HUTCHISON CHINA MEDITECH

AIM/Nasdaq: HCM

Christian Hogg
Chief Executive Officer

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The Royal Society of Medicine
Saturday, 16 September 2017

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Agenda

1. China: a major unmet medical need

2. Chi-Med: a global-focused BioPharma in China

3. Targeting cancer: world-class chemistry for versatile cancer drugs
   - ↗ "Clean", selective drugs for a future of combinations
   - ↗ Case study: savolitinib, a highly selective c-MET inhibitor

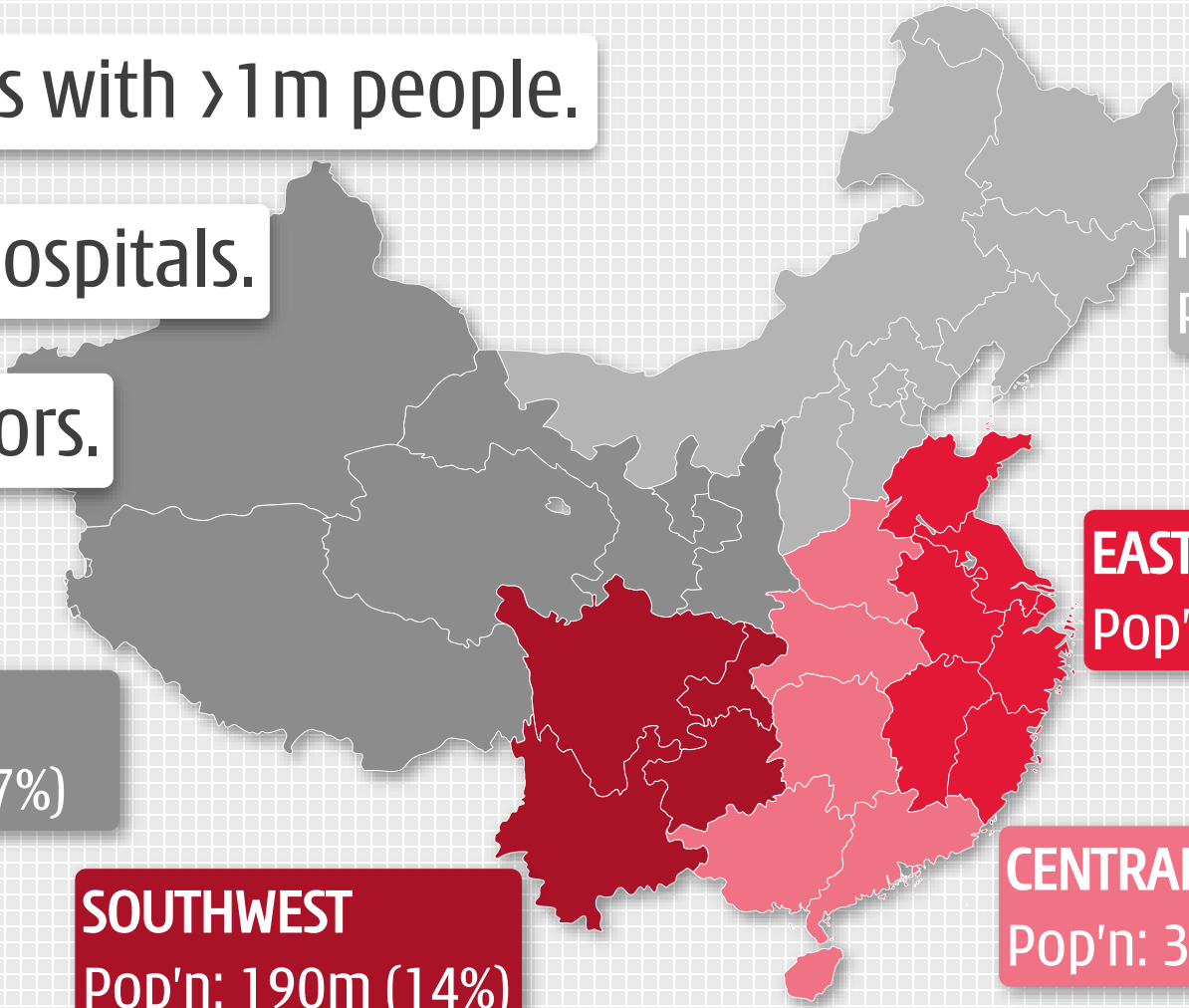
4. Our drug candidates in research and development

A major unmet medical need in China

Oncology needs are large, growing, and often unmet

China scale: 1.4 billion people

- ›100 cities with ›1m people.
- ›25,000 hospitals.
- ~3m doctors.



