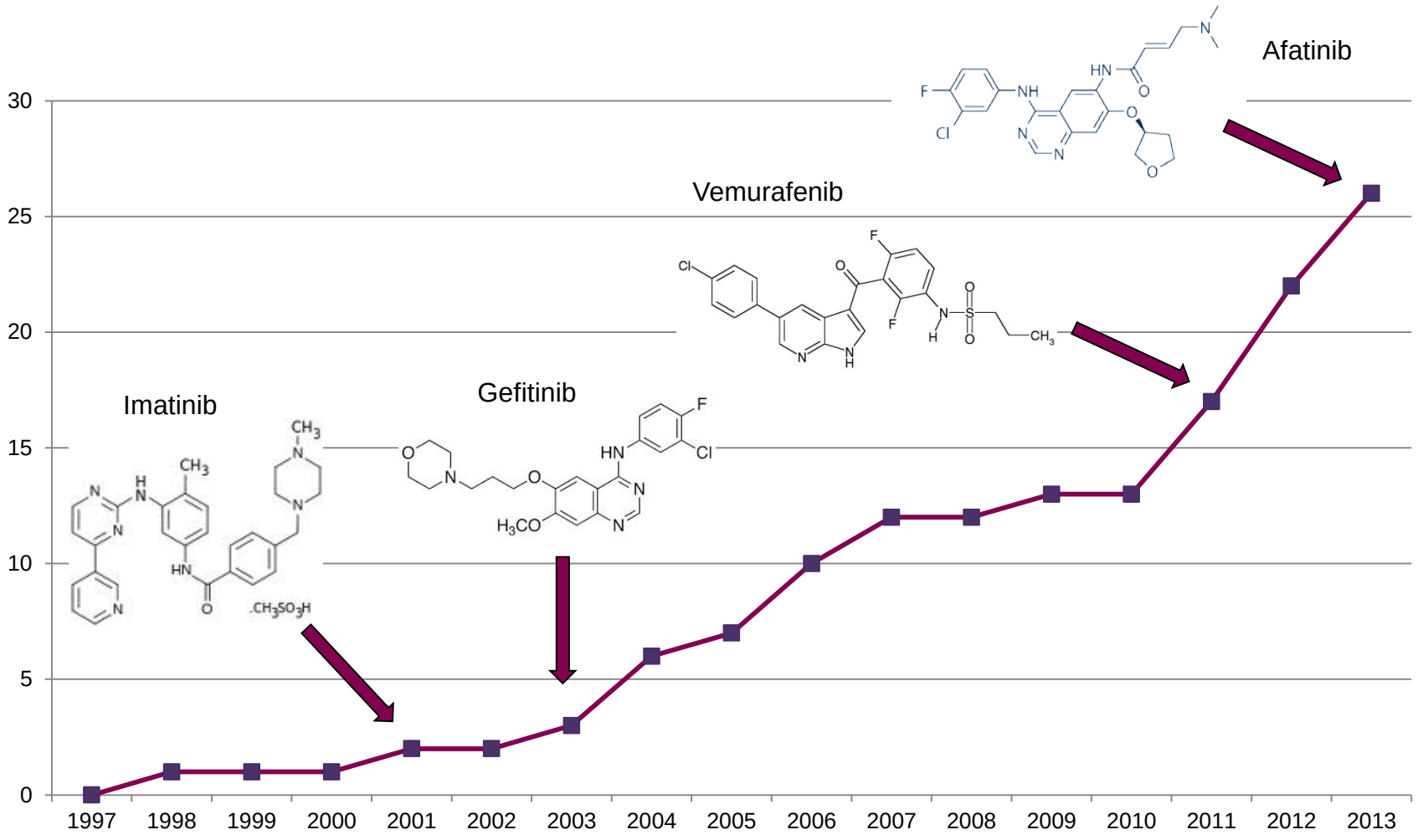
The Kinase Revolution

- More than 50% of current oncology clinical trials

- Kinases are still the most ‘drugable oncogenes’
- Kinase inhibitors have been at the forefront of personalised medicine and diagnostic development
- Launch of Imatinib/Glivec was truly revolutionary



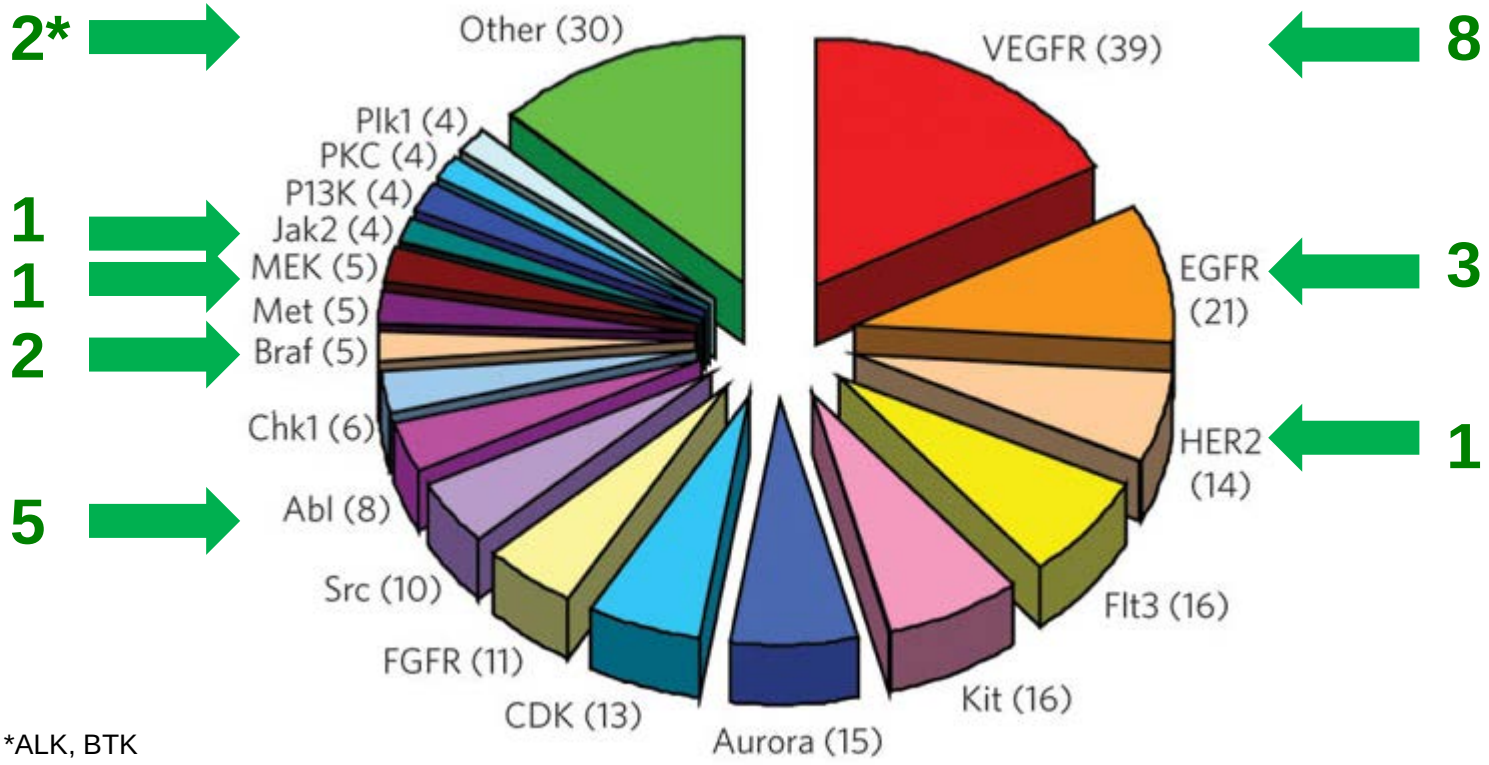
FDA Approved kinase inhibitors for cancer - Approvals have doubled since 2010



Most of kinome has yet to be drugged

- Tyrosine kinase inhibitors dominate approved drugs

- Literature review highlighted the total clinical pipeline in 2010.
- Of 23 FDA-approved small molecule inhibitors, 16 are in just 3 classes (VEGFR, EGFR, Abl)
- This analysis suggests that Flt3, c-kit, Aurora, CDK, FGFR, Src have failed to realise potential



*ALK, BTK

Nature Chemical Biology, 2010, 6, 166169

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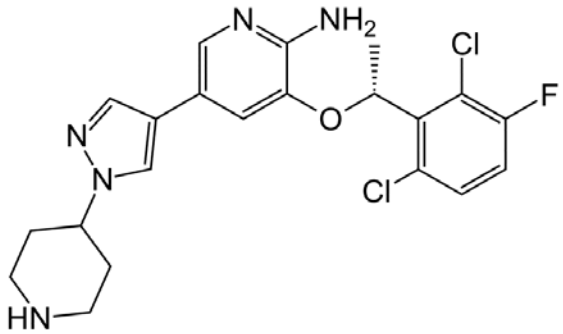
When lack of selectivity pays off...
- Crizotinib and Vandetinib

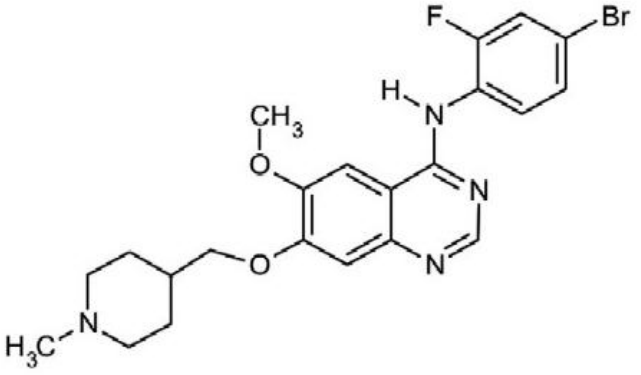
- Crizotinib, originally selected as a c-Met inhibitor, first dosed to patients in 2006
- ALK activity established pre-clinically in 2005 (20 fold more potent) ...also ROS1
- First reports on EML4-ALK fusion published July 2007
- First ALK-fusion patient dosed with Crizotinib in December 2007

- FDA approval in EML4-ALK NSCLC cancer granted in 2011

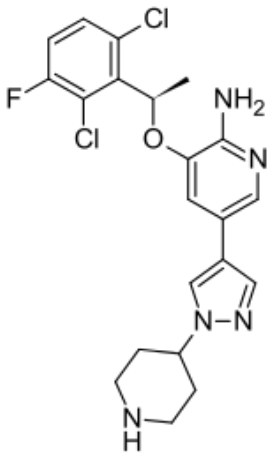


- Vandetanib originally developed as VEGFR inhibitor with some EGFR activity
- Completed a Phase III study in NSCLC in combination with docetaxel (2009)
- Ret activity demonstrated after start of Phase I by collaborator (2002)
- Clinical studies in thyroid cancer started in 2004

- FDA approval in medullary thyroid cancer granted in 2011

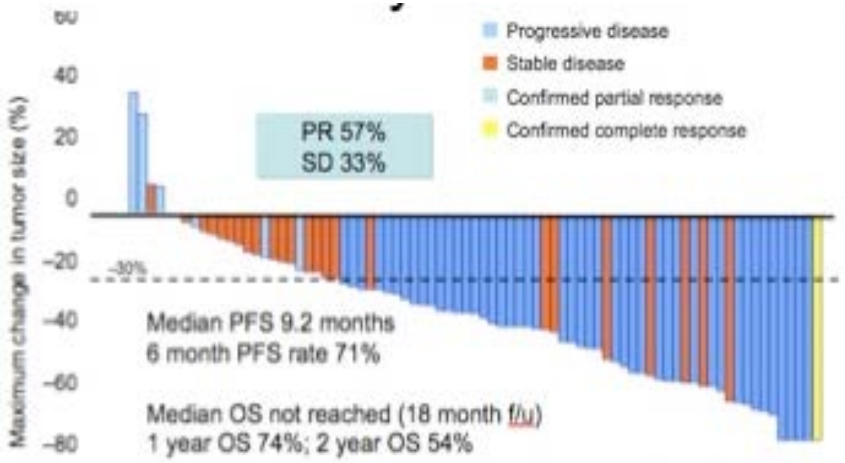


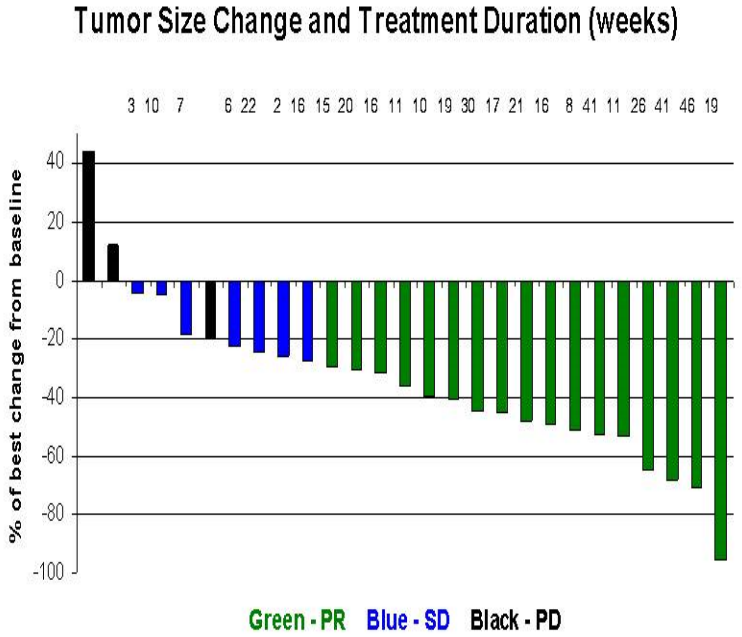
But, ultimately, selectivity is important - Crizotinib v PF-06463922



Issues with Crizotinib

- **Weak activity against other mutant forms of ALK**
- **Limited brain penetration**
- **Response rate 'only' 57%**
- **Limited duration of response (~7 months)**
- **>60% patients suffer visual impairment**
- **~0.4% incidence of fatal liver failure**

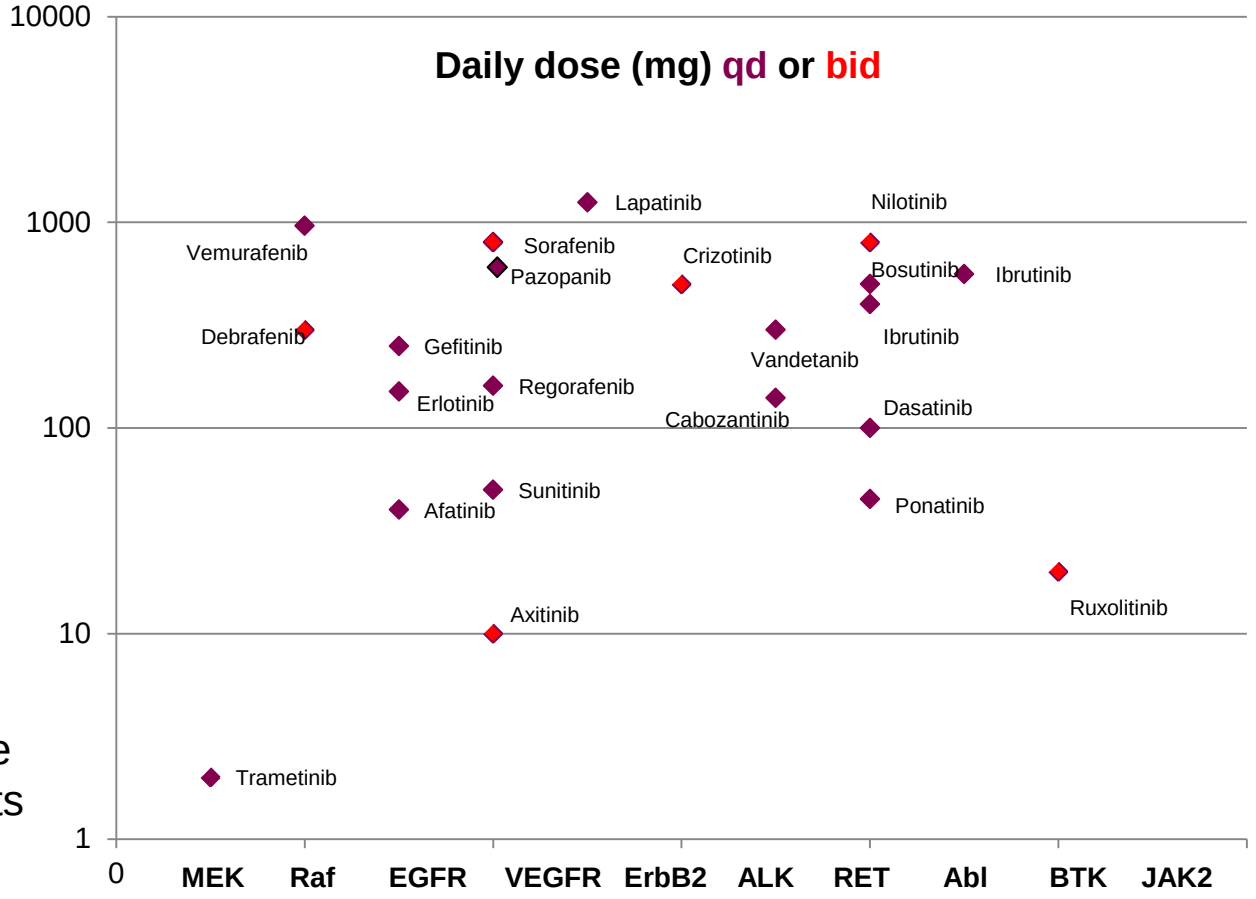




Dose and Schedule
- Monotherapy still dominates

- With exception of Lapatinib, kinase inhibitors typically dosed as continuous monotherapy
- Three quarters of compounds given once daily (qd)
- Median daily dose is 275 mg/day although this is lower for recently approved compounds

Lapatanib – 1250mg qd dose delivered as 5 x 250mg tablets



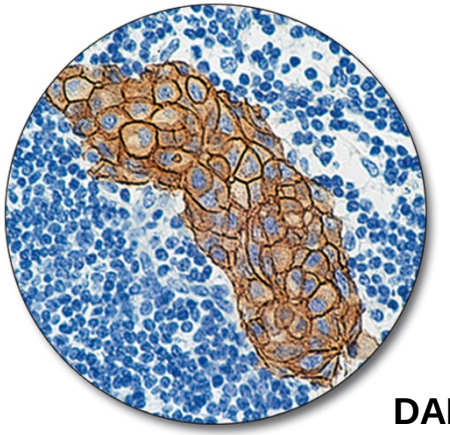
Tolerability of kinase inhibitors

- Better than cytotoxics but not clean...

- In a study of 34 patients on Sorafenib and Sunitinib :
  - 10 patients (34%) had stabilization of disease, 8 patients (28%) had a partial response, and 11 patients (38%) had progression of disease
  - Grade 3 or 4 adverse event occurred in 19 patients (56%)
  - 8 patients (24%) required drug discontinuation and 11 patients (32%) required dose reductions, but were able to resume the targeted dose
- Toxicity due to both lack of selectivity and role of kinases in normal physiology
- 11 of 26 FDA-approved kinase inhibitors carry black box warnings :

Drug	Sponsor	Target	Black box warning(s)	FDA AD
Trastuzumab	Genentech	HER2	Pulmonary toxicity, cardiomyopathy and a confusion warning	25/09/1998
Bevacizumab	Genentech	VEGF	GI perforation, haemorrhage and wound healing complications	26/02/2004
Sunitinib	Pfizer	VEGFR, PDGFR	Hepatotoxicity	26/01/2006
Panitumumab	Amgen	EGFR	Dermatologic reactions and infusion reactions	10/10/2006
Lapatinib	GlaxoSmithKline	ErbB2	Hepatotoxicity	13/03/2007
Nilotinib	Novartis	Bcr-Abl	QT interval prolongation and electrolyte anomalies	29/10/2007
Pazopanib	GlaxoSmithKline	VEGFR, PDGFR, c-KIT	Hepatotoxicity	19/10/2009
Vandetanib	AstraZeneca	VEGFR, EGFR, RET, BRK	QT interval prolongation	21/04/2011
Regorafenib	Bayer	RET, VEGFR, PDGFR	Hepatotoxicity	27/09/2012
Cabozantinib	Exelixis	RET, c-Met, VEGFR	GI haemorrhage, perforation and fistula	29/11/2012
Ponatinib	ARIAD	Bcr-Abl, PDGFR, FGFR, ...	Liver failure, blood clots and hepatotoxicity	14/12/2012

Patient selection strategies - Diagnostic Development



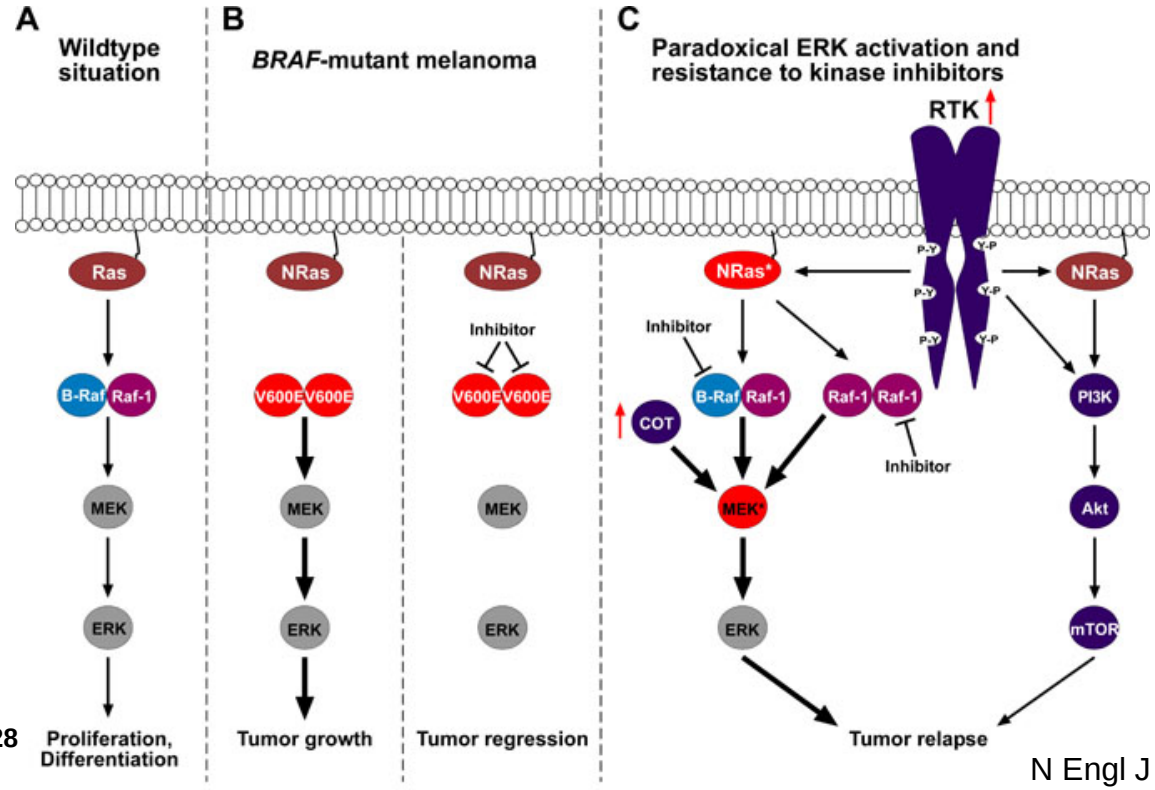
DAKO Herceptest

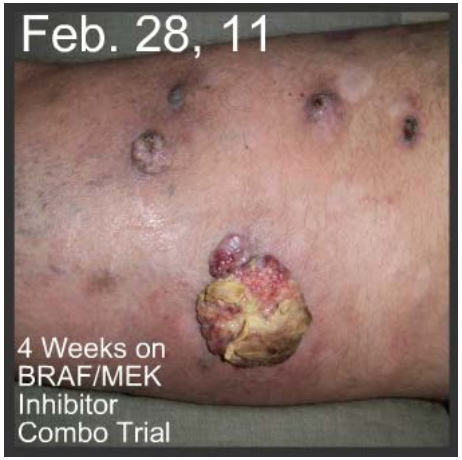
- 18 (of19) FDA-approved companion diagnostics for oncology are for kinase targets, of which 10 are for Her2
- Imatinib uses Philadelphia chromosome status (Ph+)
- Numbers of diagnostics set to increase rapidly

FDA	Device Trade Name	Product	Target	Device Manufacturer
1	*therascreen* KRAS RGQ PCR Kit	Cetuximab	Kras (EGFR-wt)	Qiagen Manchester, Ltd.
2	DAKO EGFR PharmDx Kit	Cetuximab, Panitumumab	EGFR	Dako North America, Inc.
4	therascreen EGFR RGQ PCR Kit	Afatinib	EGFR	Qiagen Manchester, Ltd.
5	DAKO C-KIT PharmDx	Imatinib	c-Kit	Dako North America, Inc.
6	INFORM HER-2/NEU	Trastuzumab	Her2	Ventana Medical Systems, Inc.
7	PATHVYSION HER-2 DNA Probe Kit	Trastuzumab	Her2	Abbott Molecular Inc.
8	PATHWAY ANTI-HER-2/NEU (4B5) Rabbit Monoclonal Primary Antibody	Trastuzumab	Her2	Ventana Medical Systems, Inc.
9	INSITE HER-2/NEU KIT	Trastuzumab	Her2	Biogenex Laboratories, Inc.
10	SPOT-LIGHT HER2 CISH Kit	Trastuzumab	Her2	Life Technologies, Inc.
11	Bond Oracle Her2 IHC System	Trastuzumab	Her2	Leica Biosystems
12	HER2 CISH PharmDx Kit	Trastuzumab	Her2	Dako Denmark A/S
13	INFORM HER2 DUAL ISH DNA Probe Cocktail	Trastuzumab	Her2	Ventana Medical Systems, Inc.
14	HERCEPTEST	Trastuzumab, Pertuzumab	Her2	Dako Denmark A/S
15	HER2 FISH PharmDx Kit	Trastuzumab, Pertuzumab	Her2	Dako Denmark A/S
16	THxID™ BRAF Kit	Trametinib, Debrafenib	Braf	bioMérieux Inc.
17	cobas EGFR Mutation Test	Erlotinib	EGFR	Roche Molecular Systems, Inc.
18	VYSIS ALK Break Apart FISH Probe Kit	Crizotinib	EML4-ALK	Abbott Molecular Inc.
19	COBAS 4800 BRAF V600 Mutation Test	Vemurafenib	Braf	Roche Molecular Systems, Inc.