NORTH
Pop'n: 320m (23%)

EAST
Pop'n: 393m (28%)

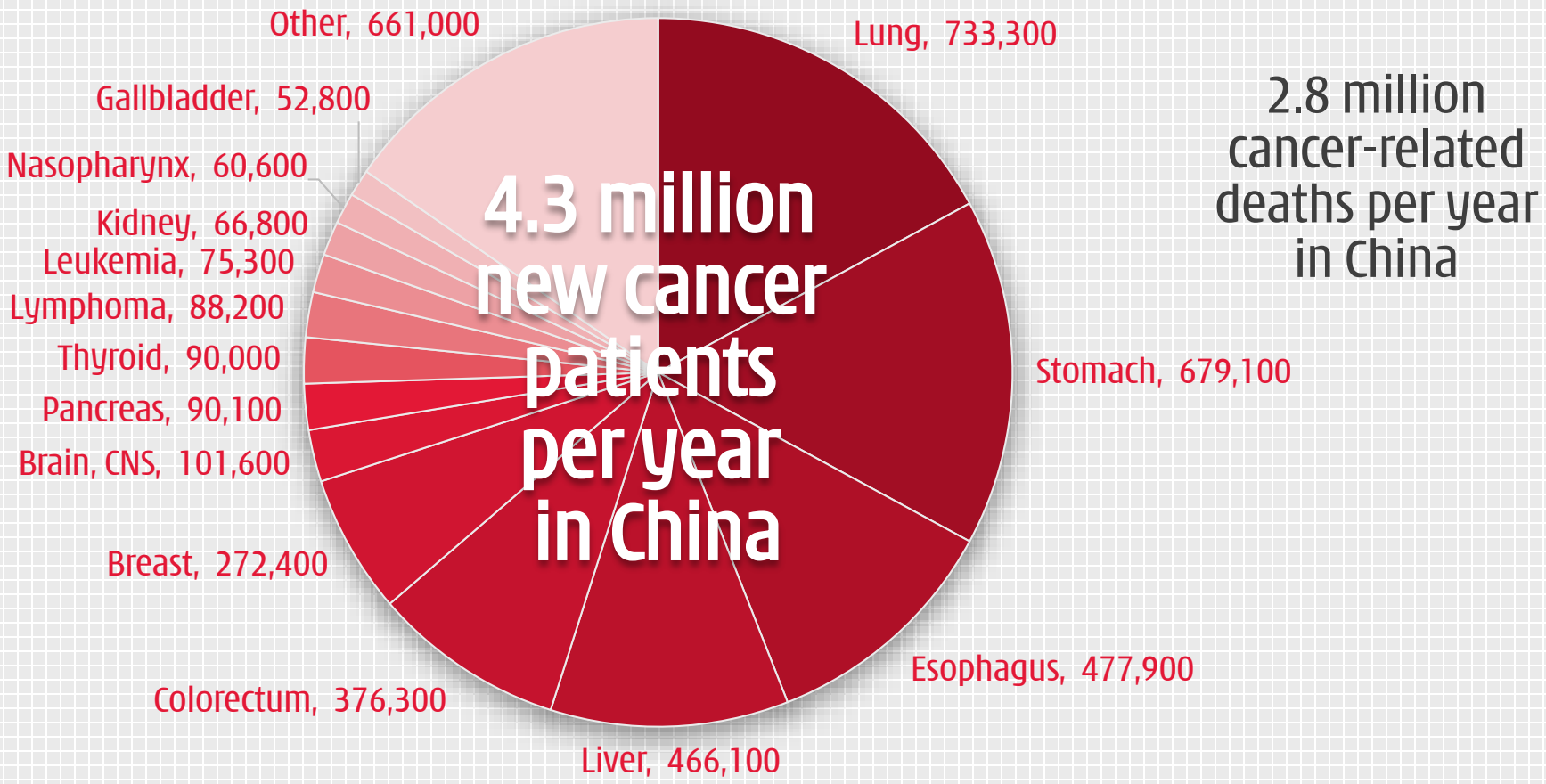
WEST
Pop'n:100m (7%)

CENTRAL-SOUTH
Pop'n: 383m (28%)

SOUTHWEST
Pop'n: 190m (14%)

Notes: 2010 Population - China State Census.
Chi-Med Rx sales team data = 31 December 2016.

High unmet medical needs in China



2.8 million cancer-related deaths per year in China

Source: Chen, W., Zheng, R., Baade, P. D., Zhang, S., Zeng, H., Bray, F., Jemal, A., Yu, X. Q. and He, J. (2016), Cancer statistics in China, 2015. CA: A Cancer Journal for Clinicians, 66: 115-132. doi:10.3322/caac.21338.

Non-Small Cell Lung Cancer (NSCLC)
China 1st in both incidence and in deaths/capita globally

	new cases/year	deaths/year
Global	1.82 million	1.59 million
U.S.	222,500	155,900
China	733,300	610,200

Risk factors

- Smoking: 80-90% linked to smoking, including second-hand smoking
- Family history of lung cancer
- Air pollution, radon, other substances
- Radiation therapy to the chest

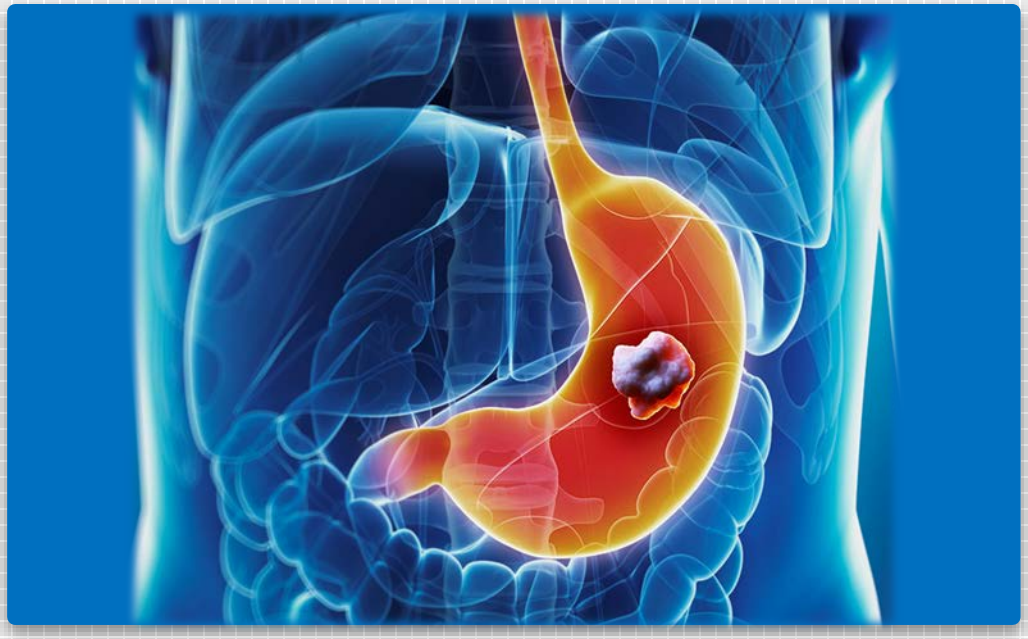
Symptoms

- Coughing
- Chest pain
- Shortness of breath
- Wheezing
- Coughing up blood

Sources: Ferlay J et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015; 136:E359-386. Chen W et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016; 66:115-132.

Gastric Cancer (GC)
China 5th in incidence and 2nd in deaths/capita globally

	new cases/year	deaths/year
Global	951,000	723,000
U.S.	28,000	10,900
China	679,100	498,000



Risk factors

- Diet high in salty, smoked, preserved foods
- Foods contaminated with aflatoxin fungus
- Family history of stomach cancer
- Infection with *Helicobacter pylori*
- Long-term stomach inflammation
- Smoking

Symptoms

- Severe, persistent heartburn/pain
- Severe, unrelenting indigestion
- Persistent nausea and vomiting
- Fatigue

Sources: Ferlay J et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015; 136:E359-386. Chen W et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016; 66:115-132.

A global-focused BioPharma in China

Innovation Platform

Deep late-stage pipeline

- ✓ 8 oncology drug candidates in 31 studies worldwide.
- ✓ 8 ongoing or completed Phase III trials; 4 enrolling & 3 in-planning.

Commercial Platform

Solid cash flow funds operations

- ✓ ›3,300-person China Sales Team (~2,200 med. reps).
- ✓ Can commercialise Innovation Platform drugs in China.