Rational combinations need clean drugs - Braf-MEK combination

- Comparison of Trametinib + Debrafenib v Debrafenib
- Median PFS for the combination was 9.4 months, as compared with 5.8 months for Debrafenib (HR = 0.39)
- 0.25 to 0.62; P<0.001)
- The rate of CR/PR was 76%, (54% for monotherapy)





N Engl J Med 2012; 367:1694-1703

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- **Future directions**

How do we define ‘next generation’ inhibitors - Clinical benefit beyond first generation

- **Greater inhibition of primary pharmacology / target**
  - Inadequate inhibition of primary target typically limits efficacy (e.g. Crizotinib)
  - Lack of potency means many compounds have high dose and poor PK (e.g. Lapatanib)
  - Precise mechanism of action still unclear in some patients (e.g. Sorafenib)

- **Inhibition of adaptive response / acquired resistance**
  - Critical to target resistant clonal forms of kinases (e.g. Bcr-Abl)
  - Greater separation of activity – wild type v mutant (e.g. Gefitinib, Erlotinib)
  - Ability to combine is critical for optimal pathway inhibition (e.g. MEK + Braf)

- **Avoidance of off-target pharmacology / toxicity**
  - Estimated that at least 2/3rds of approved kinase inhibitors have doses limited by off target activity
  - Significant clinical burden associated with ‘black box’ warnings (e.g. Nilotinib)
  - Polypharmacology is typically unhelpful as we move to greater focus on personalized healthcare

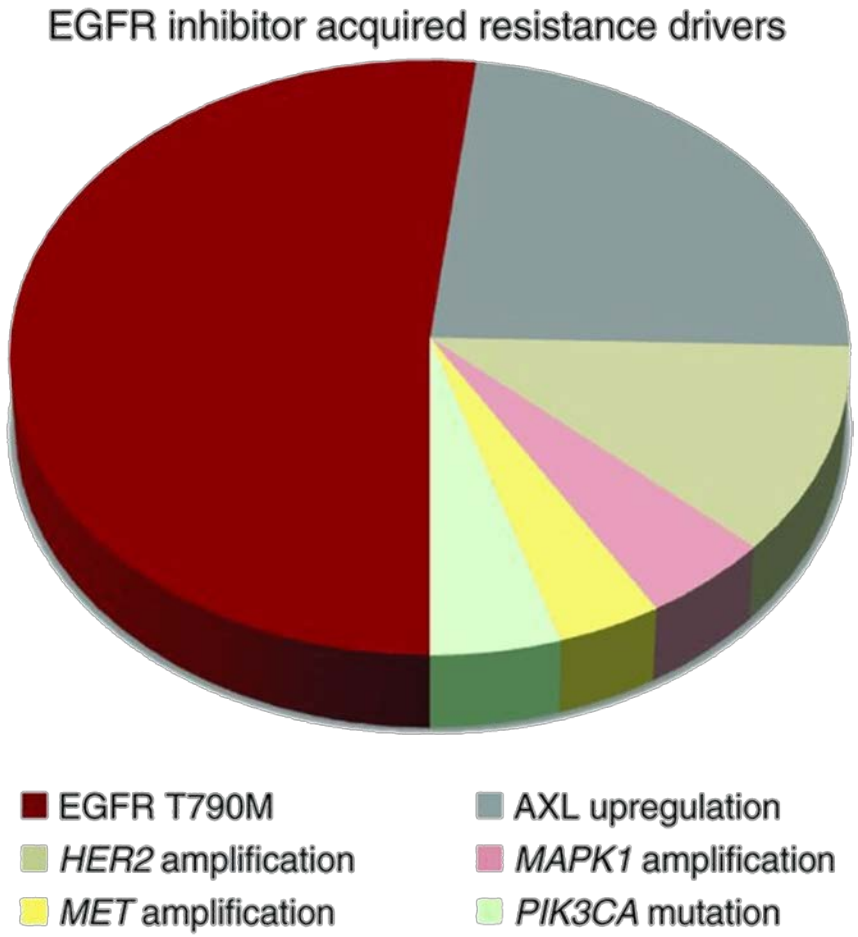
- **Optimised dose / schedule / combinations**
  - For many targets, continuous dosing is non ideal (e.g. AKT)
  - For targets with narrow therapeutic margin, non-oral dosing routes may be desirable (e.g. VEGFR, Aurora)
  - Polypharmacology of first generation inhibitors makes drug combinations unfeasible

Mutant kinases

- EGFR : post Gefitinib or Erlotinib

- Median time on Erlotinib or Gefitinib is around 10 months
- Afatinib (irreversible) claims to increase this by 2 months but toxicity is greater
- In contrast to Imatinib, T790M is the dominant resistant clone
- Activation of other RTKS (cMet, her2) also important resistance mechanisms
- Transformation to Small Cell Lung Cancer (or squamous histology)is reported, but incompletely understood

- Only about 4% of patients have <u>detectable</u> T790M at first biopsy



cMet and T790M in second line EGFRm NSCLC - Data is immature but suggest 16-21% cMet +ve

Table 4. T790M and MET detection in clinical reports

First author	Paitents' no.	Samples' no. pre[a]	Samples' no. post[b]	MET pre	T790M pre	MET post	T790M post	T790M+MET
Onitsuka T (6)	10 TKI-resistant	8	10	0	0	0	7	0
Chen HJ (12)	29 resistant	9	29	NA	0	5	14	2
	53TKI-naive	53	NA	2	NA	NA	NA	NA
Turke AB (13)	27 TKI-resistant	16	27	NA	0	4	15	2
Costa DB (16)	18 resistant	0	7	0	0	0	6	0
Bean J (19)	43 resistant	0	43	0	0	9	20	4
	62TKI-naïve	62	NA	2	NA	NA	NA	NA
Jiang SX (20)	6	6	6	Not done	0	1	3	0
Engelman JA (30)	18 resistant	8	18	0	0	4	NA	1

[a]Numbers of samples before the TKI therapy using for T790M detection; [b]Numbers of samples after the TKI therapy using for T790M detection.

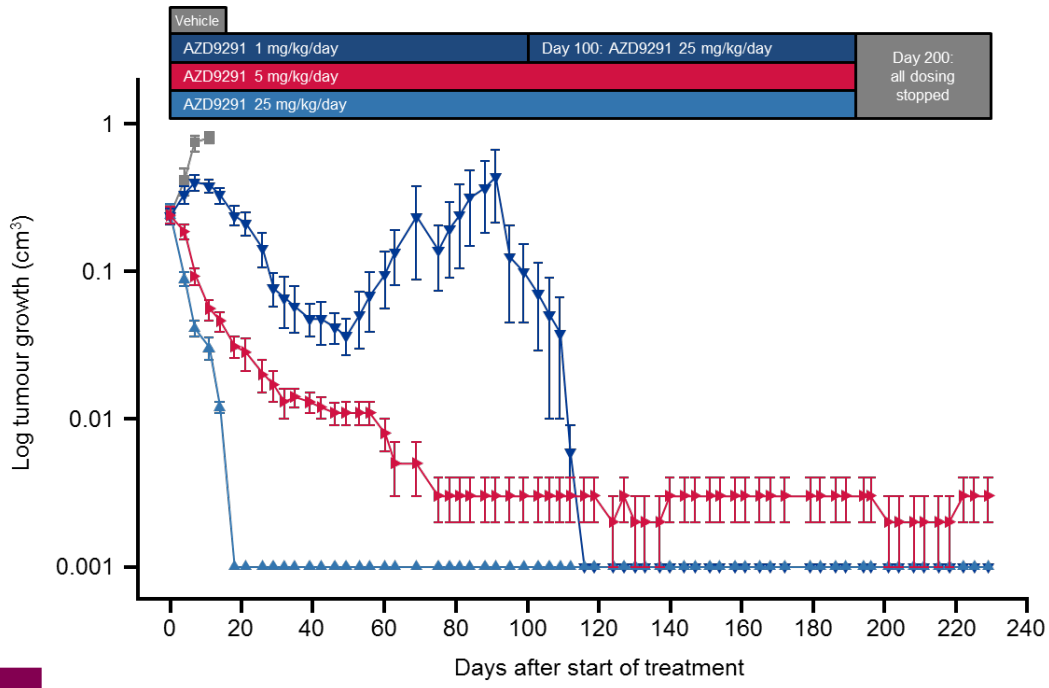
- Adding all data suggests 23 / 140 patients are cMet +ve (16%)
- Largest single data source (Bean) suggests 9 / 43 are cMet +ve (21%)
- Of these approximately 40% are also T790M +ve

In vivo activity of AZD9291

- Data from ASCO 2014 Meeting

- AZD9291 is a potent oral, irreversible inhibitor of *EGFR* that contains EGFR-TKI-sensitising (*EGFR*+) and resistance mutations (T790M)
- Good potency and high selectivity demonstrated in enzymatic and cellular *in vitro* assays[1]

Updated long-term dosing of H1975 (L858R/T790M) xenograft with indicated doses of AZD9291



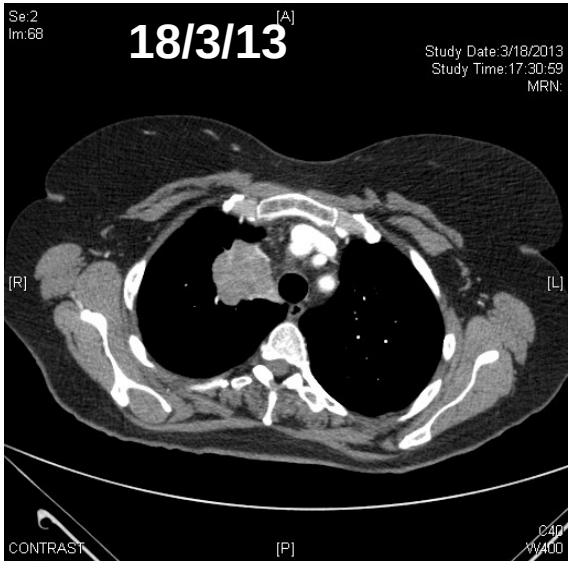
Model	Wild-type LoVo cells	*EGFR*+ PC9 cells	*EGFR*+/ T790M H1975 cells
AZD9291 phospho-EGFR IC_{50} nM	480	17	15

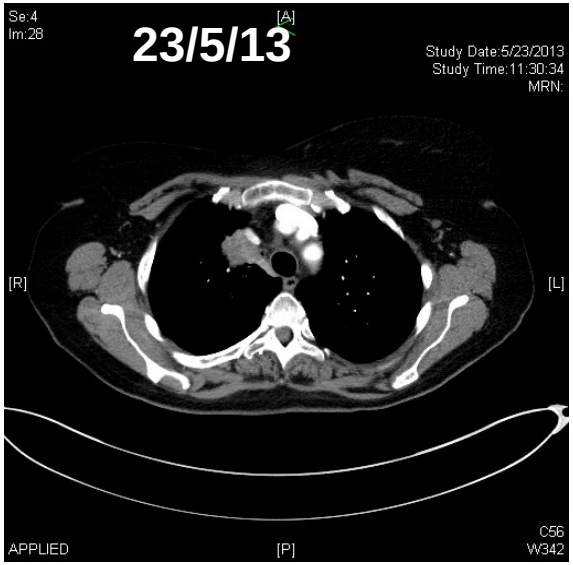
- **Profound regression in EGFR-mutant tumour models, showing sustainable complete macroscopic tumour response out to at least 200 days**

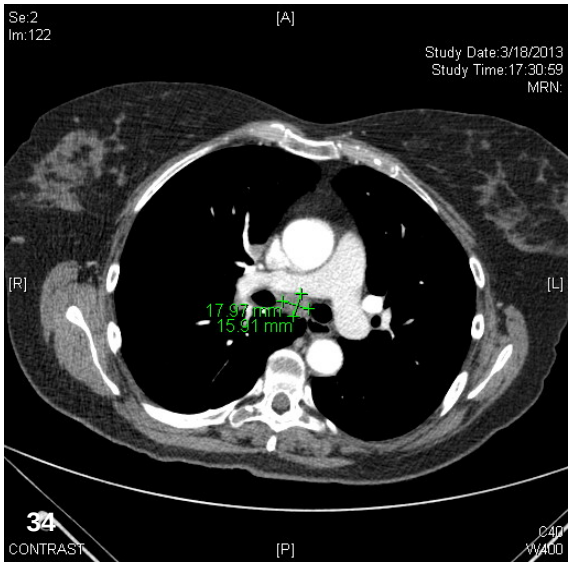
Cross et al. Abstract A109, AACR-EORTC-NCI conference, Boston, 2013

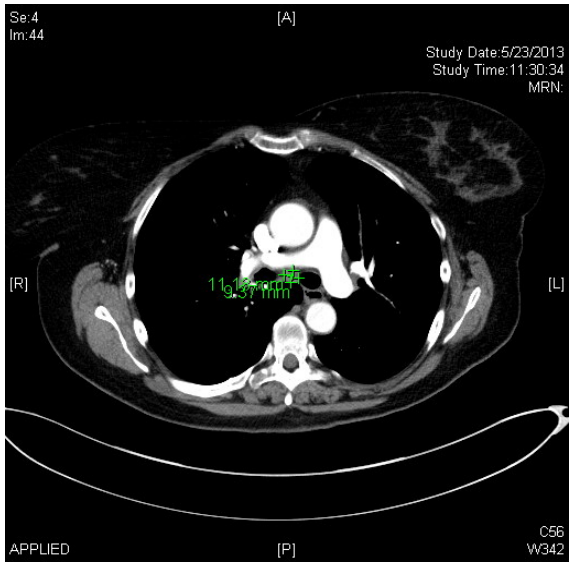
PR # 2 (Cohort 1, 20mg qd)

- Data from ASCO 2014 Meeting



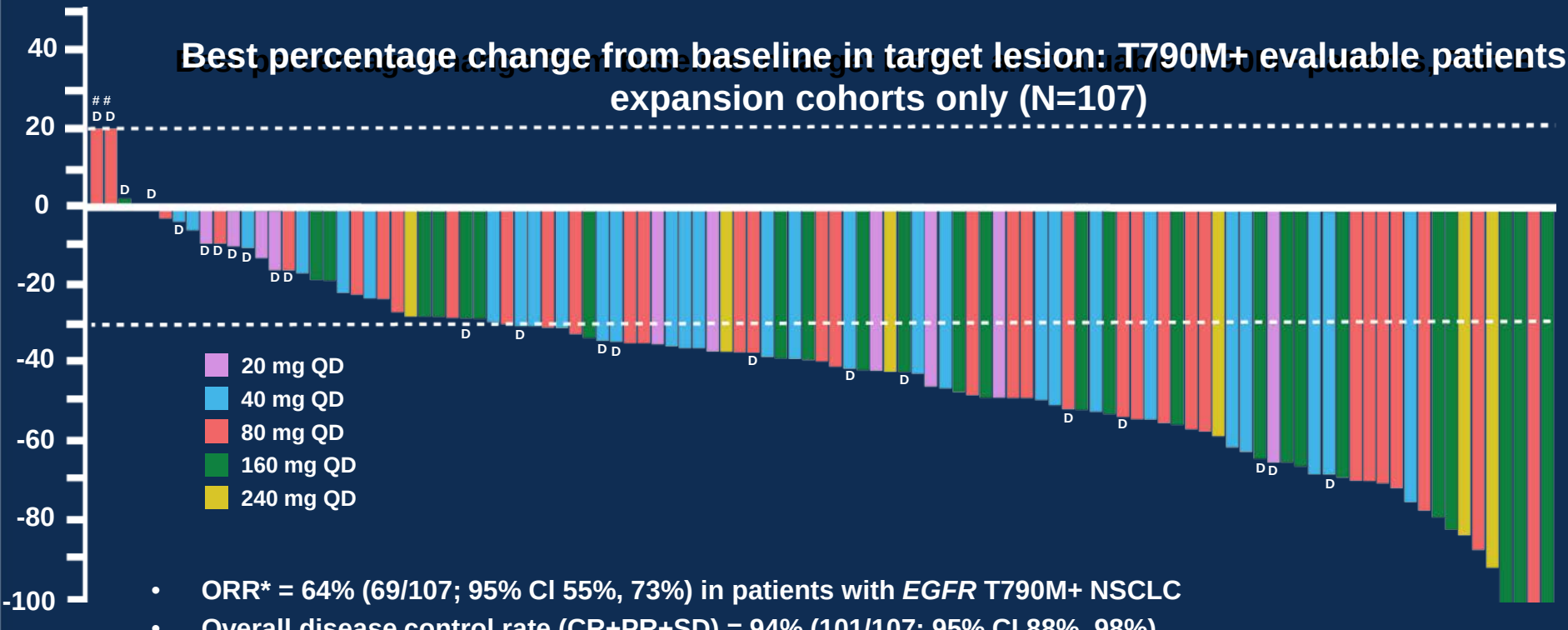






- F/57, NSCLC stage IV, diagnosed in December 2010
- EGFR sensitising mutation: deletion in exon 19 and T790M mutation
- Life long non-smoker
- Diagnosed Dec 2010 with stage 4 Adenocarcinoma, Exon 19 deletion and T790M mutation
- 1st line gefitinib Jan12 to Mar 13
- Initial partial response with eventual PD through gefitinib
- AZD9291 20mg/day, C0 D1 April 8th 13, C1D1 Apr 15th 13
- Well tolerated-G1 diarrhoea
- PR at cycle 2 assessment (**38% improvement**)

Response rate* in T790M+ (central test)

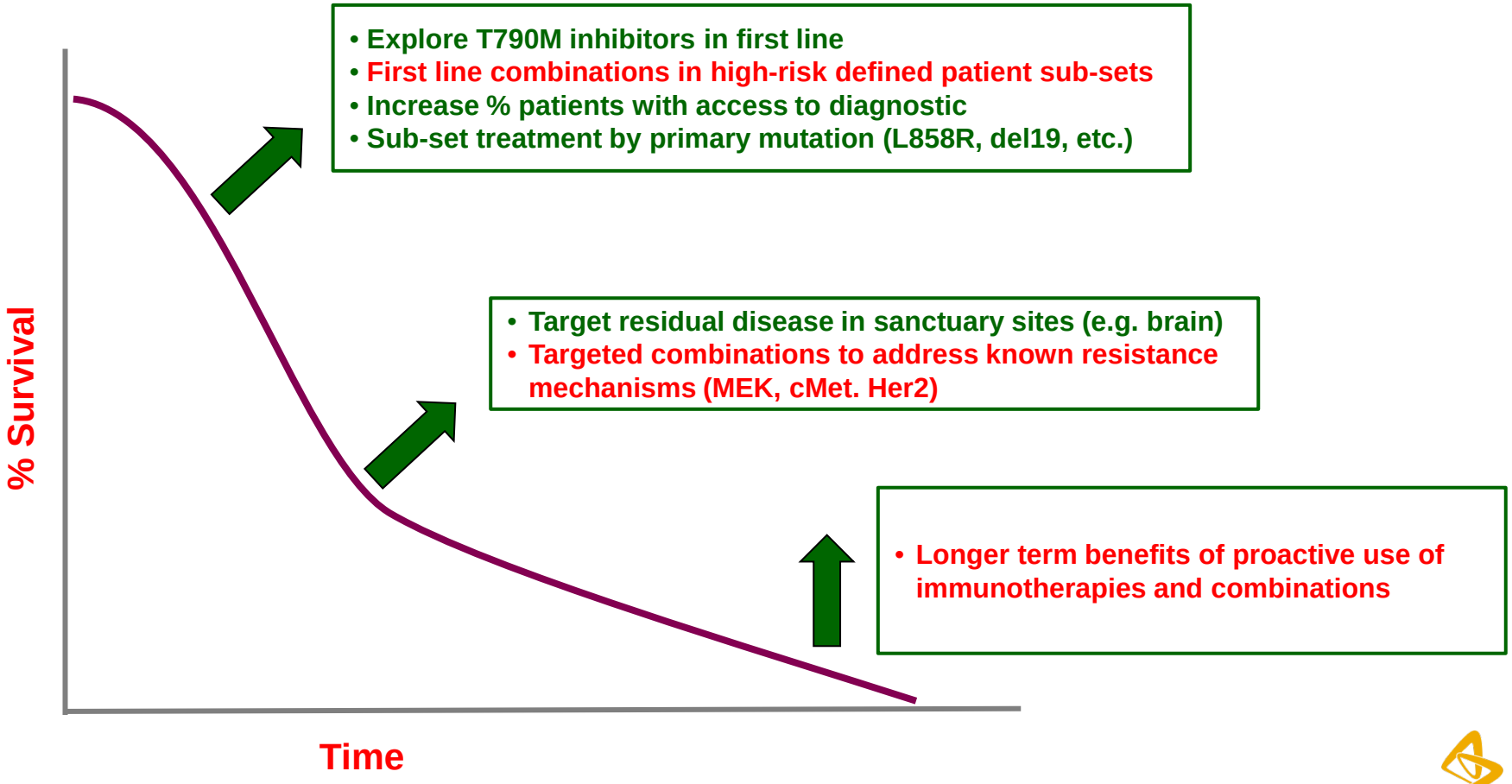


- ORR* = 64% (69/107; 95% CI 55%, 73%) in patients with *EGFR* T790M+ NSCLC
- Overall disease control rate (CR+PR+SD) = 94% (101/107; 95% CI 88%, 98%)

	20 mg	40 mg	80 mg	160 mg	240 mg
N (107)	10	29	34	28	6
ORR	50%	62%	68%	64%	83%

*Includes confirmed responses and responses awaiting confirmation; #represents imputed values
Population: all dosed centrally confirmed T790M+ patients with a baseline RECIST assessment and an evaluable response (CR/PR, SD, or PD), N=107 (from 120 T790M+ patients; 13 patients with a current non-evaluable response are not included). D, discontinued; QD, once daily

Further opportunities in EGFRmut lung cancer - Multiple ways to improve longer term survival



AZD6094 is a potent and selective Met inhibitor

In vitro activity of HMPL-504	IC_{50} (nM)
Biochemical activity	
c-Met WT	4
c-Met M1268T	1
c-Met D1246N	1666
Inhibition on cellular p-Met	
H441 (constitutive)	4
H1993 (c-Met amp., constitutive)	6
H69 (HGF stimulated)	2
Inhibition on HGF dependent cellular functions	
H441 Proliferation	6
H441 Migration	20
MDCK scattering	<12
Anti-angiogenesis activity	
HGF dependent proliferation, HUVEC	5
HGF dependent tube formation, HUVEC	12
HGF stimulated VEGF secretion, H441	25

- Volitinib is a highly potent inhibitor of c-MET with an IC50 of 4 nM
- >650 fold selectivity demonstrated vs 265 other kinases
- Variable activity observed against c-Met mutant enzyme isoforms
- Volitinib has good oral bioavailability in rat and dog, with a relatively short half life (1-3 hrs)

AZD6094 exhibits potent growth inhibition in vitro of MET amplified or HGF-driven, high Met protein over-expressing cell lines

Tumour Type	Cell Line	cMet Status	IC_{50} (nM) MTT
Gastric	SNU-5	Amp	3
	Hs746T	Amp	5
	MKN-45	Amp	4
	SNU-16	Low Exp	>30000
	NUGC-4	Low Exp	>30000
	N87	Mod Exp	>30000
Lung	EBC-1	Amp	2
	H1993	Amp	10
	H441	High Exp (KRAS G12V)	>30000
	H69	High Exp	>30000
	H1975	High Exp (EGFR T790M)	>30000
Glioblastoma	U87MG	High Exp High HGF	>30000 sensitive in vivo