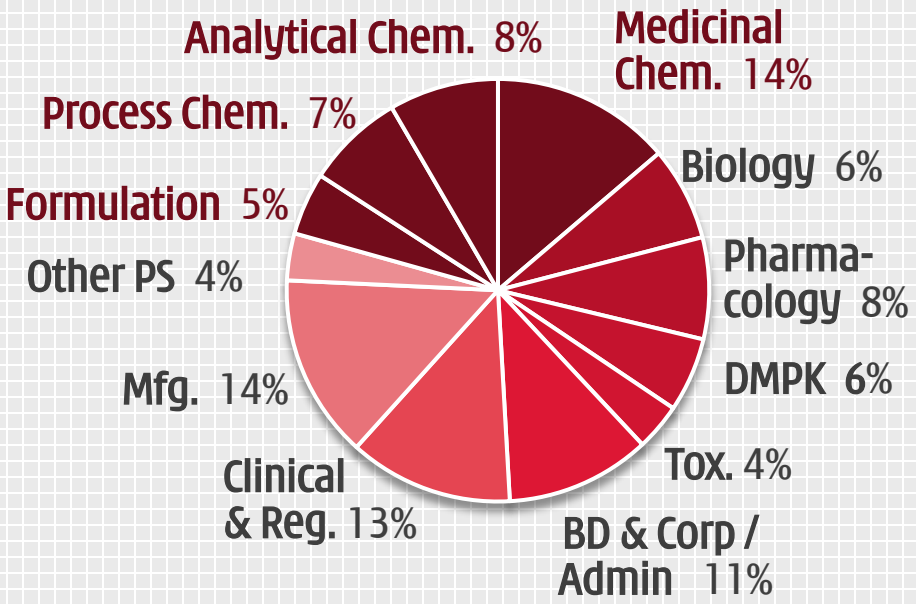
Exceptional scale for pre-approval biotech

Over 15 years with about $480 million invested to-date

One of the leading China-based innovators in oncology & immunology

~330 SCIENTISTS & STAFF[1]

- ✓ 199 with advanced technical degrees
- ✓ 22 M.D.s
- ✓ 50 doctorate degrees



✓ Fully integrated in-house platform

chemistry, biology, pharmacology, DMPK, tox., CMC, clin. & reg., and translational orgs working together.

✓ China clinical speed

major unmet medical needs, rapid development & regulatory support. Study multiple indications and proof-of-concept.

✓ Competitive costs

Clinical costs, esp. pre-PoC, fraction of US/Europe.

✓ Constancy of purpose

15+ years with continuous financial support.

[1] Headcount as of June 30, 2017; Chem. = Chemistry; DMPK = Drug, Metabolism, & Pharmacokinetics; Tox. = Drug Safety Evaluation; PS = Pharmaceutical Science (CMC); Mfg = Manufacturing; Reg. = Regulatory; BD = Business Development.