Competitor activity

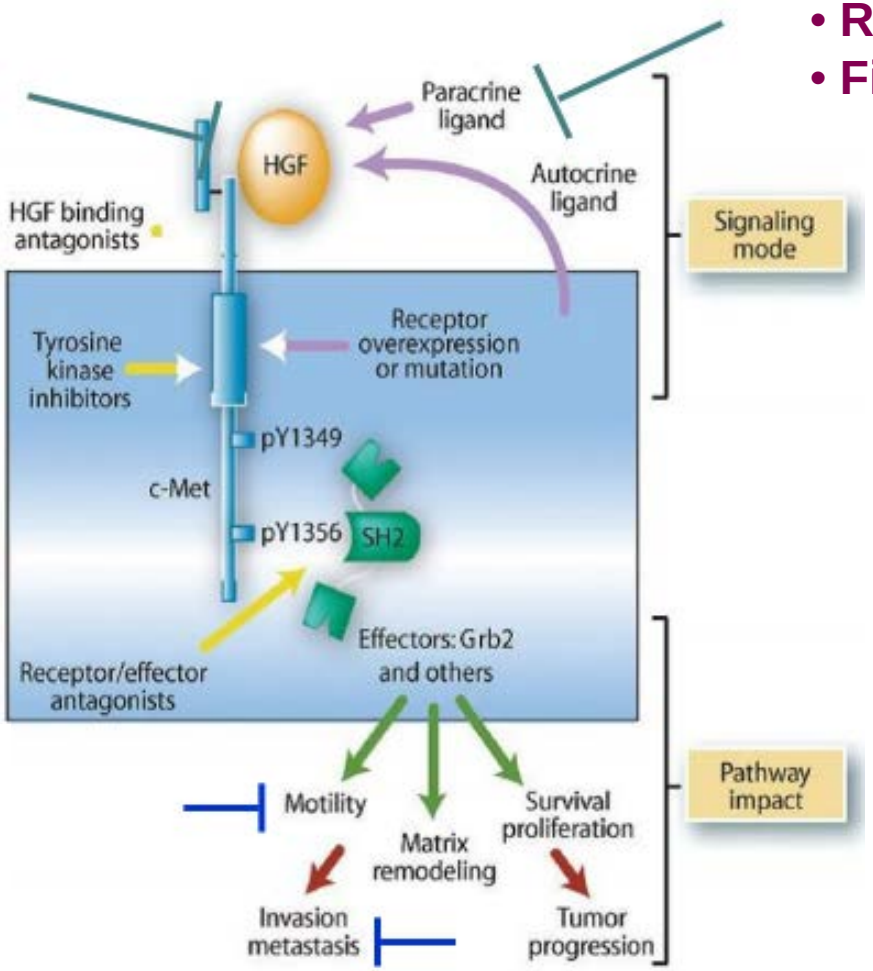
- MET Pathway inhibitors

Anti-MET mABs
- Onartuzumab
- LY2875358

Anti-HGF mABs
- Rilotumumab
- Ficlatuzumab

Selective TKIs
- Volitinib
- AMG337
- EMD1214063
- INC280

Non-selective TKIs
- Crizotinib
- Cabozantinib
- E7050
- LY2801653



Activity of Investigational "Met pathway" - Agents in RCC and PRCC

TABLE 1. Phases I and II Studies Investigating HGF/c-Met Blockade in RCC

Drug	MOA	Trial	n/Dosing	PR	PFS, mo	OS, mo
Rilotumumab[58] (AMG102)	Fully human monoclonal, neutralizing antibody to HGF/SF	Phase II, All histologies	61	1.6%		
			10 mg/kg	2.5%	3.7	14.9
			20 mg/kg	0%	2.0	17.6
Foretinib[59] (XL-880)	Multi–tyrosine kinase inhibitor: c-Met, VEGFR2, AXL, Flt-3, KIT, PDFGR, Tie-2	Phase II, papillary	74	13.5%	9.3	NR
			240 mg 5 of 14 d		11.6	
			80 mg daily		9.1	
Tivantinib[60,61] (ARQ197)	Selective, non-ATP competitive inhibitor of c-Met	Phase I solid tumors		0%		
		10 RCC	10–360 mg twice daily			
		Phase II MiT* tumors	6 tRCC	0%	1.9	15
Cabozantinib[62] (XL-184)	Multi–tyrosine kinase inhibitor: c-Met, VEGFR2, AXL, Flt-3, KIT, PDFGR, KIT, RET	Phase I		28%	14.7	NR
		25 Clear cell	140 mg → 60 mg			

MOA indicates mechanism of action; PR, partial response; NR, not reached; MiT, microphthalmia-associated tumor.

Harshman and Choueiri, 2013

- **Some activity (13.5% ORR) in PRCC for Foretinib (non-selective TKI)**
- **Minimal activity noted for mABs**

Key Points of Differentiation - versus non-selective TKIs

1. **AZD6094** is selective for c-Met over 265 kinases by >650 fold and has shown cellular activity in only cMet amplified cell lines (4, from a Sanger panel of 268 cell lines)
2. **Crizotinib** (c-Met, Alk, Ros, Tie2, TrkA, TrkB) and **Cabozantinib** (Met, VEGFR2, Ret, Kit, Axl,Tie2, Flt3) “off-target” activities likely to limit ability to achieve high exposures and maximally target c-Met
   - Preclinically, Crizotinib must be dosed at 50mg/kg to achieve efficacy results (stasis in c-Met-amp Gastric Cancer models) equivalent to **AZD6094** at 1-2.5 mk/kg.
   - Clinically, **AZD6094**(600mg QD) achieves exposures significantly in excess of those achieved by Crizotinib (250 mg BD) (3000 ng.hr/ml), with some overlapping toxicities (e.g. nausea/vomiting) but not others (Crizotinib: vision, QTc, pneumonitis) that may result from “off-targets”
   - Crizotinib has 45 trials completed or ongoing (including a trial recruiting Type 1 PRCC patients), yet has only 1 reported response in a c-Met-driven patient (NSCLC; c-Met-amp)[5]

Future Directions
- Predictions for 2020...

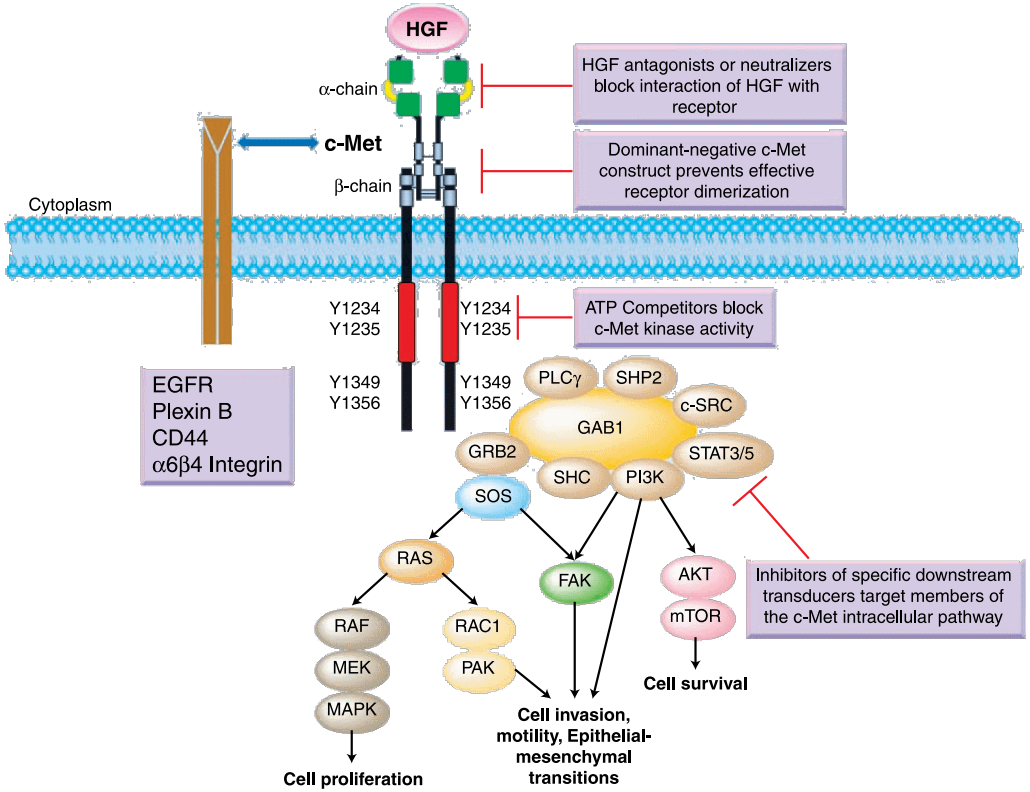
- Rational combinations of kinase inhibitors – Braf / MEK will not be unique
- More effective combinations with non-chemotherapy backbone treatments
- More sophisticated scheduling to maximise pathway inhibition

- Other protein kinases will have approved inhibitors, e.g.
  - CDK4/6, CDK9, PLK1, Aurora A/B,
  - Wee1, Chk1/2, ATR,
  - IRAK4, AKT
- Lipid kinase inhibitors will be approved (e.g. PI3Kα, PI3Kδ...)
- Increasing use of non-ATP competitive inhibition strategies

- Patients will stay on therapy longer due to improved efficacy in resistant clones
- Patient selection will use Next Generation Sequencing (NGS) and will be provide longitudinal data
- Disease monitoring will routinely use blood borne markers (e.g. cfDNA)

Met and AZD6094 (HMPL-504/volitinib)

Background of HGF/c-Met signalling pathway



- Aberrant HGF/Met pathway activation leads to uncontrolled tumour 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

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

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Met activation detected in many tumour types representing major unmet medical needs and commercial opportunity

Tumour	Gene Amplification	Over Expression	Mutations
Lung	1-4%	67%	8%
EGFR TKI-resist NSCLC	15-20%		
Stomach	10%	40%	1%
Colorectal	1-2%	65%	
EGFR-resistant mCRC	18%		
Esophagus	4%	92%	
Kidney (clear cell)		79%	13%
Kidney (PRCC)	40-75%		100% (HPRCC)
Brain	2%	74-88%	

Emerging, strong clinical evidence seen amongst multiple tumour types with gene amplification by Met inhibitors, including AZD6094

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A safe Met inhibitor that can completely cover the target might be needed to address tumours with overexpression

Tumour	Gene Amplification	Over Expression	Mutations
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Brain	2%	74-88%	

Clinical efficacy on the broader market potential in Met overexpression is less clear

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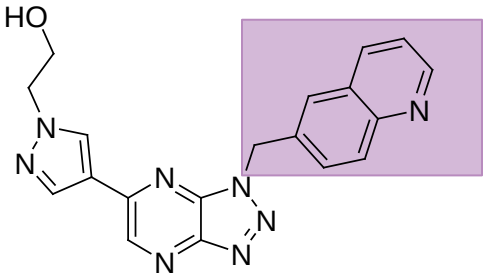
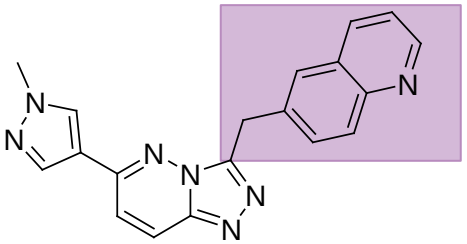
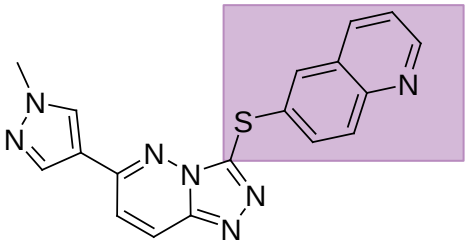
AZD6094 (volitinib) is designed to minimize potential for renal toxicity



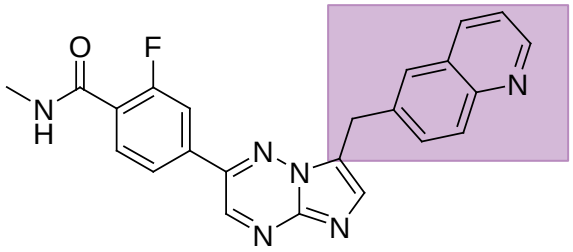
Pfizer



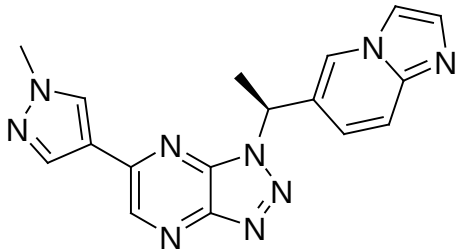
JNJ

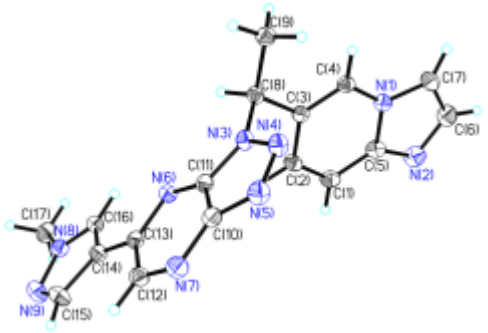


SGX/Lilly



Incyte





AZD6094

J. Med. Chem. dx.doi.org/10.1021/jm500510f

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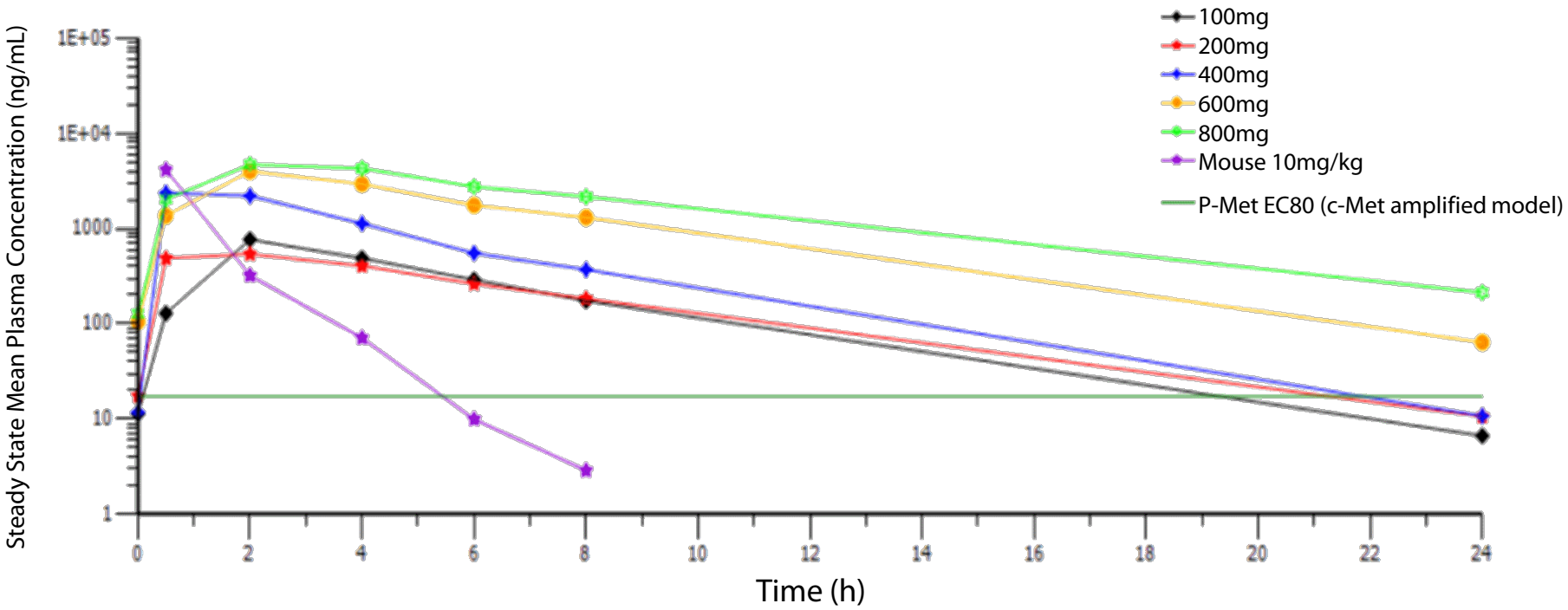
AZD6094 is capable of providing complete target inhibition over 24 hours

Mean Steady State Plasma Concentration vs. Time



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AZD6094 clinical strategy

- **Aggressively pursue gene amplification indications**
- **Explore overexpression via monotherapy and in combinations**

Tumour	Gene Amplification	Over Expression	Mutations
Lung	1-4%	67%	8%
EGFR TKI-resist NSCLC	15-20%		
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AZD6094 clinical update

- **Phase I Australia & China trials completed**
  - Phase II doses QD and BID identified
- **Met gene amplification studies started so far**
  - Phase II papillary renal cell carcinoma (PRCC) initiated in May 2014
  - Phase I/II TKI-resistant NSCLC in combination with AZD9291 initiated in August 2014
- **Further gene amplification & overexpression studies imminent**
  - Phase Ib monotherapy: 3rd line gastric cancer (GC) and 3rd line non-small cell lung cancer (NSCLC)
  - Phase Ib GC docetaxel combination trial
  - Exploratory studies planned in multiple indications

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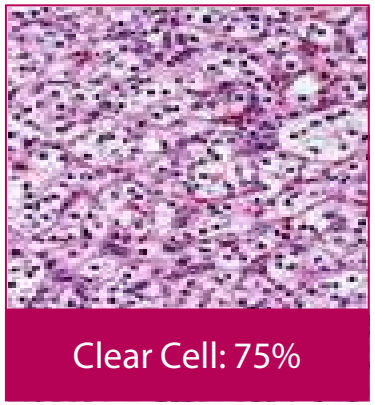
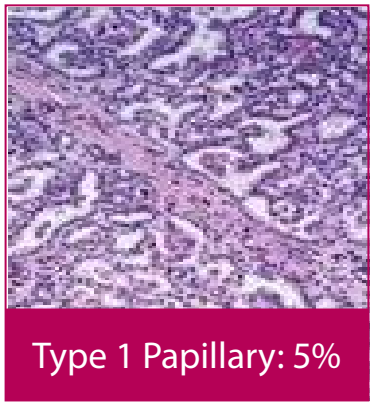
Papillary renal cell carcinoma (PRCC), AZD6094's most advanced indication

- 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 in all patients with hereditary (HPRCC) and ~10% of sporadic PRCC



Clear Cell: 75%



Type 1 Papillary: 5%

Type 2 Papillary: 10%

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Activity of Investigational "Met pathway" - Agents in RCC and PRCC

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Tivantinib (ARQ197)	Selective, non-ATP competitive inhibitor of c-Met	Phase I solid tumors 10 RCC	10-360 mg twice daily	0%		
		Phase II MiT* tumors	6 tRCC	0%	1.9	15
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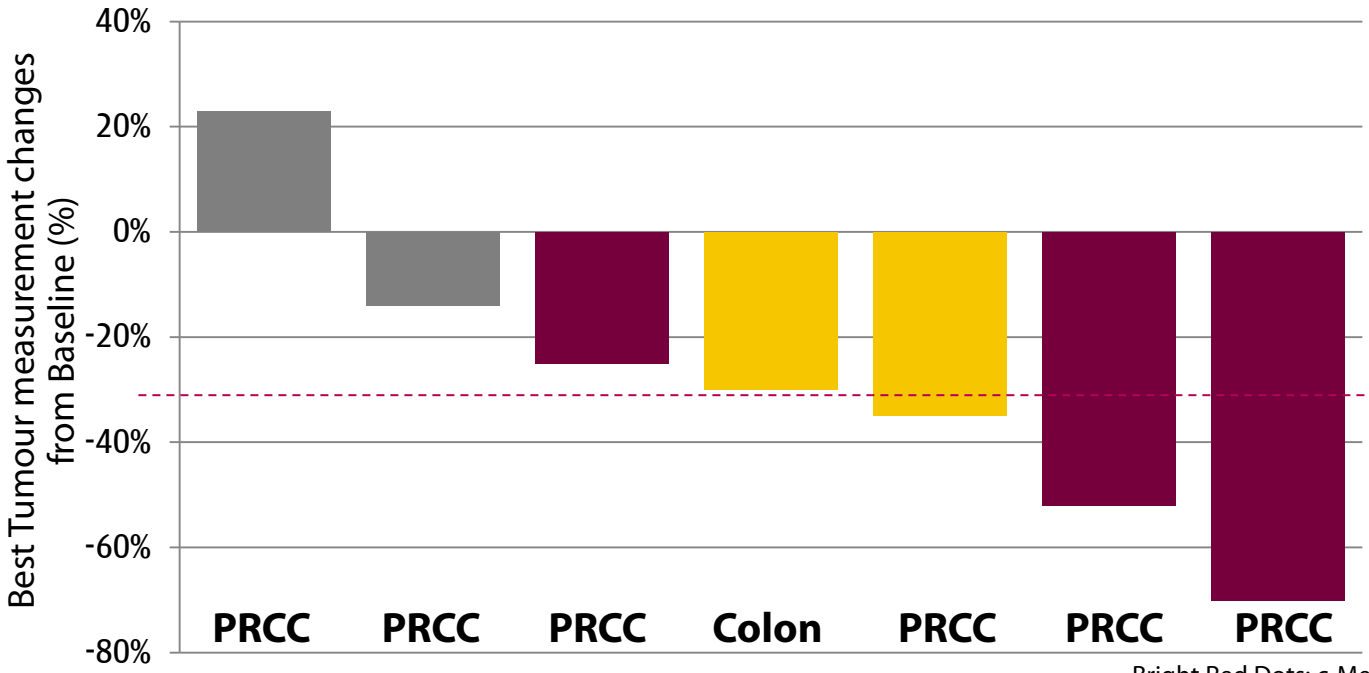
MOA indicates mechanism of action; PR, partial response; NR, not reached; MiT, microphthalmia-associated tumor.

Harshman and Choueiri, 2013

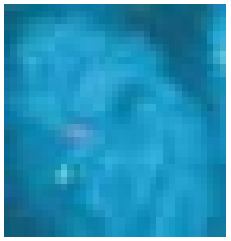
- **Some activity (13.5% ORR) in PRCC for Foretinib (non-selective TKI)**
- **Minimal activity noted for mABs**

AZD6094 Phase I data summary in 35 patients

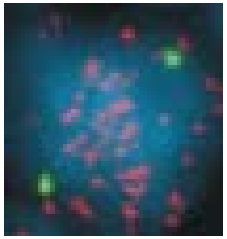
- Well tolerated, has good safety, tolerability and PK profile
- Tumour response directly correlated to level of Met amplification
- **Objective response rate of 50%** and **disease control rate of 83%** in six PRCC patients (April 2014)



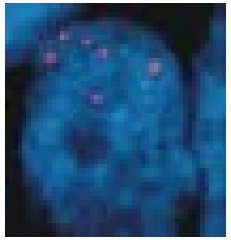
No Focal MET or Chr7 changes (no MET+)



Focal MET gene gain (MET+ in parts of tumour)



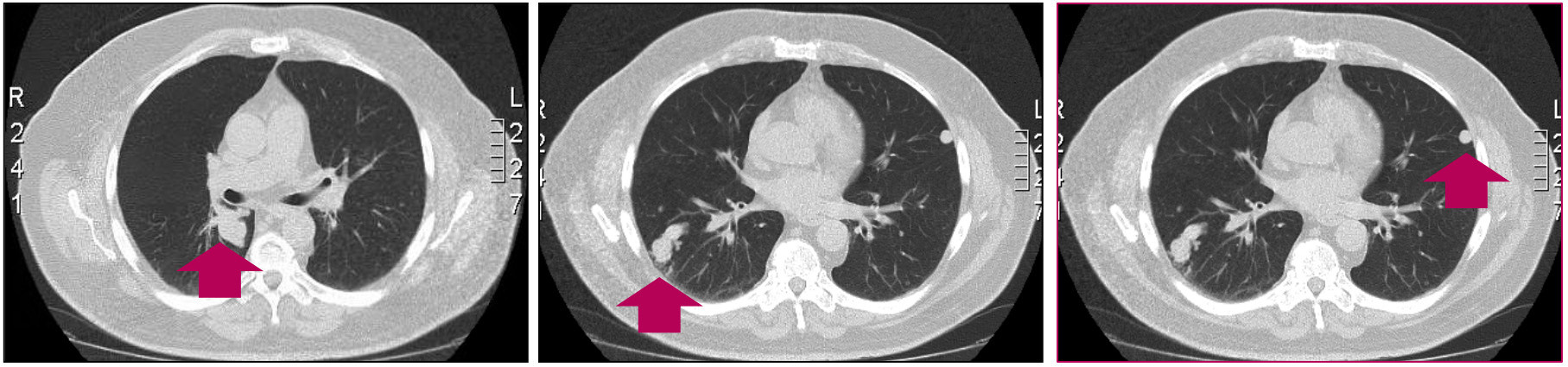
Gains in Chr7[5] (MET+ over entire tumour)

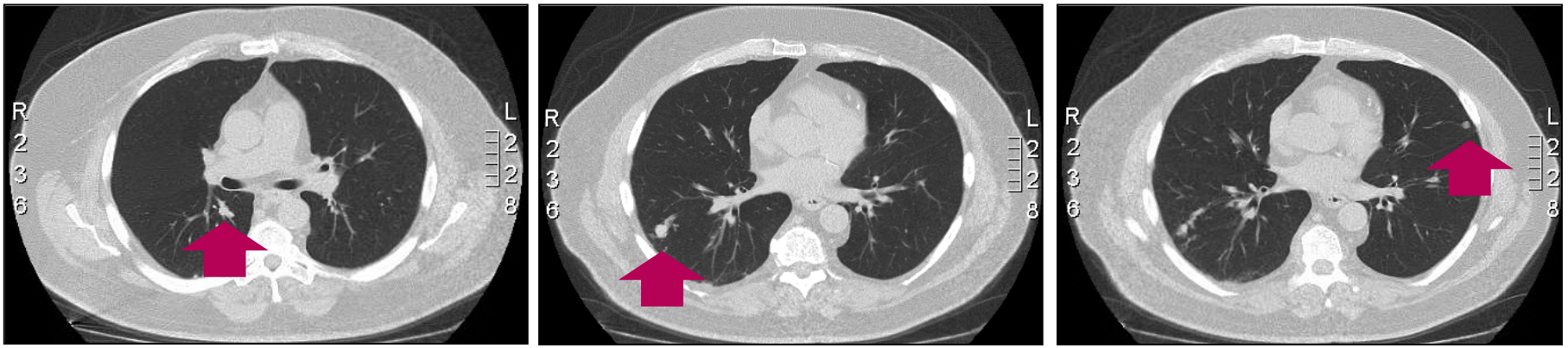


Bright Red Dots: c-Met; Fluorescent Green Dots: CEP7.

CT scans of a PRCC patient who responded to AZD6094

Baseline





After 5 months

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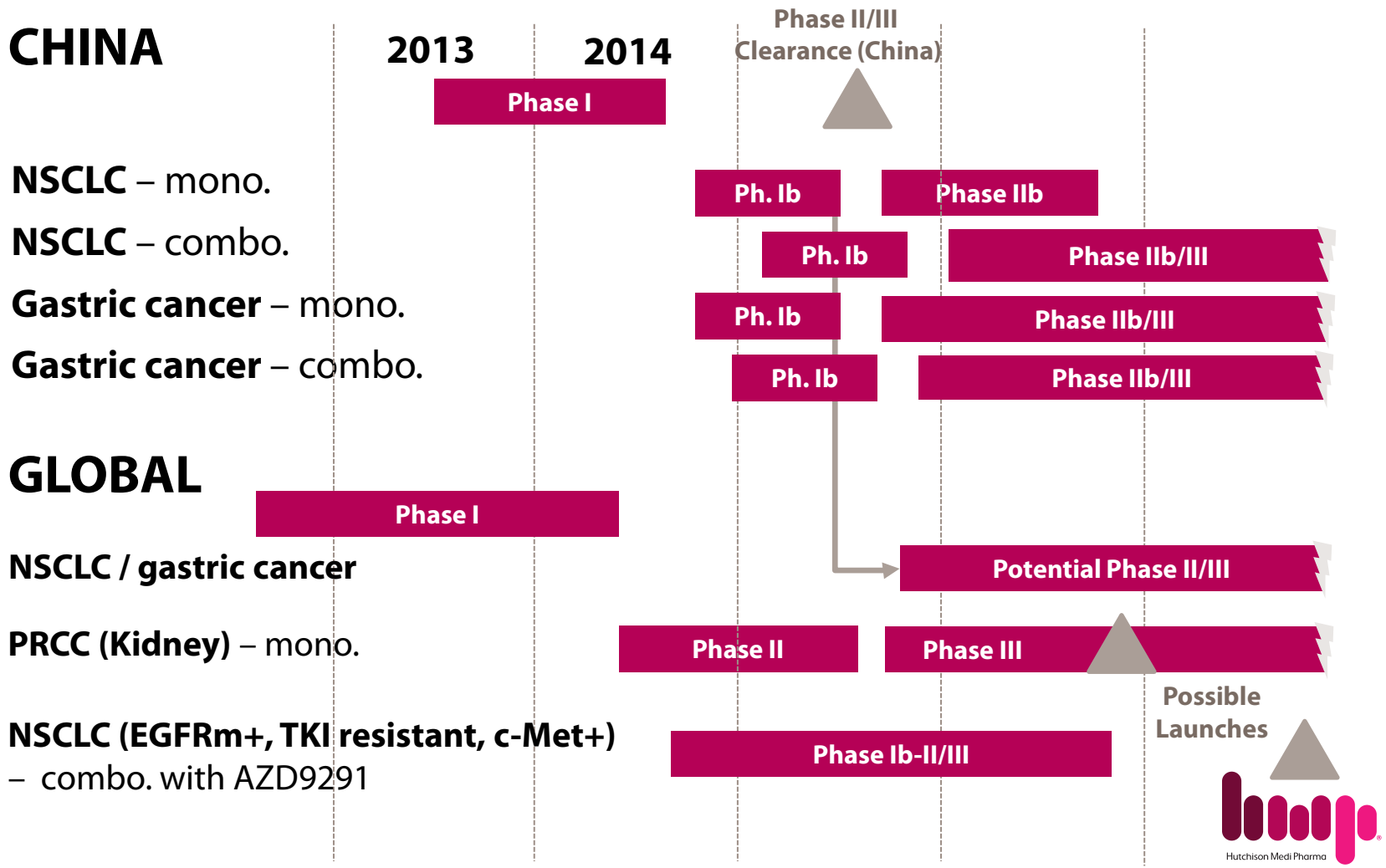
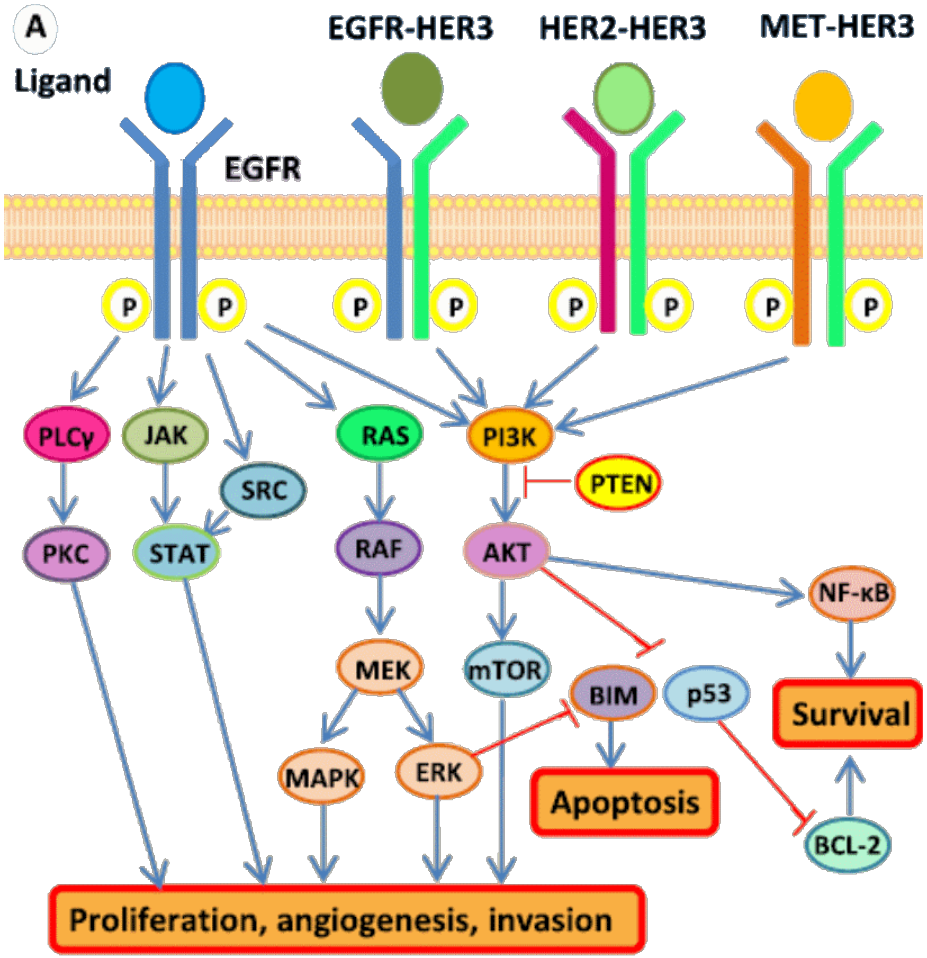
AZD6094 development plan



EGFR, epitinib and theliatinib

Epidermal growth factor receptor (EGFR) and cancer



- A transmembrane receptor involved in cell growth, survival and invasion
- There are four main mechanisms of activation:
  - Mutations
  - Gene amplification
  - EGF/EGFR protein over expression
  - Cross talk with other RTKs
- Aberrant EGFR activation present in multiple tumour types, including lung, CRC, esophagus, head and neck, breast, GBM, etc.

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EGFR activation affects multiple tumour types with many remaining unaddressed

Tumour Types	Wild type: Gene Amplification	Wild type: Over Expression	Mutations
Lung (NSCLC)		62%	**13-64% (TKIs)**
Oesophagus	8-30%	30-90%	12% (EAC)
Stomach	29%	44-52%	<5%
Colorectal (CRC)		**53% (mAbs)**	
Pancreatic		20-48% (TKI)	3-9%
Head and neck	10-30%	**66-90% (mAbs)**	42% (vIII)
Glioblastoma	36-51%	54-66%	27-54% (vIII)
Ovarian	4-22%	9-62%	4%
Breast (basal)	34%	68%	11%

- EGFRm+ lung and colorectal cancer successfully treated TKIs and mAbs, respectively
- Opportunities for EGFR therapies in many other tumours
- Currently the annual sales of TKIs and mAbs **have reached $4.7 billion**

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Epitinib and Theliatinib: two novel, differentiated EGFR TKIs targeting unmet medical needs

- **Epitinib (HMPL-813) designed for optimal brain penetration**
  - EGFRm+ NSCLC with brain metastasis
  - Glioblastoma EGFR mutations or gene amplification

- **Theliatinib (HMPL-309) designed for wild type EGFR**
  - NSCLC, oesophageal cancer, head & neck cancer with gene amplification and/or over expression

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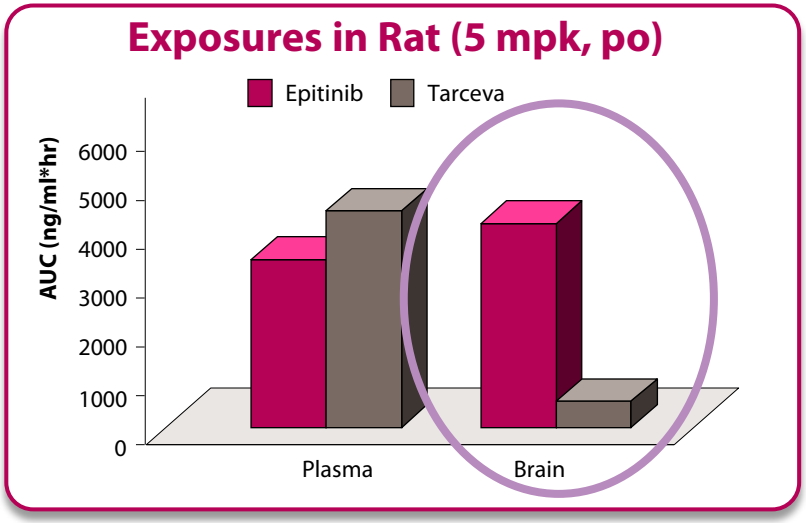
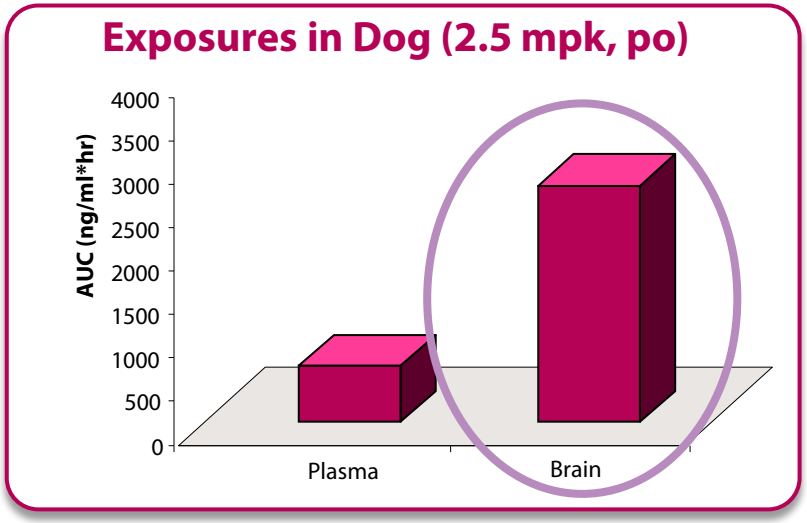
Epitinib: EGFR inhibitor optimised for brain penetration

- In China, 10% lung cancer patients with brain metastasis at initial diagnosis, 80% after 2 years
  - In addition, 30-50% GBM with EGFRvIII potentially could benefit

- Epitinib demonstrated good brain penetration in rat and dog





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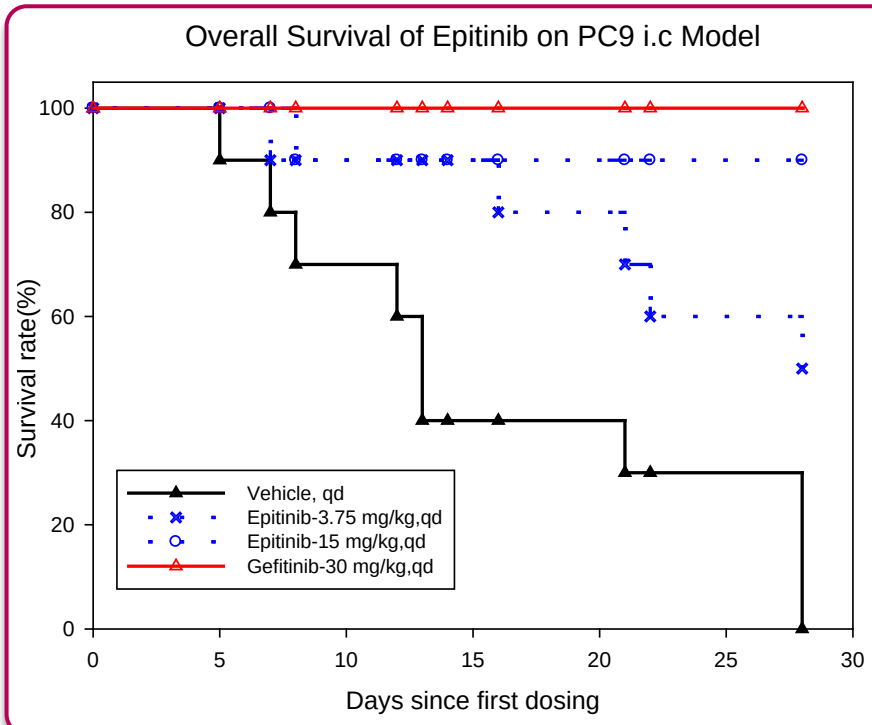
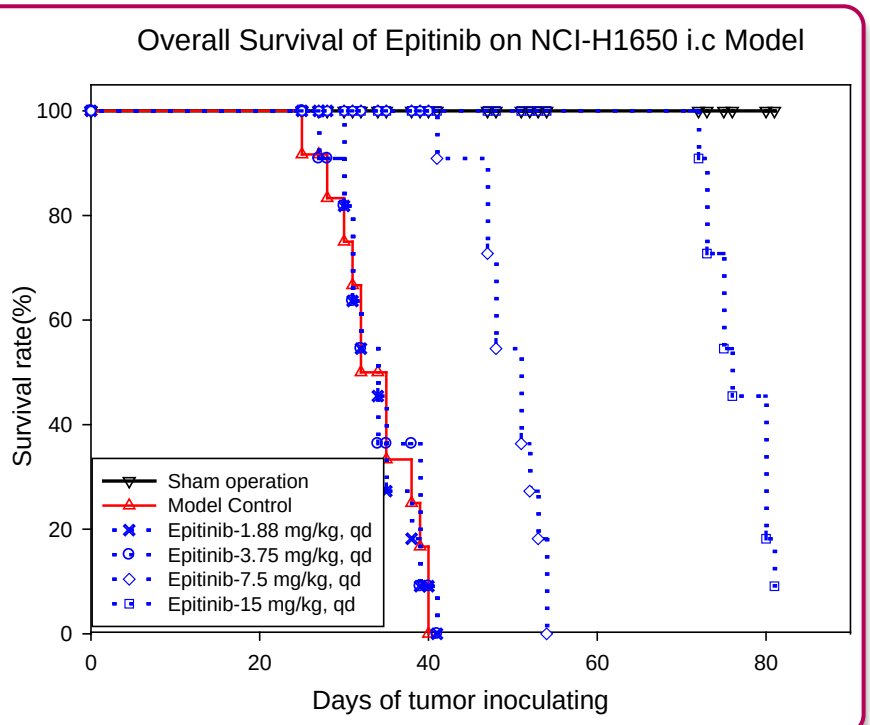
Epitinib showed better survival in mice with brain tumours

- **Clinical drug exposures far exceeds exposures in mouse at 30 mg/kg**
- EGFR mutation positive NSCLC cell lines: PC9 with PTEN wild type, H1650 with PTEN del
- High dose gefitinib (15 times the equivalent clinical dose) used as a control in PC9 study





Epitinib Phase I clinical trial status

- **Phase I dose escalation**
  - Initiated in Q4 2011
  - 35 patients with advanced solid tumours enrolled and treated in 7 dose cohorts of once daily (QD)
  - Drug exposures are already **well above expected efficacious** levels, despite MTD has not been reached

- **Phase Ib in EGFR+ NSCLC patients with brain metastasis**
  - Initiating in Q4 2014
  - Enrol ~30 patients

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Epitinib Phase I PK and safety summary

- **Good PK properties**
  - Drug exposure increasing with increased dose
  - No drug accumulation

- **Good safety profile**
  - Relatively low incidence of adverse events; well tolerated
  - Low grade skin rash common – expected as this is target-related
  - No DLT was seen in any dose level

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Targeting wild type (wt) EGFR tumours with theliatinib

- Large population and largely unmet
  - Multiple tumour types: lung, particularly lung squamous cell carcinoma, colorectal, oesophagus, head and neck, breast, etc.
  - mAbs less effective for gene amplified population
  - Frequently overlap with other targets and may require combination therapies

- A high bar, but theliatinib may have the horsepower
  - **High affinity** to wt EGFR that can better compete with ATP
  - **High drug exposures** achieved in humans that provide sustained strong target inhibition
  - **Right patient:** Clear patient selection strategy in place for NSCLC, esophageal cancer and head and neck cancer with wt EGFR activation to ensure maximum efficacy for theliatinib

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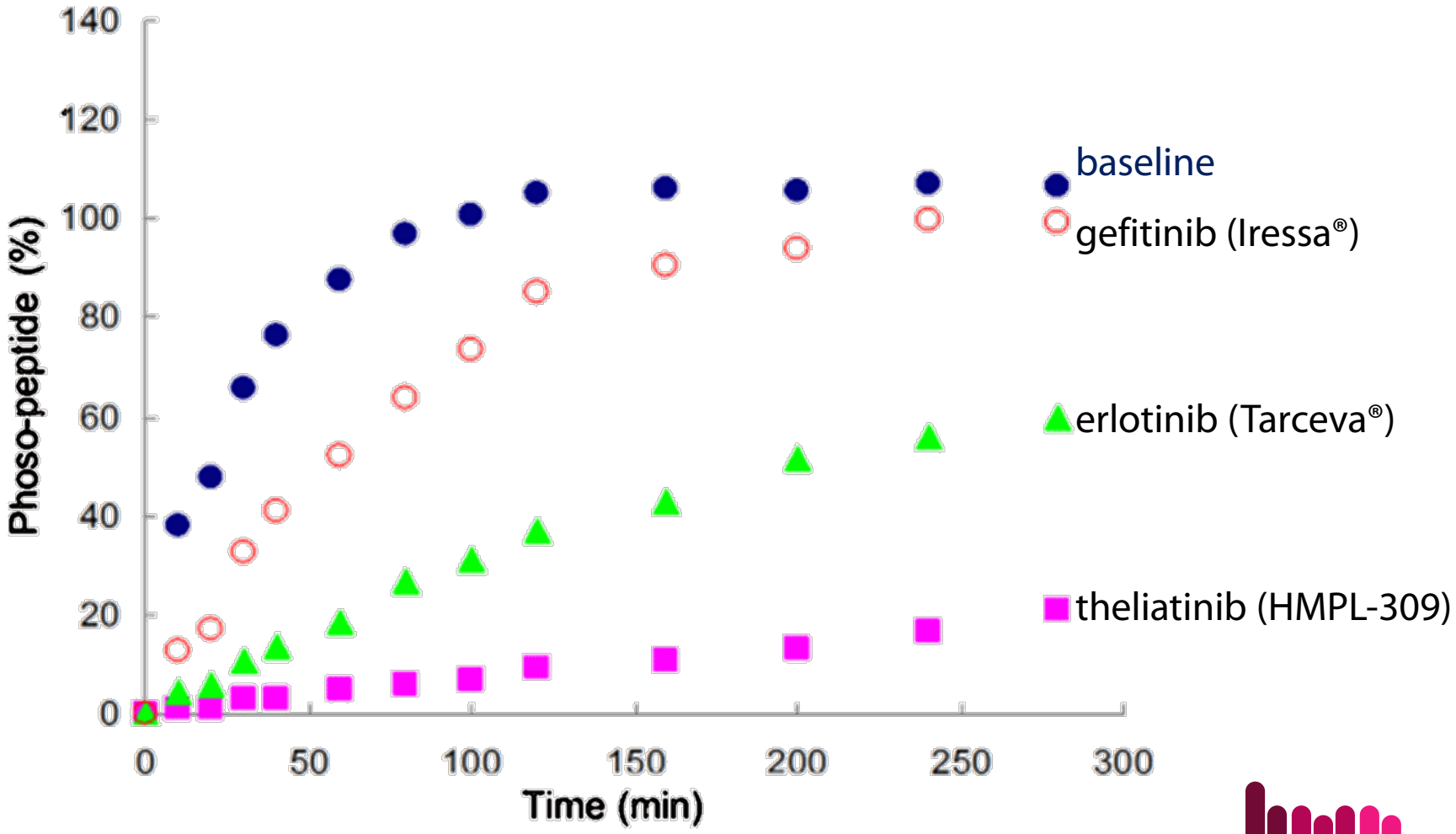
Theliatinib has highest affinity to wild type EGFR



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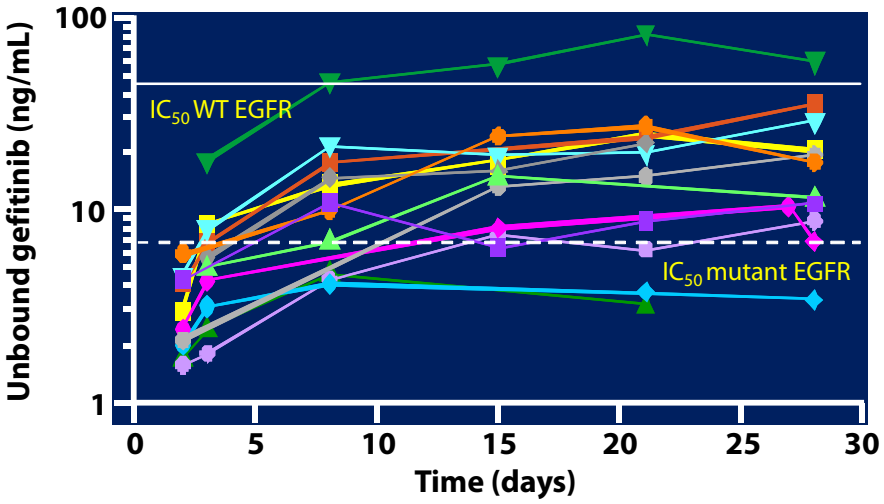
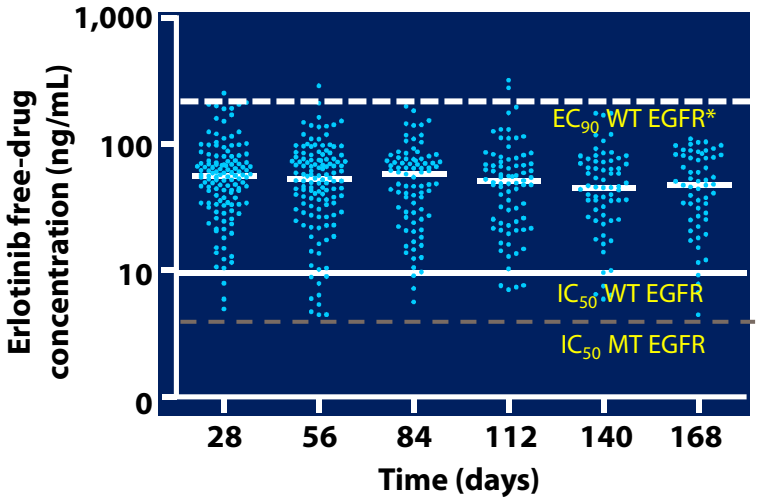
Erlotinib and gefitinib reach insufficient drug concentrations to suppress wild type EGFR effectively

Plasma concentrations versus time in 13 cancer patients, following gefitinib 250mg/day[1]



Trough plasma concentrations versus time in patients with NSCLC, following erlotinib 150mg/day (BR.21[2])



* In house data, EC90=670 ng/mL in mouse (n=2)

- In WT EGFR, complete suppression (>90%) is highly desired for tumor regression
- Neither agents seemed able to produce complete EGFR suppression at MTD

[1]Li J, et al. JNCI 2006; [2]PK data from BR.21 study and plasma protein binding study OSI-774-TILL-01; Cellular inhibition of kinase activity IC_{50} values: Carey KD, et al. Cancer Res 2006

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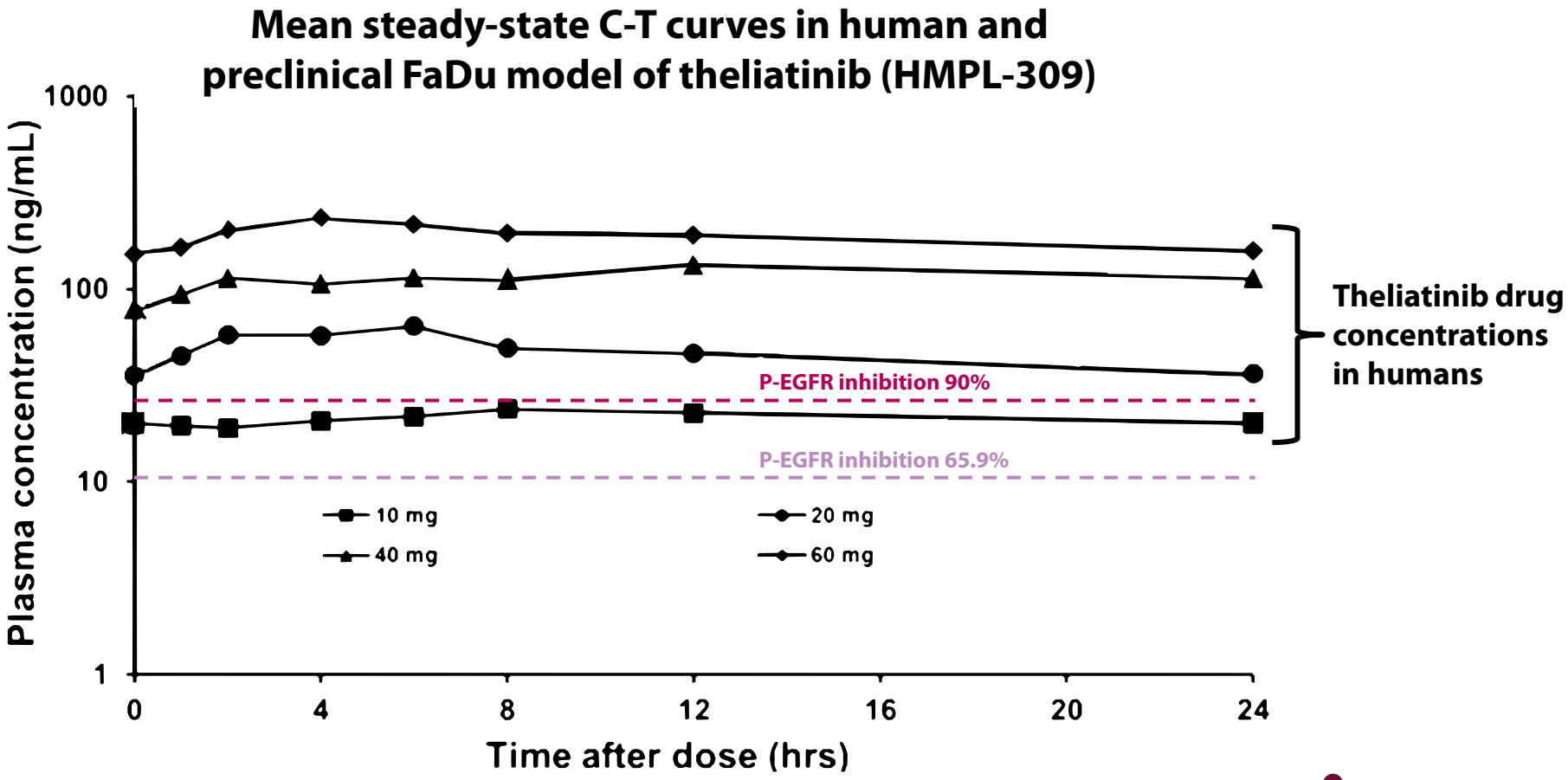
Theliatinib has already achieved drug concentrations that are effective at inhibiting wild type EGFR



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Theliatinib Phase I clinical trial progress

- **Four dose cohorts completed, fifth cohort screening ongoing**
- **Preliminary safety summary**
  - No DLT, MTD not reached
  - Safe and well tolerated
- **Good pharmacokinetic properties**
  - Drug exposure increasing with increased dose
  - No drug accumulation

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Theliatinib development next steps

- **Continue Phase I dose escalation**

- **Initiate Phase Ib/POC trials targeting tumour types with wild type EGFR activation in Q1 2015**
  - Oesophageal cancer
  - Head & neck tumour
  - Non-small cell lung cancer

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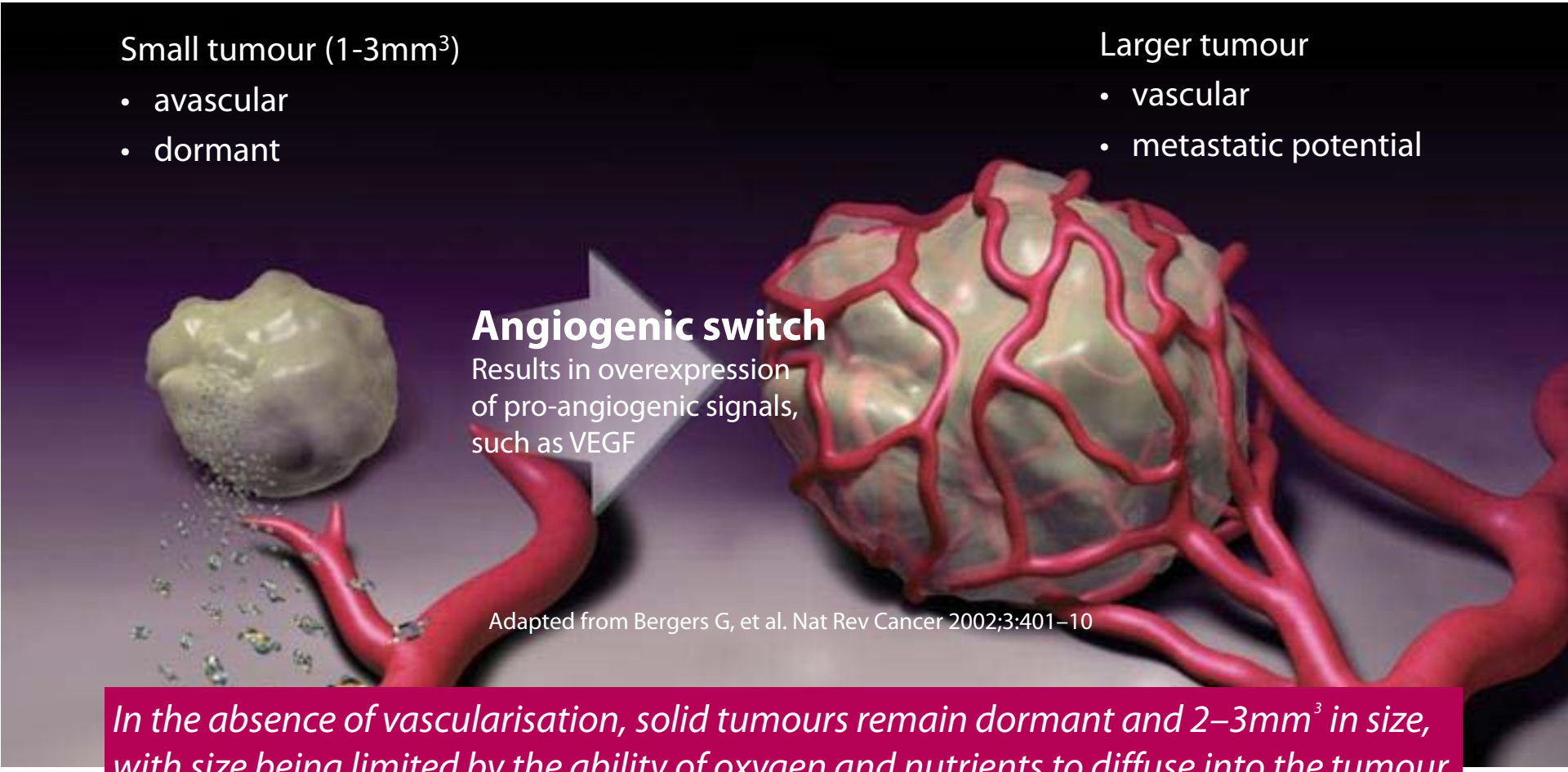
Coffee break

10 minutes

VEGFR, fruquintinib & sulfatinib

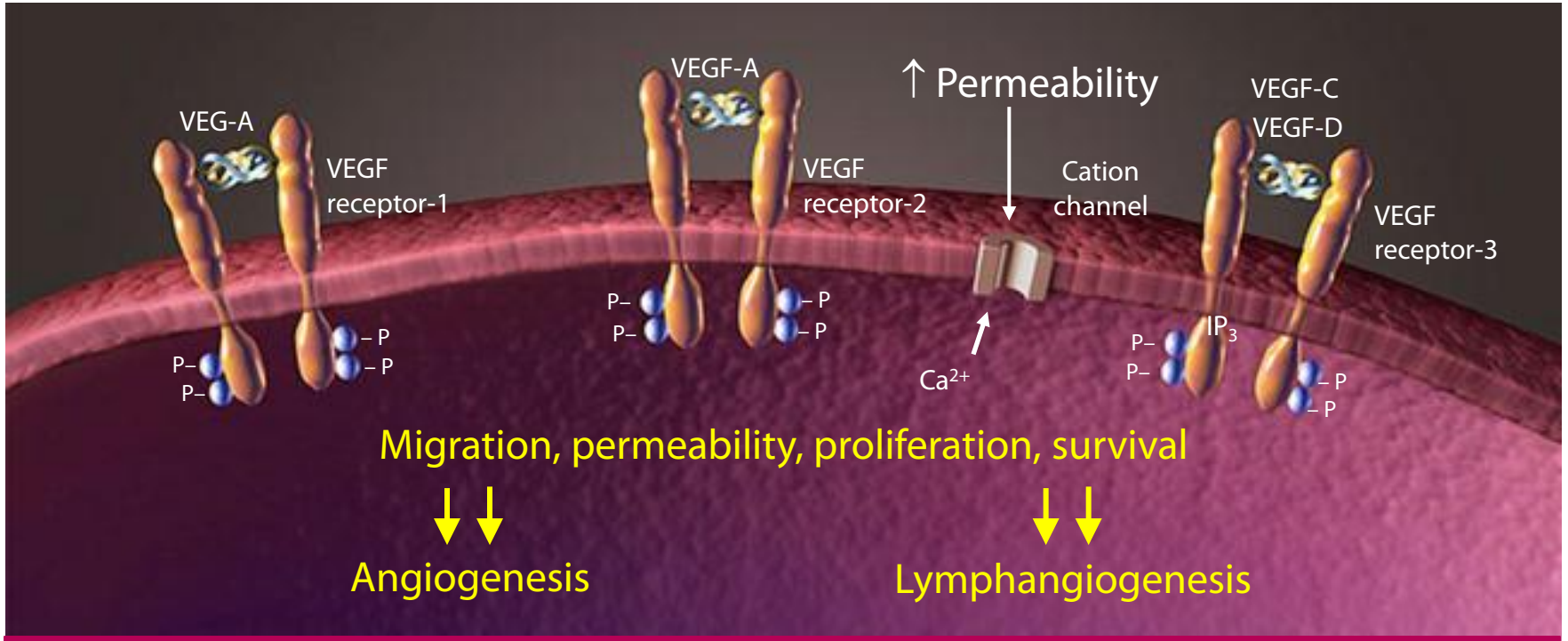
Angiogenesis and tumour growth and metastasis



In the absence of vascularisation, solid tumours remain dormant and 2–3mm³ in size, with size being limited by the ability of oxygen and nutrients to diffuse into the tumour

--J. Folkman (Nature, 1971)

VEGF/VEGFR signaling and angio/lymphangiogenesis



- VEGF, vascular endothelial growth factor, is one of the most powerful pro-angiogenic factors
- Binding of VEGF to its receptors VEGFR) on endothelial cell surface leads to angiogenesis and lymphangiogenesis

Shibuya M. Cell Struct Funct 2001;26:25–35

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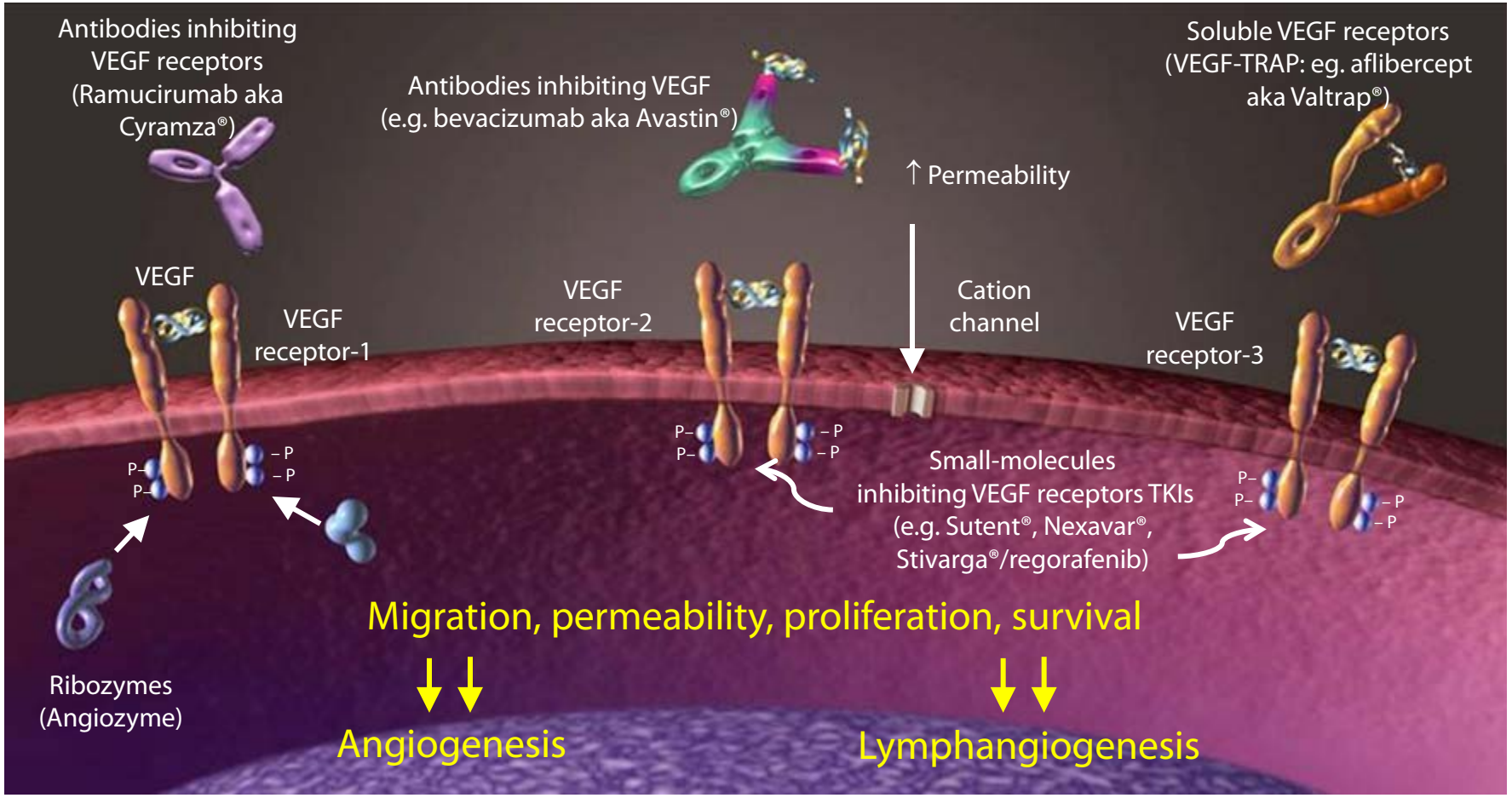
Targeting VEGF/VEGFR signaling for cancer



Collectively anti-angiogenic agents have been approved for major cancer types, such as lung, colorectal, kidney, liver, stomach, brain tumor with **annual sales of $15 billion**

Opportunities still exist for better VEGFR inhibitors

- Many newer TKIs failed in clinical trials, particularly in combination with chemos in the past mainly due to excessive toxicities
- Some progress in the past 2-4 years, including positive/encouraging results for:
  - Regorafenib in 3rd mCRC
  - Apatinib in 3rd line GC
  - Lenvantinib in 3rd line NSCLC and thyroid
  - BIBF1120 in 2nd line NSCLC in combo with docetaxel
  - Ramucirumab in 3rd gastric and 2nd line lung/CRC
- Combination with targeted therapies in exploration
  - VEGFR+c-Met (Axitinib+crizotinib) in RCC
  - VEGFR+EGFR (Avastin+erlotinib) in EGFRm+ NSCLC
  - VEGFR+PARP (Cedarinib+olaparib) in Pt-sensitive OC

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Fruquintinib and sulfatinib: two novel VEGFR inhibitors

Designed to be highly differentiated from other small molecule VEGFR tyrosine kinase inhibitors (TKIs)

- **Better kinase selectivity** to minimize "off-target" toxicities
- Capable of achieving high drug exposures to provide **sustained target inhibition** required for robust anti-angiogenic and anti-tumour activity

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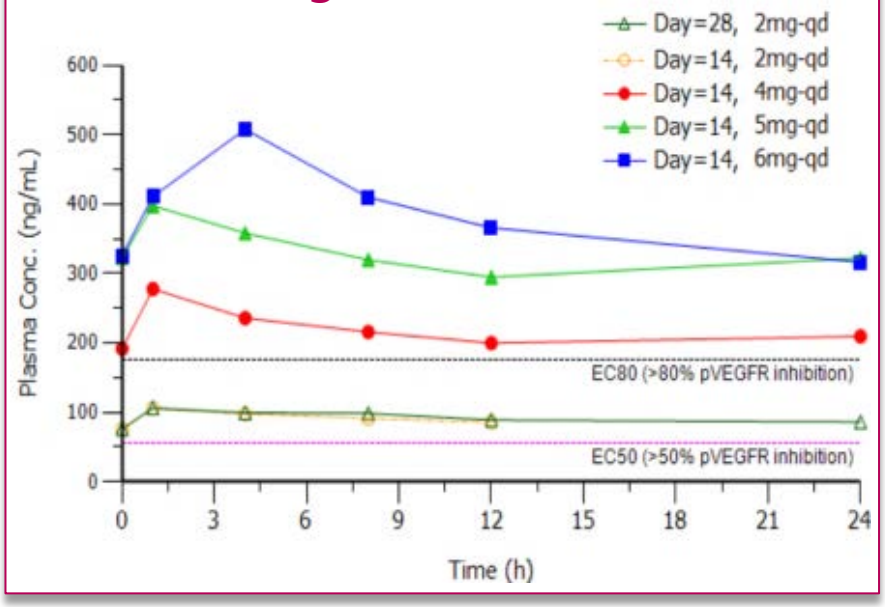
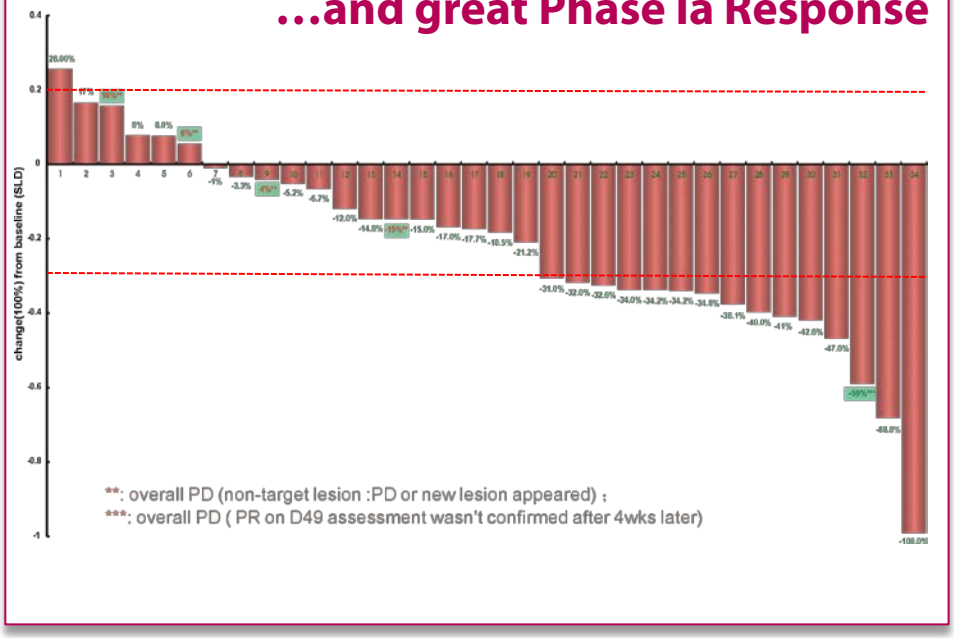
Fruquintinib: a potent, highly selective VEGFR inhibitor

- **Sustained target inhibition** and **strong Phase I clinical efficacy** results in **multiple tumour types**, such as CRC, NSCLC, breast, gastric, etc
- Low risk of drug-drug interaction profile favourable for combination therapies
- Multiple POC clinical studies ongoing

Sustained target inhibition…



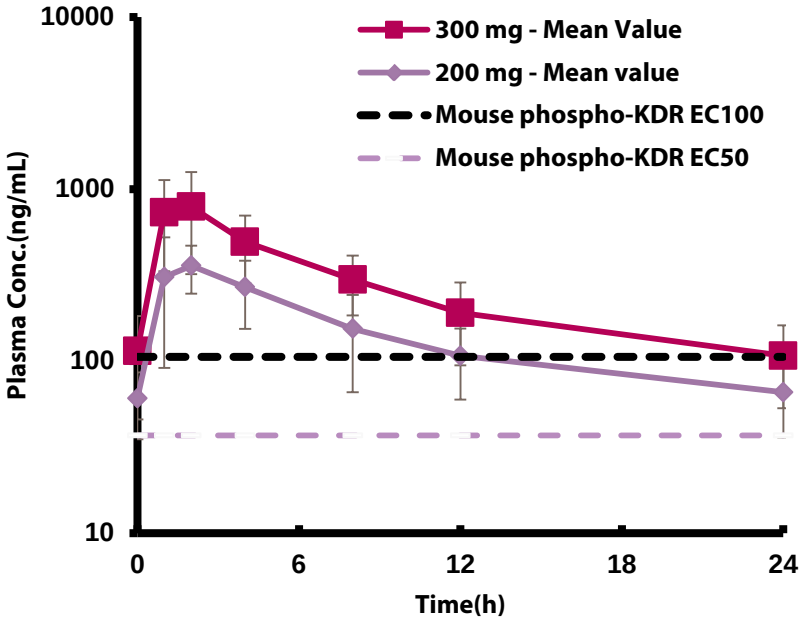
…and great Phase Ia Response



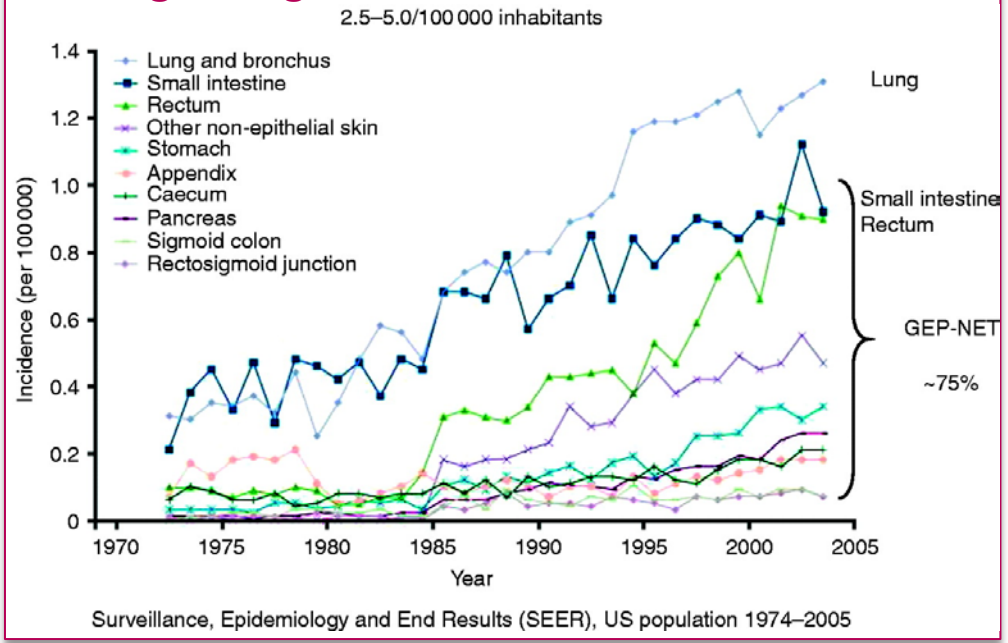
Sulfatinib: selective VEGFR/FGFR1 dual inhibitor

- Recommended Phase II dose (RP2D) selected with good safety and tolerability
- **Sustained target inhibition** and **strong clinical efficacy** in Phase Ia study
- Neuroendocrine tumours (NET) represent a **major unmet medical need** with **potential for breakthrough therapy** designation in the US
- Potential for multiple tumour types, including NET, liver, breast, and thyroid

Consistent sustained target inhibition



NET: a growing and unmet medical need



Fruquintinib: Phase I & Ib completed and Phase II well underway – CRC study fully enrolled

Phase I, dose escalation (3+3) MTD study (N=40)

40 patients with advanced solid tumours enrolled and treated at 5 fruquintinib doses given once daily continuously (QD) and 2 doses given once daily 3wks on and 1 wk off (3/1 wk);

4 mg QD and 6 mg 3/1wk were identified as MTD, respectively.

Phase Ib ≥3rd line CRC two-stage design (N=62)

1. 40 patients equally randomized and treated with 2 dose regimens of 4mg QD or 5mg 3/1wk; 5mg 3/1wk was selected as RP2D;

2. Dose expansion:
22 patients received 5mg 3/1wk regimen

Phase II PoC ≥3rd line CRC (N=71)

Randomized, double-blind, placebo-controlled study of fruquintinib + Best Supportive Care (BSC) vs. placebo + BSC (2:1 randomization)

Fully enrolled (20Aug2014) in 8 centres

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Fruquintinib Phase Ib 3rd line CRC safety: AEs reflect better VEGFR coverage, with less liver toxicity

AE TERM % all grade (% G3/4)	Fruquintinib 5 mg 3/1 wk N=42	Asian CONCUR Regorafenib 160 mg 3/1 wk N=136	Global CORRECT Regorafenib 160 mg 3/1 wk N=505
Any AE	100 (54.8)	100 (71.3)	100 (unknown)
HFS	78.6 (9.5)	74.3 (16.2)	45 (17)
Hypertension	**57.1(21.4)**	**25 (11.8)**	**30 (8)**
Proteinuria	45.2 (0)	unknown	60 (<1)
Hepatotoxicity (liver function abnormality)	**11.9 (2.4)**	**Bilirubin- 48.5 (11.8) ALT increased- 31.6 (8.1)**	**19.8**
Platelet count decreased	21.4 (0)	11.8 (3.6)	41(3)
Thyroid Dysfunction (TSH increased)	64.3 (0)	Unknown	Unknown
Cardiac Ischemia and Infarction	0	Unknown	1.2
Artery/Venous Thromboembolic Events	0	Unknown	3.8 (2.4)
GI perforation	0	unknown	0.6

Fruquintinib (HMPL-013) Phase Ib 3rd line CRC efficacy: Early results very encouraging

	Fruquintinib 5 mg 3/1 wk N=42	Asian CONCUR Regorafenib 160 mg 3/1 wk N=136	Asian CONCUR Placebo N=68	Global CORRECT Regorafenib 160 mg 3/1 wk N=505	Global CORRECT Placebo N=255
Overall Response Rate (ORR)	10.8%	4.4%	0.0%	1.0%	0.4%
Disease Control Rate (DCR)	84.6%	45.6%	7.4%	41.0%	14.9%
Median Progression Free Survival (PFS)	**5.3 months**	**3.2 months**	**1.7 months**	**1.9 months**	**1.7 months**
Median Overall Survival (OS)	not mature (62% at 9 months)	8.8 months	6.3 months	6.4 months	5.0 months

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Initiating Proof of Concept (POC) trials in 3 indications

- **Colorectal cancer (CRC)**
  - ≥3rd Line monotherapy Phase II POC initiated in April 2014, enrolment completed in August 2014, and results available in H1 2015
  - ≥3rd Line monotherapy Phase III initiating in Q4 2014
- **Non-small cell lung cancer (NSCLC)**
  - 3rd Line Phase II POC initiated in May 2014, with enrolment expected to complete in Q1 2015
  - Results available in mid 2015
- **Gastric cancer (GC)**
  - 2nd line Phase Ib dose finding, in combination with chemotherapy to initiate in Q4 2014

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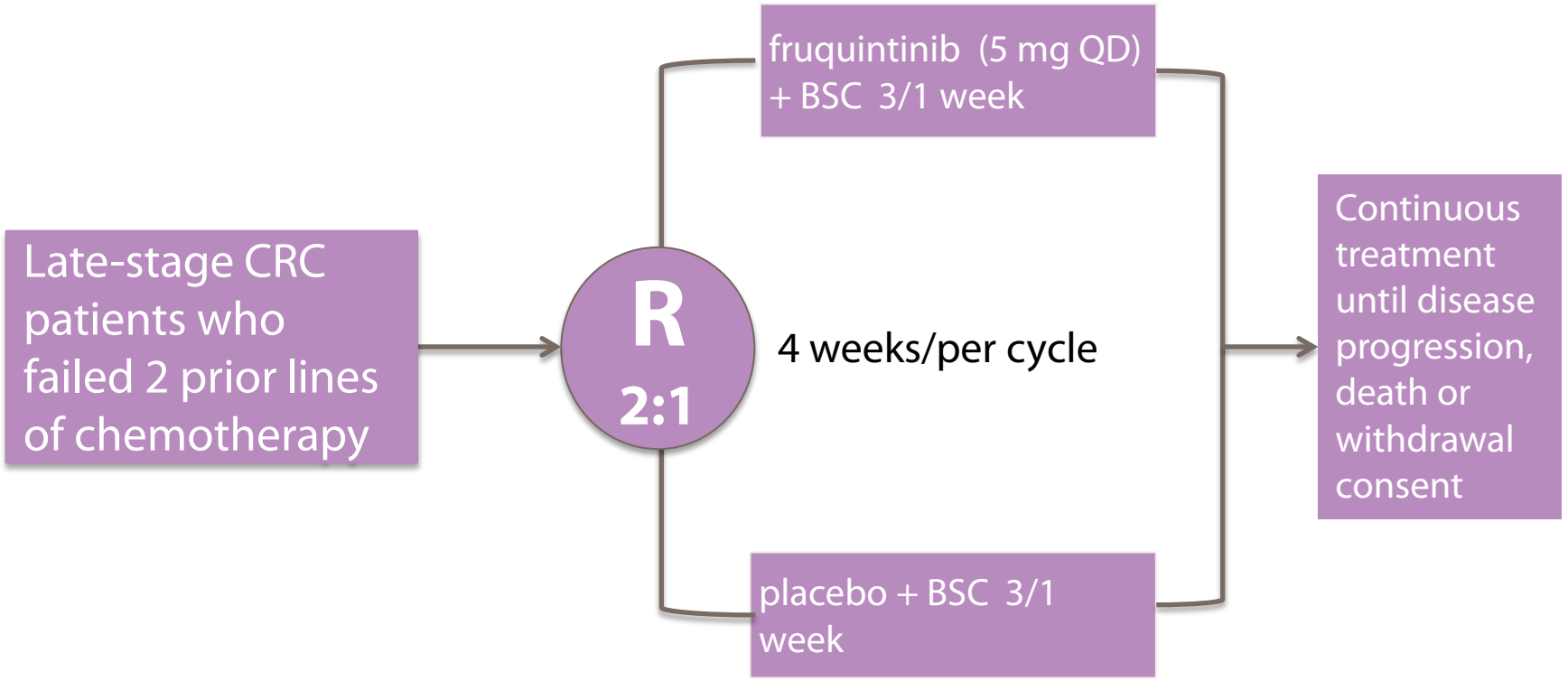
Fruquintinib (HMPL-013) Phase III ≥3rd line CRC trial



- **Primary endpoint: Overall Survival (OS)**
- **Secondary endpoints: PFS, ORR, DCR, DoR**

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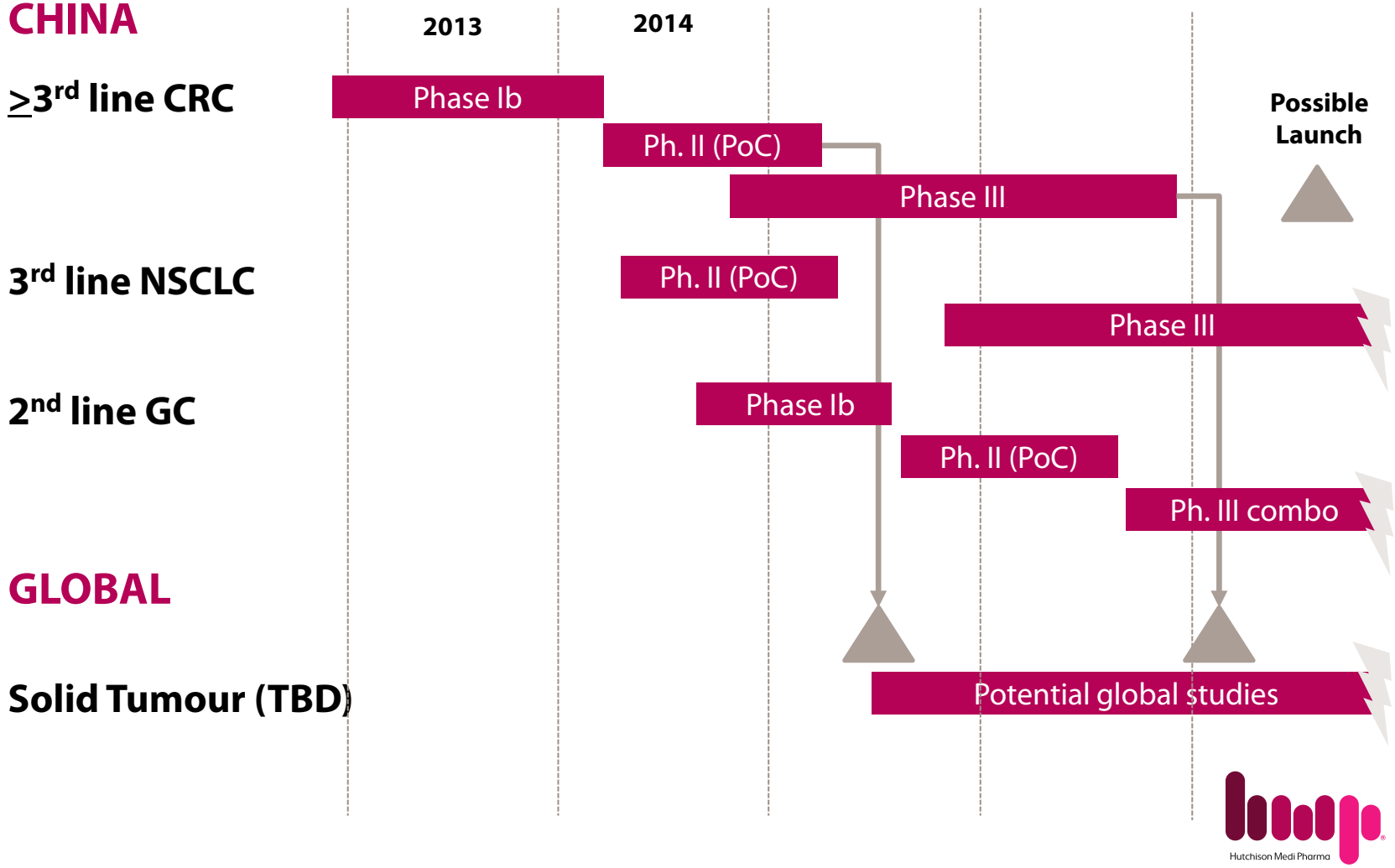
Fruquintinib near term development plans: 4 studies in 3 tumour types by the end of 2015



Sulfatinib (HMPL-012) Phase I study status

Old formulation

- Initiated in 2010
- 43 patients enrolled in seven QD dose cohorts and two BID dose cohorts
- Well tolerated but variable pharmacokinetic profile; dose-escalation was placed on hold March 2012

New micronised/milled formulation started in March 2013

- 33 patients in 3 cohorts: 200mg QD (7), 300mg QD (17), 350mg QD (9) *(as of mid August 2014)*
  - 21 neuroendocrine tumours (NET) patients – 17 evaluable

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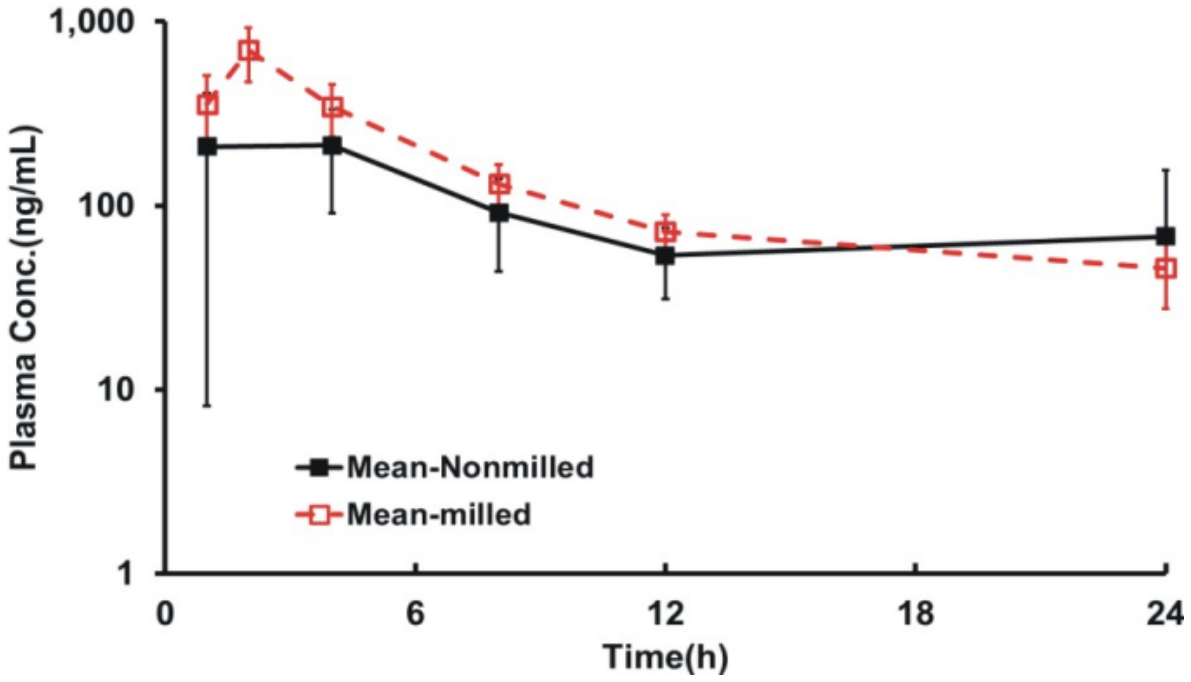
Sulfatinib Phase I new formulation data summary: good safety and much improved pharmacokinetic profile

- **Safe and well tolerated:** most common AEs are diarrhea, proteinuria, hypertension, elevated AST, hypoalbuminemia, fatigue etc.
- **Improved pharmacokinetic profile:** higher drug exposure and dramatically lower variability



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Sulfatinib Phase I new formulation data summary: strong efficacy in the new formulation

- 22 evaluable patients

- **100% disease control rate (DCR) among 17 neuroendocrine tumour patients**
  - Partial response (PR) observed in 5/17 NET patients
  - Stable disease (SD) on all others
  - Durable efficacy seen in a broad spectrum of NET sub-types including carcinoid, liver, lung, pancreatic, rectal, sacroiliac, NET of unknown origin (lymph node metastases)

- Anti-tumour activity observed in other tumour types

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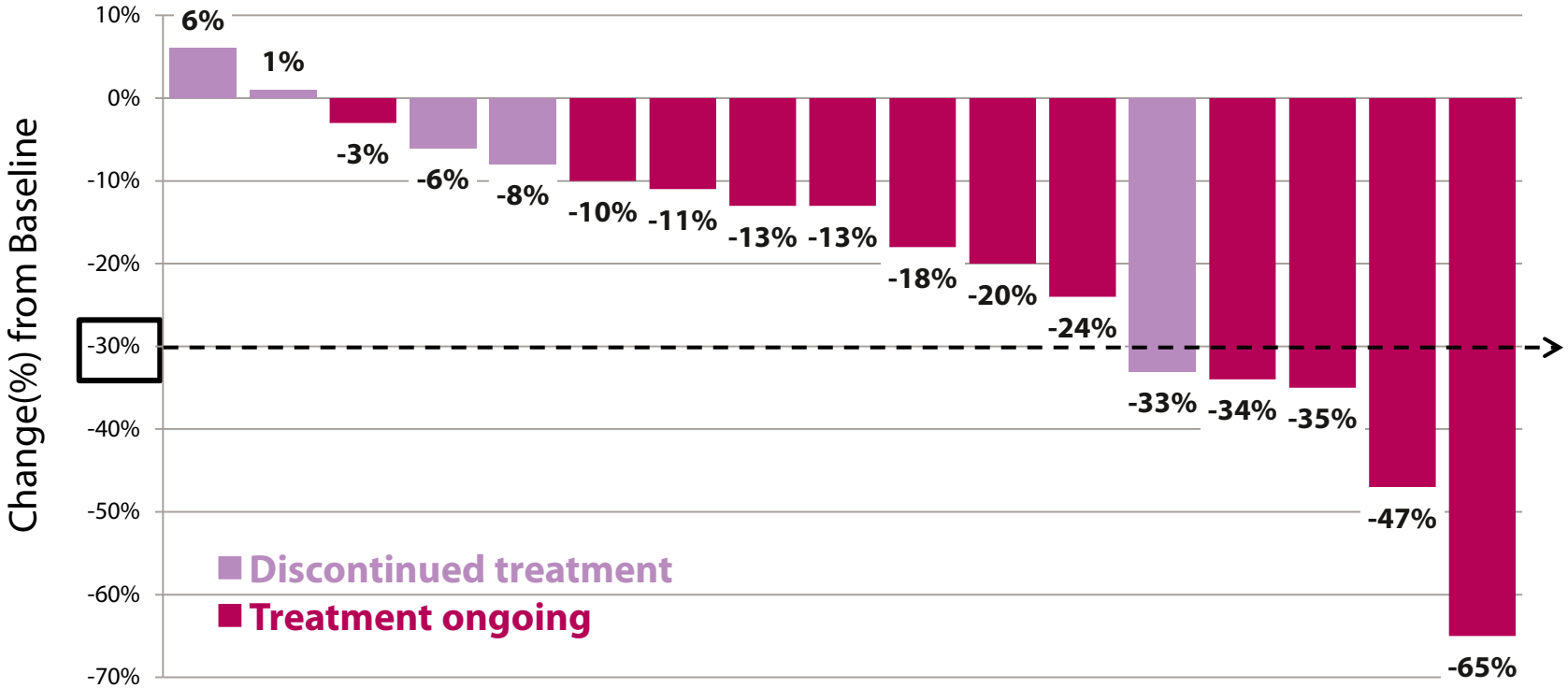
Sulfatinib (HMPL-012) Phase I study tumour assessment

- NET patients treated with new formulation (17 evaluable patients)

- **29.4% (5/17) overall response rate (ORR) & 100% disease control rate (DCR)**
- **Potential for higher ORR – as response can occur after many cycles**



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Sulfatinib: a broader spectrum NET therapy than existing treatments, and better efficacy in pancreatic NET

Existing treatments

- **Somatostatin:** approved for all NET
  - Generic: ORR 6%; DCR 35-45%
- **Targeted therapies:** only approved for pancreatic NET (none approved for other NET)
  - Sutent (Pfizer): ORR 9%; DCR 72%; PFS 11.4 mo (vs. 5.5 mo placebo)
  - Afinitor (Novartis): ORR 5%; DCR 78%; PFS 11.0 mo (vs. 4.6 mo placebo)

Market potential

- Sulfatinib has potential across all NET sub types
  - GI tract ~50%
  - Lung ~20%
  - Pancreas ~6%
  - Others ~24%
- **Large market potential due to long survival:** 12,000–15,000 new NET patients per year in US with a prevalence in the US of ~125,000

Possible Breakthrough Therapy if Phase I ORRs repeat in Phase Ib/II

Int. J. Cancer: **131**, 1013-1022 (2012)

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Sulfatinib is a very high priority: clinical development proceeding at full speed through two clinical trials

- **China: an open-label multi-centre Phase Ib study to evaluate the safety, tolerability, PK and preliminary efficacy of sulfatinib in all NET patients**
  - Initiating in October 2014
  - Enrol ~30 NET patients of different sub-types
  - Objective is to evaluate the safety, tolerability and efficacy of sulfatinib in all NET patients

- **USA: a Phase I/II monotherapy study in NET patients**
  - IND submission under preparation
  - Study to initiate in H1 2015

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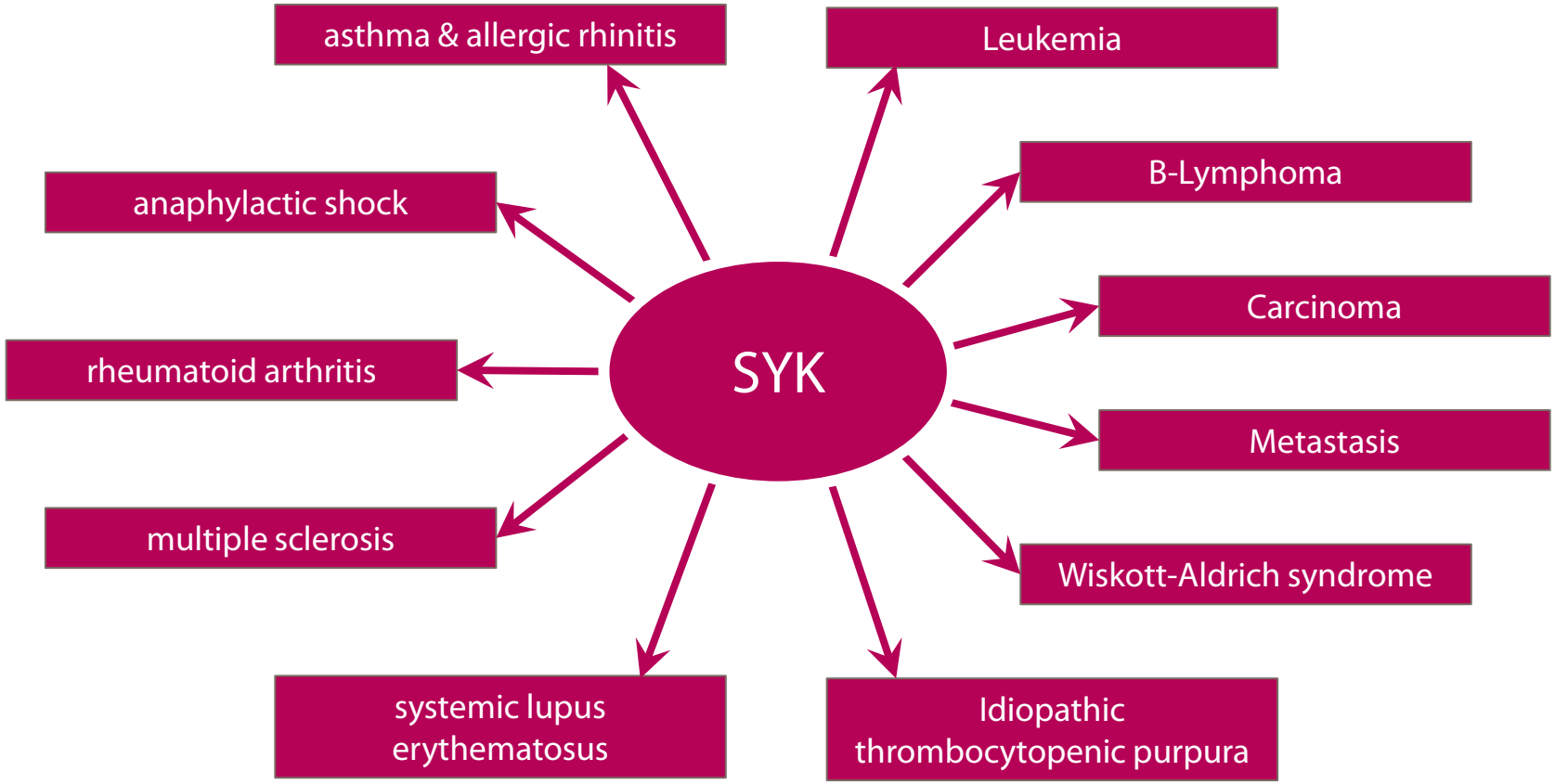
Syk and HMPL-523

Syk (spleen tyrosine kinase) activation is associated with many diseases, including inflammation, allergy and cancer



Drug Discovery Today, Volume 15, Page 13 (2010)

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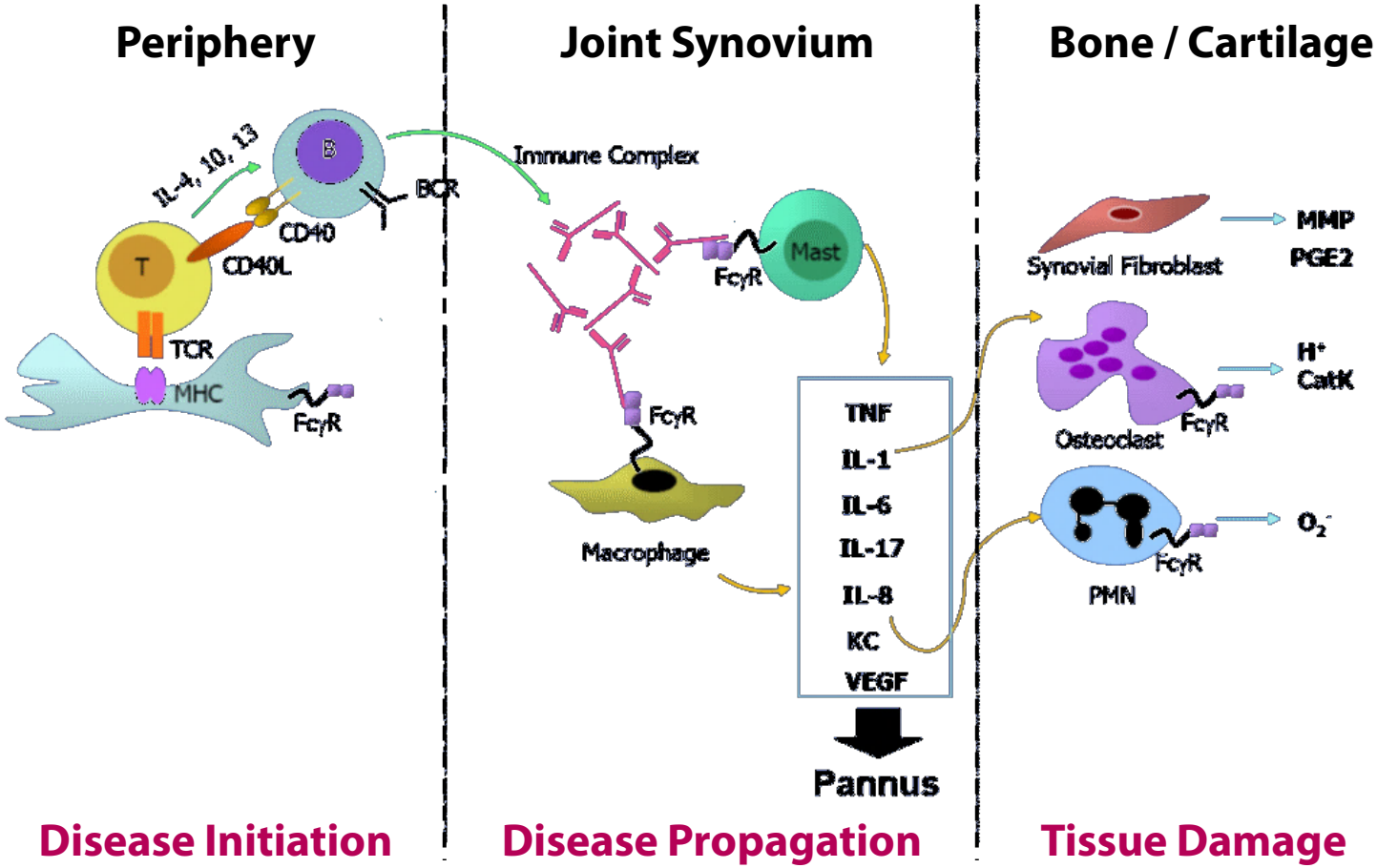
About Syk inhibition for *inflammation*

Syk plays key roles in the pathogenesis of rheumatoid arthritis and lupus



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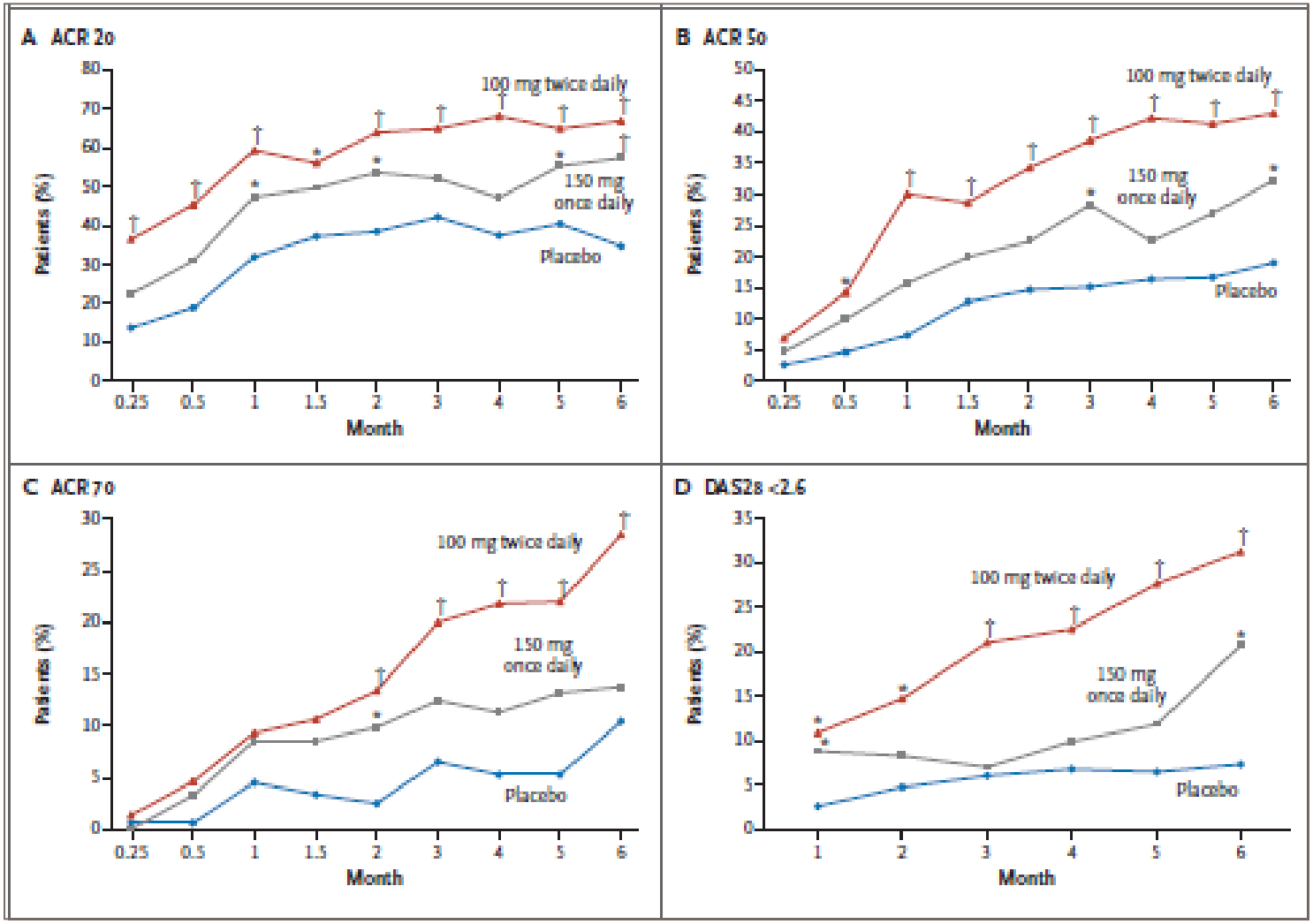
Most advanced Syk inhibitor to date, fostamatinib (R406/R788) showed strong POC data for rheumatoid arthritis



* P<0.01
† P<0.001

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Overcoming compound related issues

- **Lessons learned from fostamatinib's Phase III RA trial failure**
  - Off-target toxicity resulted from **poor kinase selectivity** capped the doses and led to insufficient target inhibition
  - High **variation in drug exposures** due to varied rate of hydrolysis of the pro-drug, compromising target inhibition

- **HMP approach**
  - Enhance **whole blood activity**
  - **Improve kinase selectivity** to reduce off-target toxicities to allow dosing flexibility
  - **Improve pharmacokinetic properties** to reduce variation and ensure consistent target coverage

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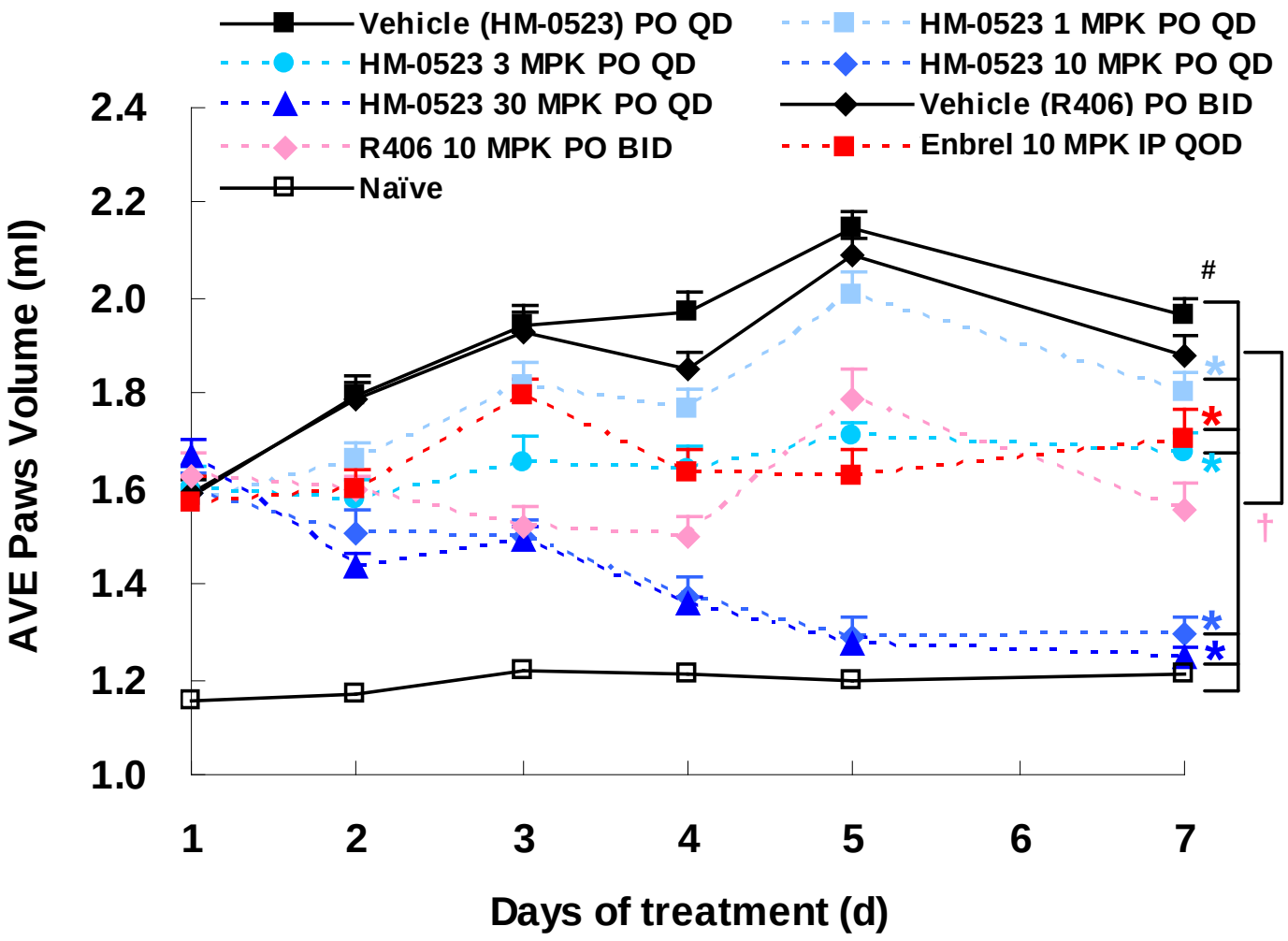
HMPL-523 activity in RA model in Wistar rat



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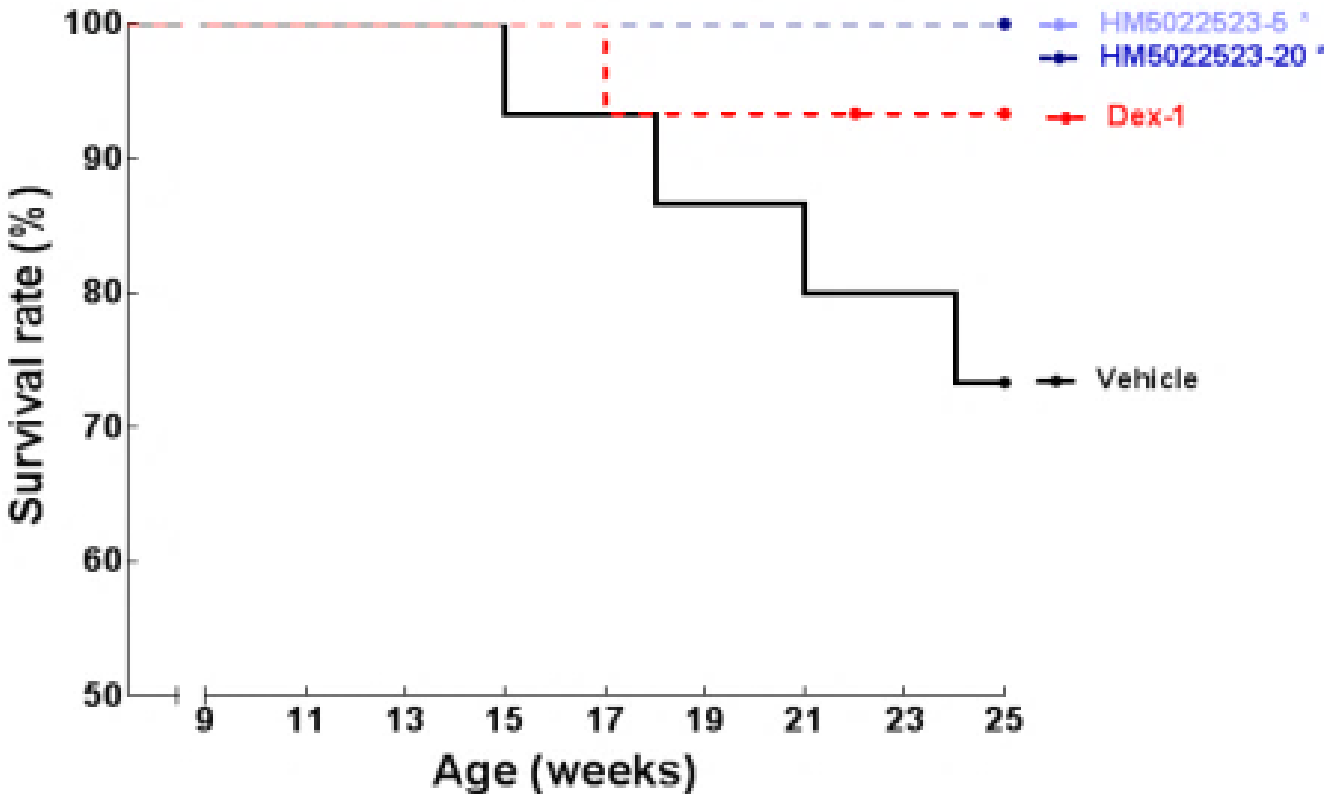
HMPL-523 activity in lupus model in mouse

Survival rate in MRL/*lpr* mice



* $p<0.05$ vs vehicle group with Log-Rank Test

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HMPL-523 preclinical summary

- **Key attributes**
  - Much improved kinase selectivity
  - Good pharmacokinetic properties
  - Strong efficacy in animal models of rheumatoid arthritis and lupus

- **Current status**
  - In Phase I single ascending dose escalation trials: linear PK, no safety issues to date
  - Expected to conclude Phase I trial 1Q/2015

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HMPL-523 Phase I Australia trial

- **Objective is to assess safety, tolerability and pharmacokinetics of single ascending doses and multiple ascending doses of HMPL-523 in healthy male volunteers**

- **Status: single ascending dose escalation ongoing with no major safety issues to date**
  - 6 cohorts completed
  - 48 subjects enrolled
  - Drug exposure increased with dose

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Targeting Syk for *B-cell malignancies*

New Cases of Lymphoma by Gender 2014

Type	Total	Male	Female
Hodgkin Lymphoma	9,190	5,070	4,120
Non-Hodgkin Lymphoma	70,800	38,270	32,530
Total	**79,990**	**43,340**	**36,650**

Cancer Facts & Figures 2014. American Cancer Society; 2014.

- Lymphoma incidence has grown rapidly to about 15-20/100,000
- ~80,000 new cases/year and 17,000 deaths/year in the US
- 90,000 new cases/year in China, ranking it 8th in all cancers

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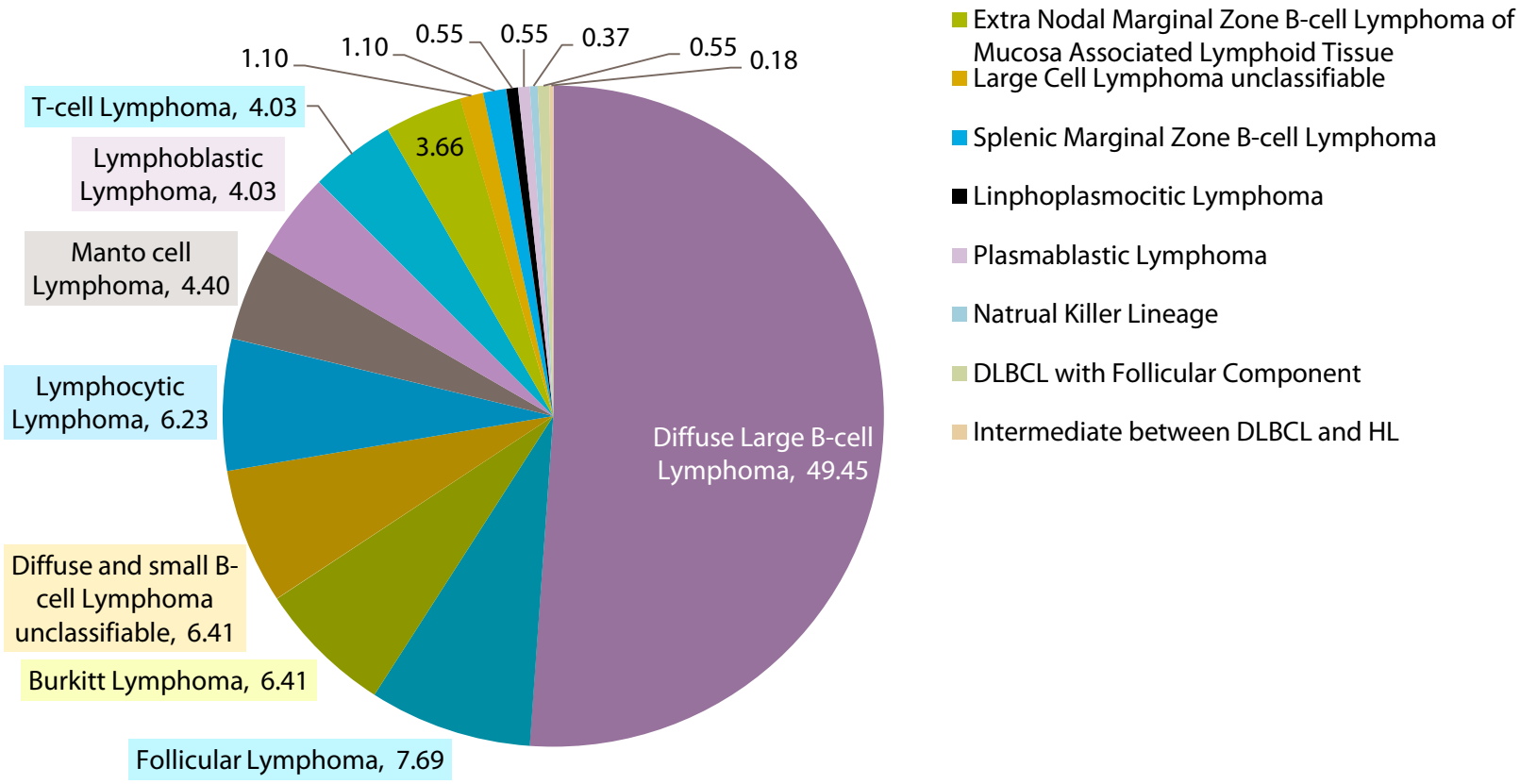
Types of lymphomas



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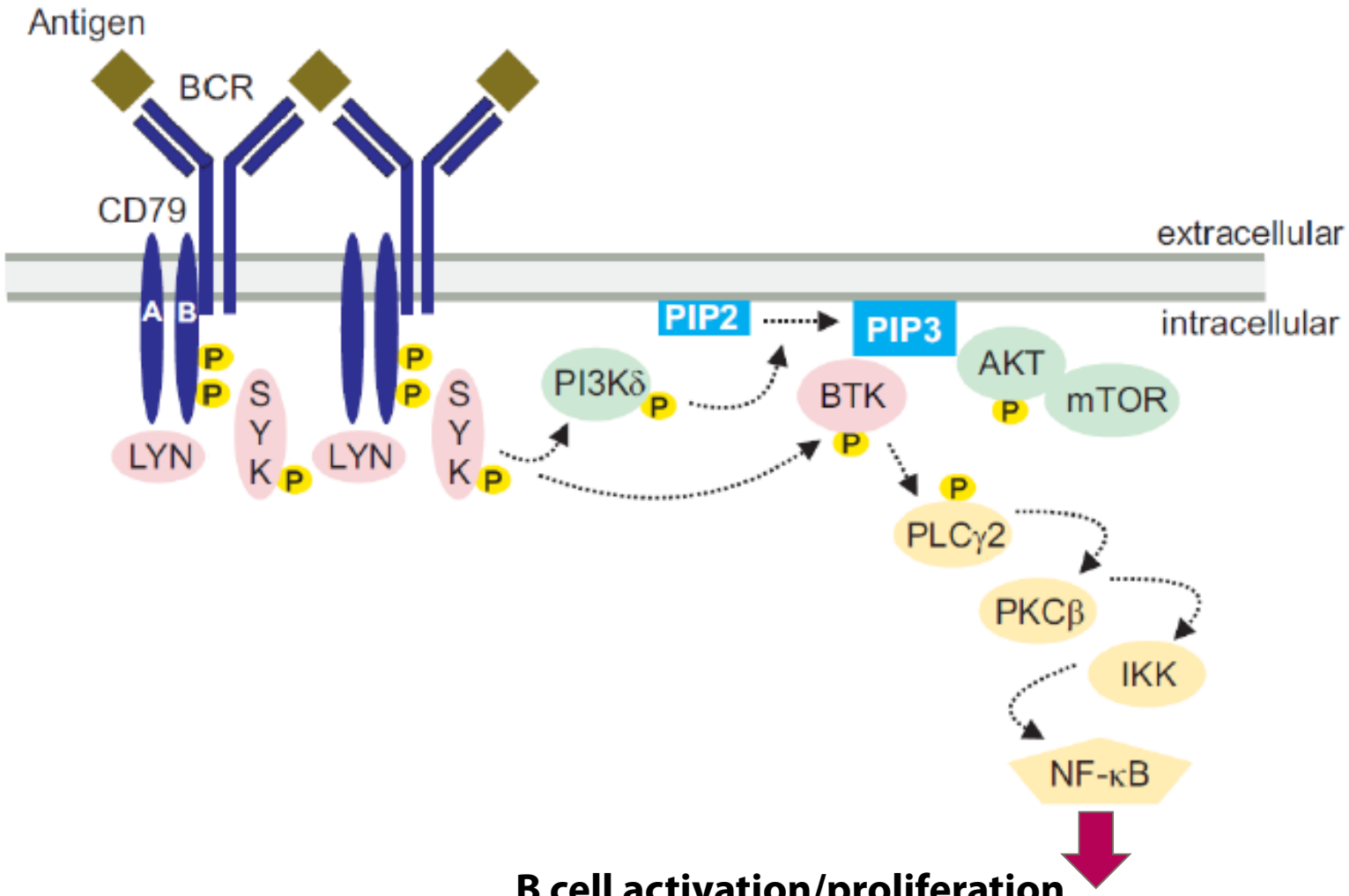
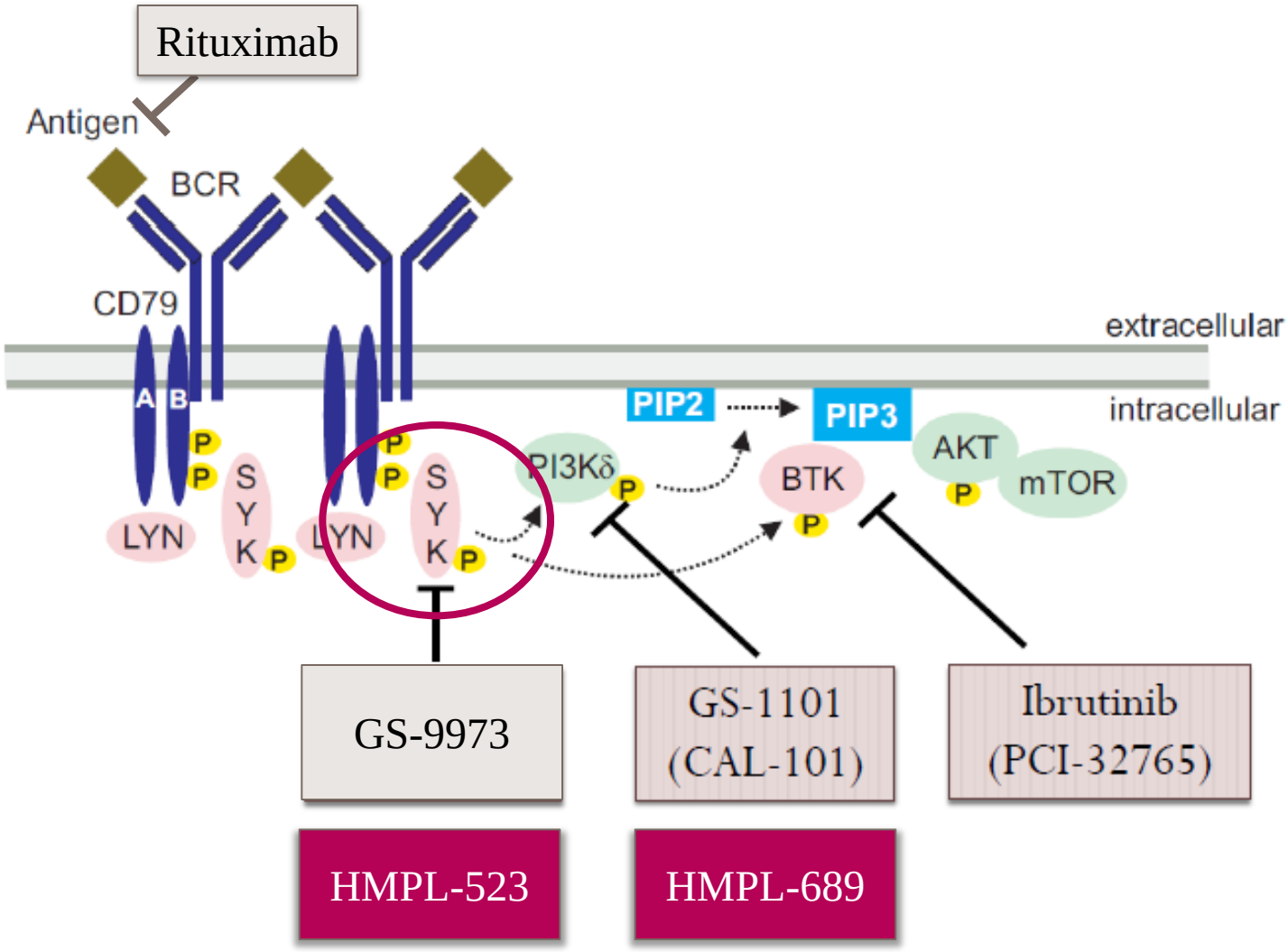
Targeting BCR signalling for inflammation and B cell malignancies



Targeting BCR signalling for inflammation and B cell malignancies



Syk inhibitor GS-9973 Phase II studies in B cell lymphoma

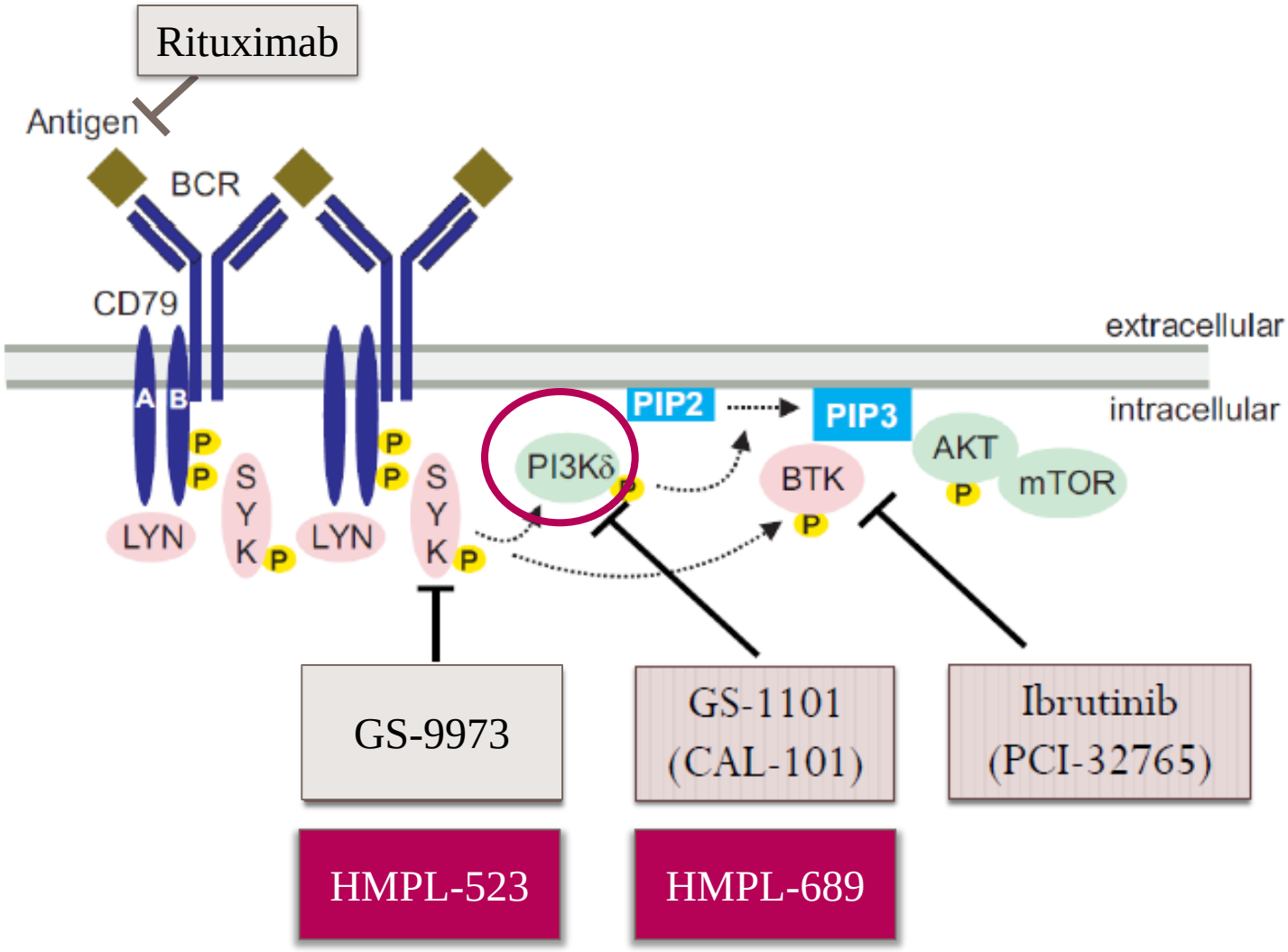
- Phase II in CLL/200 patients (single agent): ongoing
  - 44 subjects had been enrolled
  - 28 (64%) achieved a decrease of ≥ 50% in tumour bulk

- Phase II in combination with GS-1101 in CLL and NHL: suspended
  - 66 subjects with CLL (36) or NHL (30) had been enrolled
  - 14/20 (70%) CLL subjects achieved a decrease of ≥ 50% in tumour bulk
  - 7/20 (35%) NHL subjects achieved a decrease of > 50% in tumour bulk
  - The study was terminated early due to toxicity

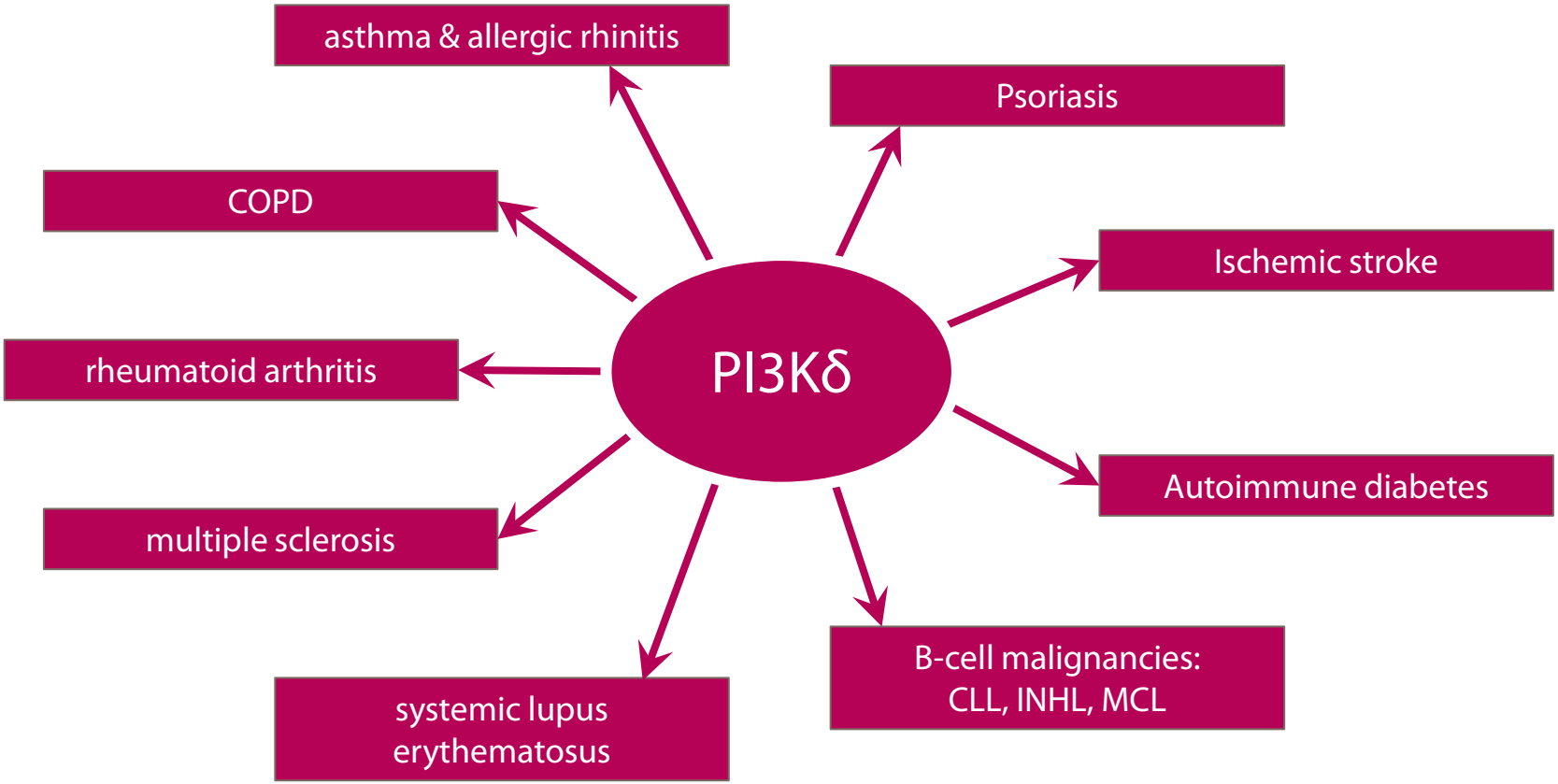
Target validated, but toxicity clearly an issue

PI3Kδ and HMPL-689

Targeting BCR signalling for inflammation and B cell malignancies



PI3Kδ activation is associated with many diseases in allergy, inflammation and oncology



PI3Kδ = phosphoinositide-3-kinase δ

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Competitive landscape

Compound	Sponsor	Indication	Status
Idelalisib (Zydelig) (PI3Kδ)	Gilead Sciences	chronic lymphocytic leukaemia, non-Hodgkin's lymphoma	Registered
		Hodgkin's lymphoma	Phase II Trial
		Waldenstrom`s hypergammaglobulinaemia	Preclinical
AMG-319 (PI3Kδ)	Amgen	B-cell lymphoma, non-Hodgkin`s lymphoma, T-cell lymphoma, chronic lymphocytic leukaemia	Phase I Trial
Duvelisib, IPI-145 (PI3Kγ/δ)	AbbVie/ Infinity	B-cell lymphoma, non-Hodgkin`s lymphoma, chronic lymphocytic leukaemia	Phase III Trial
		asthma, rheumatoid arthritis	Phase II Trial
		COPD, SLE, psoriasis, MS transplant rejection, allergy acute lymphocytic leukaemia, T-cell lymphoma	Phase I Trial

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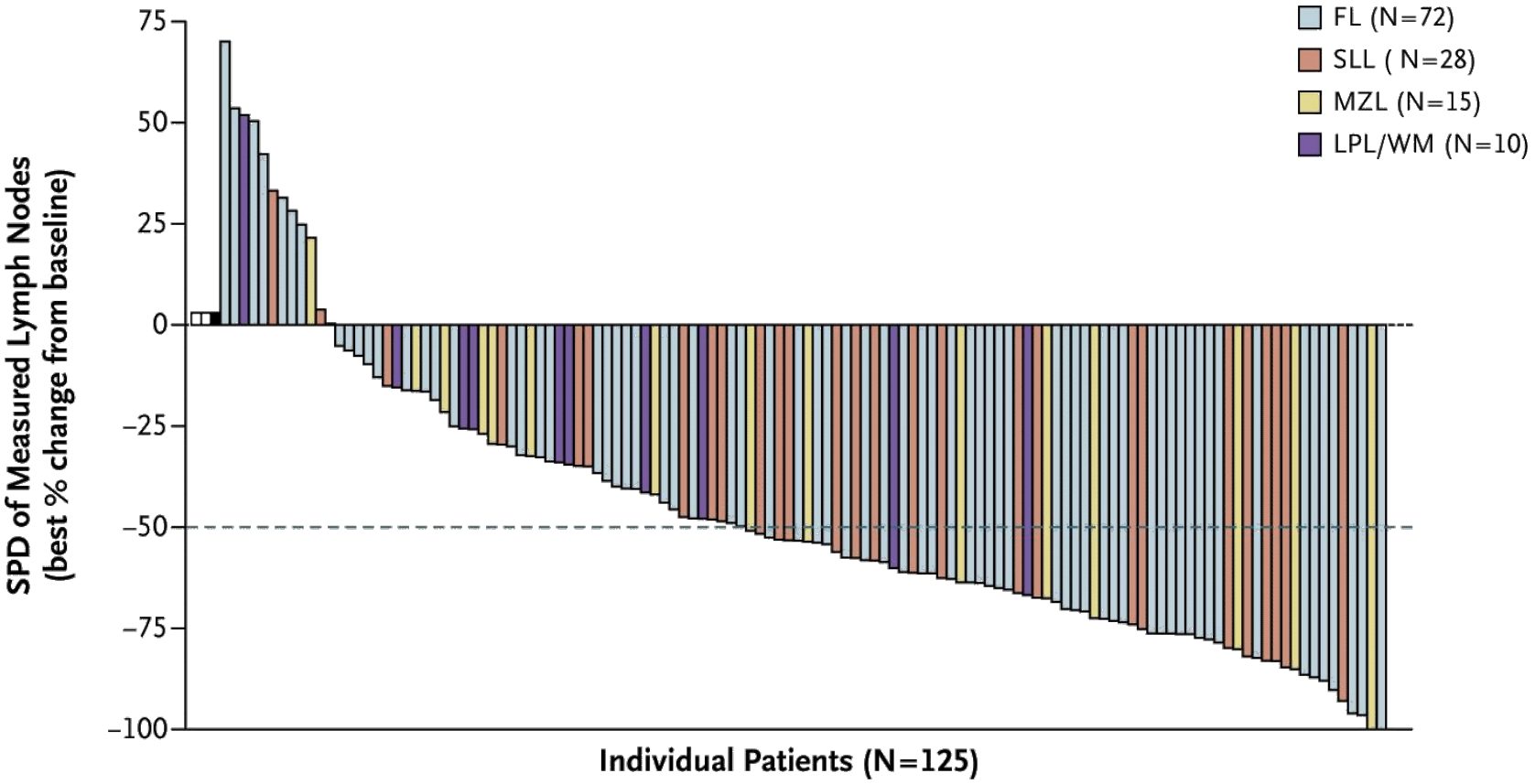
Targeting PI3Kδ for B cell malignancies: proven target

Idelalisib Phase Ib data: Waterfall plot



N Engl J Med. 2014; 370(11): 1008-18

Targeting PI3Kδ for B cell malignancies: an increasingly high profile

- **Idelalisib gained fast-track approval** in July 2014 for relapsed chronic lymphocytic leukemia (CLL), folliceular B cell non-Hodgekin lymphoma (FL) and small lymphocytic leukemia (SLL), B cell Acute lymphocytic leukemia (B-ALL)

- Evidence that PI3Kδ inhibitors are **effective in ibrutinib-resistant** mutant population, i.e. a very important therapy for several types of B-cell malignancies

- **High value:** Infinity and AbbVie entered into a licensing/co-marketing agreement for Duvelisib (IPI-145), in Phase III trials in September 2014 ($275 M upfront + $530 M milestones)

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Creating a best-in-class PI3Kδ agent

- **Improve isoform selectivity,** particularly sparing PI3Kγ to minimize serious infection seen with duvelisib due to strong immune suppression
- **Improve potency,** particularly at whole blood level to reduce daily doses to minimize compound related toxicity such as high incidence of liver toxicity seen with idelalisib (150 mg twice daily)
- **Improve pharmacokinetic properties**, particularly efflux and drug-drug interaction due to CYP inhibition/induction, as well as lower clearance for once daily dosing

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HMPL-689: a highly potent and selective PI3Kδ inhibitor

IC50 (μM)

Enzyme	HMPL-689	Idelalisib	Duvelisib
PI3Kδ	0.0008 (n=3)	0.002	0.001
PI3Kγ (fold vs. PI3Kδ)	0.114 (142X)	0.104 (52X)	0.002 (2X)
PI3Kα (fold vs. PI3Kδ)	>1 (>1,250X)	0.866 (433X)	0.143 (143X)
PI3Kβ (fold vs. PI3Kδ)	0.087 (109X)	0.293 (147X)	0.008 (8X)

HMPL-689 spares PI3Kγ

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HMPL-689: PI3Kδ program summary

- Novel, potent oral PI3Kδ inhibitor with improved selectivity for multiple indications
- Highly potent in in vitro and in vivo whole blood B cell activation assays as well as rat CIA model, resulting in low predicted effective doses in humans
- Favourable DMPK properties in mouse, rat and dog and predicted to have favourable DMPK properties in human and clean drug-drug interaction profile
- In vitro and in vivo toxicity studies indicated excellent drug safety profile
- Targeting initiation of IND-enabling GLP safety evaluation before year end and IND filing H2 2015

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Preparing for Commercialisation

HMP moving towards commercialisation – building manufacturing capabilities

Building a plant for commercialising oncology products

- An important step towards becoming a fully integrated pharmaceutical company
- Will manufacture HMP's oncology clinical and commercial products and meet global GMP standards
- Located in Suzhou, Jiangsu, about 100 kilometres from Shanghai
- Facility will be ready for use at the end of 2014
  - Will be producing a batch of phase III clinical supply for Fruquintinib at the facility in Q1 2015

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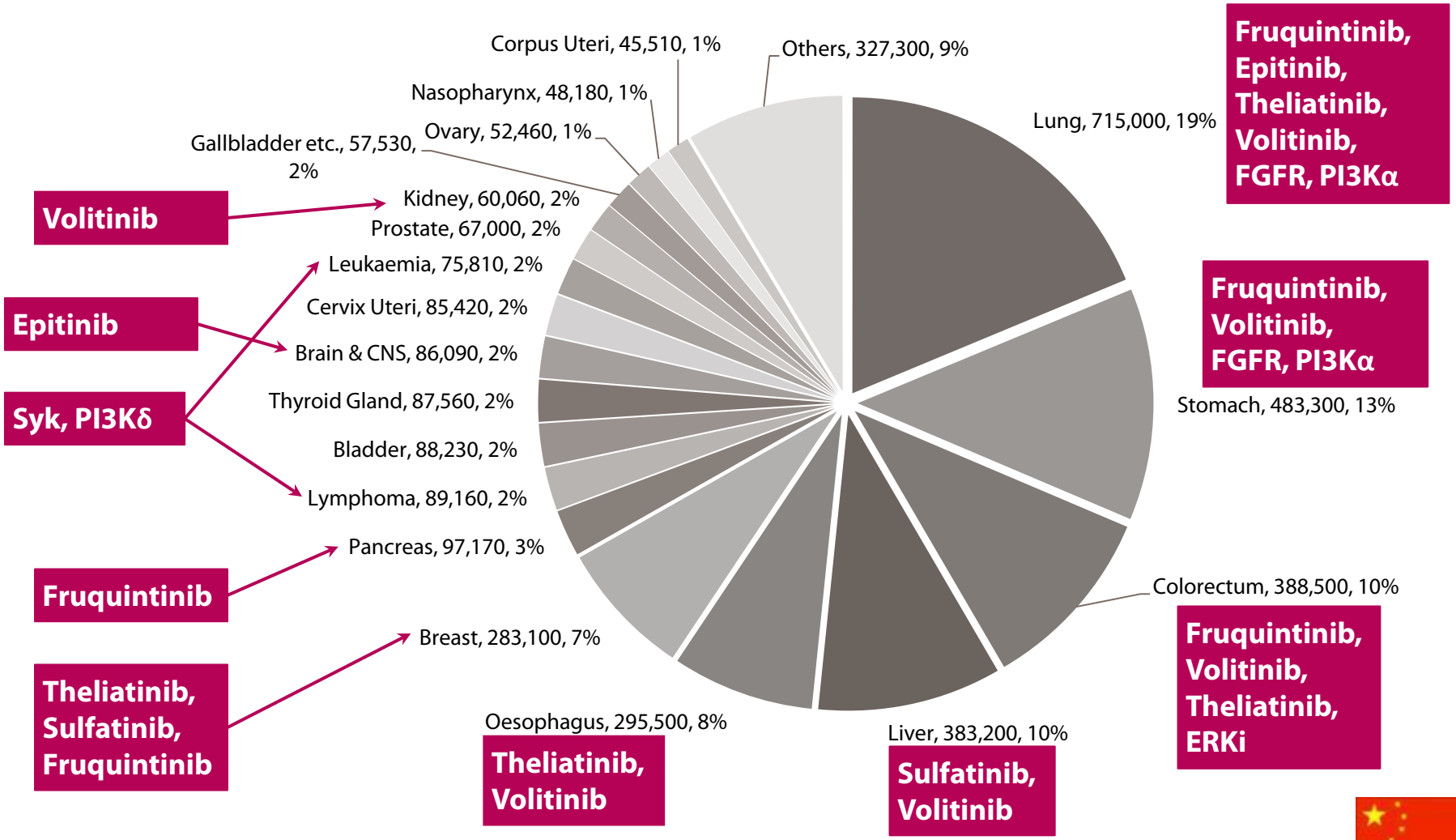
Wrap-up and Q&A

Covering major tumour types with high unmet medical needs



Source: 2012 Chinese cancer registry annual report

HMP, China's premier novel drug R&D company, is now building value at an accelerating pace

- **HMP is moving an extensive portfolio forward in multiple indications, progressing greatly since last year**
  - 13 studies by the end of 2014 (6 in October 2013)
  - 7 clinical drug candidates (6)

- **Partnership are very important to HMP to make this happen**

- **Now moving forward into the manufacturing and commercialisation stage for several compounds**

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Thank you

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Speaker biographies

Dr Andrew Mortlock

Vice President for Oncology Projects since 2010

- Responsible for all of AstraZeneca's small molecule oncology projects from lead optimization to the end of Phase IIb
- Oxford First class degree & PhD in Chemistry, under Prof. Stephen Davies
- UC Berkeley post-doctoral work with Prof. Clayton Heathcock
- Joined AstraZeneca (AZ) in 1992 (ICI/Zeneca)
  - Programmes that led to the selection of three ETA-selective inhibitors
  - Anti-cancer projects e.g. kinase, protease, integrin, GPCR, nuclear hormone receptor and protein-protein interaction targets; led the chemistry team which developed AZ's first Aurora kinase inhibitor, AZD1152
  - Director of medicinal chemistry for lead generation projects in cancer group
  - Head of global development of an oncology portfolio (pre-clinical to Phase IIb)
  - VP, Oncology Research (leading 300+ in chemistry, bioscience & drug metabolism)
- Author on more than 50 scientific papers, patents and presentations

AstraZeneca

Dr Weiguo Su

Executive Vice President and Chief Scientific Officer

- 8 years with HMP
- Bachelor's degree in Chemistry from Fudan University, Shanghai
- #1 chemist in China in 1982
- Harvard Ph.D. & post-doctoral fellowship under Nobel Laureate Prof E. J. Corey
- Director of Medicinal Chemistry at Pfizer; 15 years with Pfizer delivering several high quality new drug candidates in the area of infectious diseases, diabetes and oncology
- Served as a member of multiple technical committees at Pfizer and a faculty member of the Pfizer University
- Built HMP's highly productive research platform, including all small molecule candidates

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Dr Ye Hua

Head, Clinical Development and Regulatory Affairs

- Joined HMP in March 2014
- Bachelor of Medicine, Fudan University Medical School (1992)
- MSc in Epidemiology, McGill University, Montréal, Canada (1999)
- Research Assistant, Department of Epidemiology, Shanghai Cancer Institute (4 years)
- Senior clinical development physician with 15 years track record in registering new drugs globally: Humira, Zometa, Reclast/Aclasta, Femara, Cardioxane, Proleukin, Revlimid, and Pomalyst/Imnovid

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