Exceptional scale for pre-approval biotech

Platform delivering new candidates every 12-18 months

Suzhou drug production facility – 4,000m²

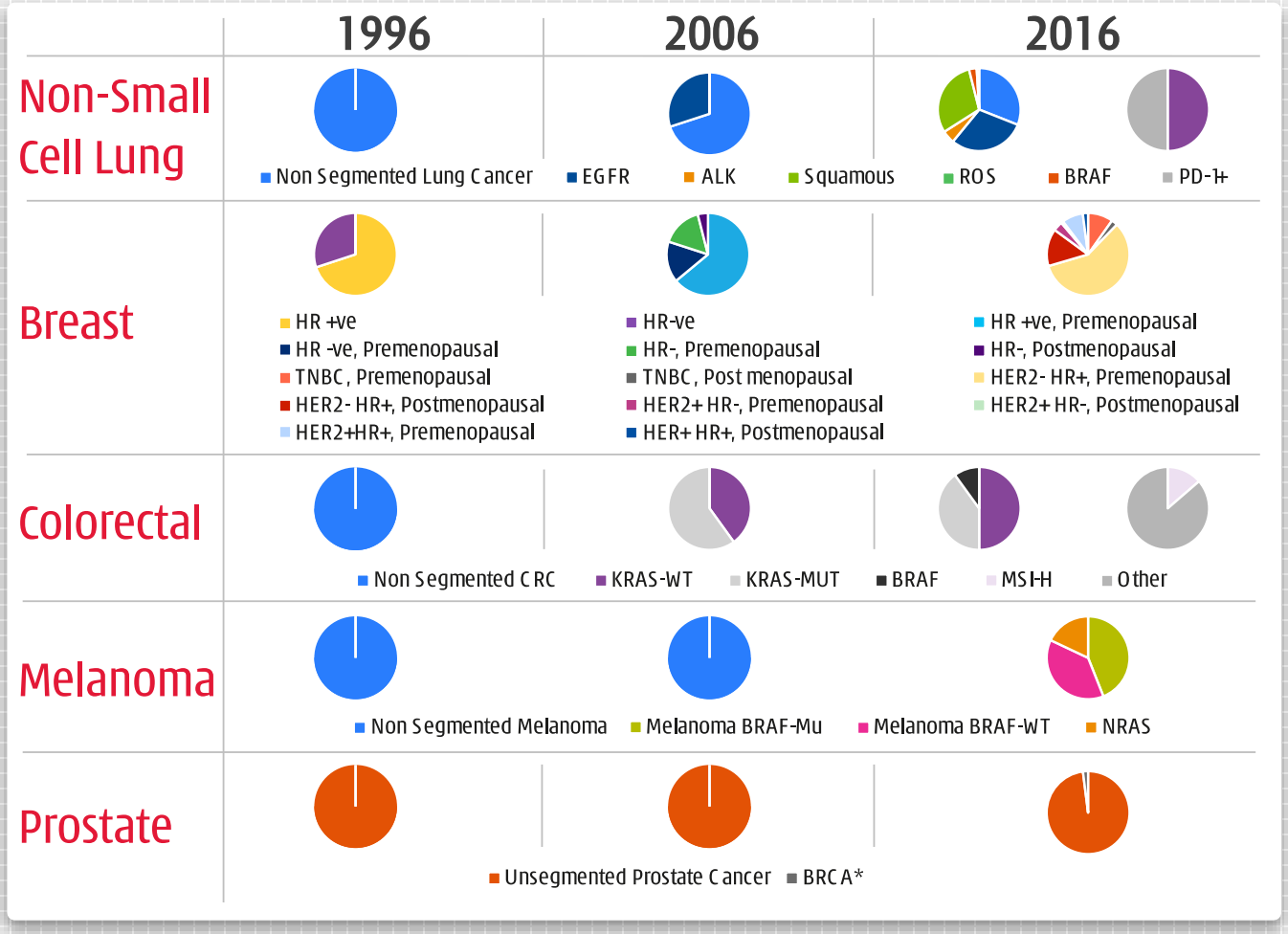
Main Shanghai R&D facility – 5,000m²

Production facility ~100km from main Shanghai R&D facility

World-class chemistry for versatile cancer drugs

Our scientific strategy to discover and develop drug candidates with better efficacy, toxicity and combinability

Cancer has been progressively redefined over the past 20 years[1]



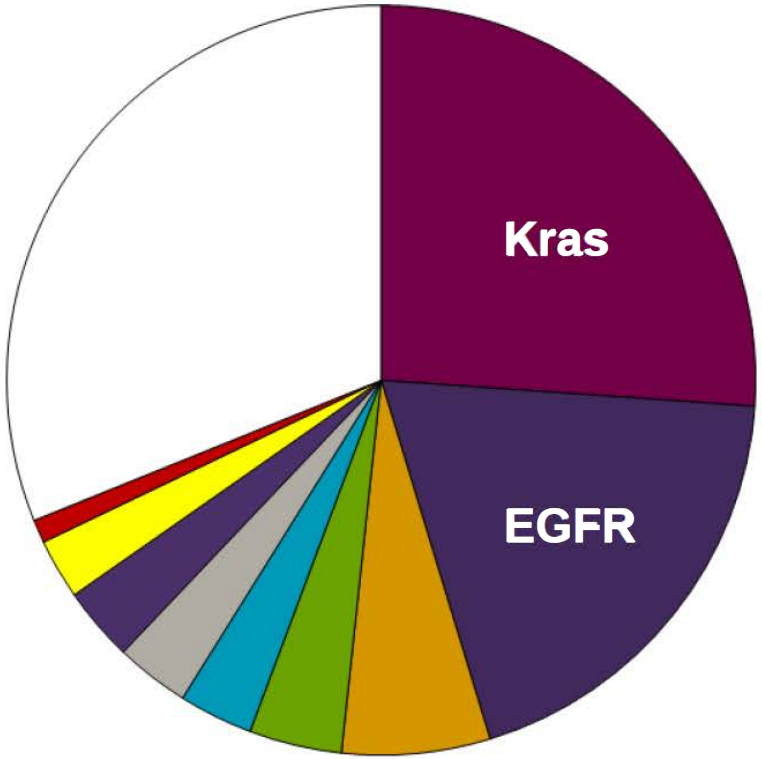
- Extensive segmentation over the past two decades
- Based on different criteria, e.g. biomarkers, age, histology
- Almost all major tumour types

Chart notes: The availability of new treatment options based on US FDA drug approvals for selected tumour types was considered for segmentation; pie graphs that total 100% indicate the biomarker was not yet available in that year. BRAF status in NSCLC included based on US FDA BTD status granted to dabrafenib/trametinib combination. BRCA status in prostate cancer included based on FDA BTD status granted to olaparib.

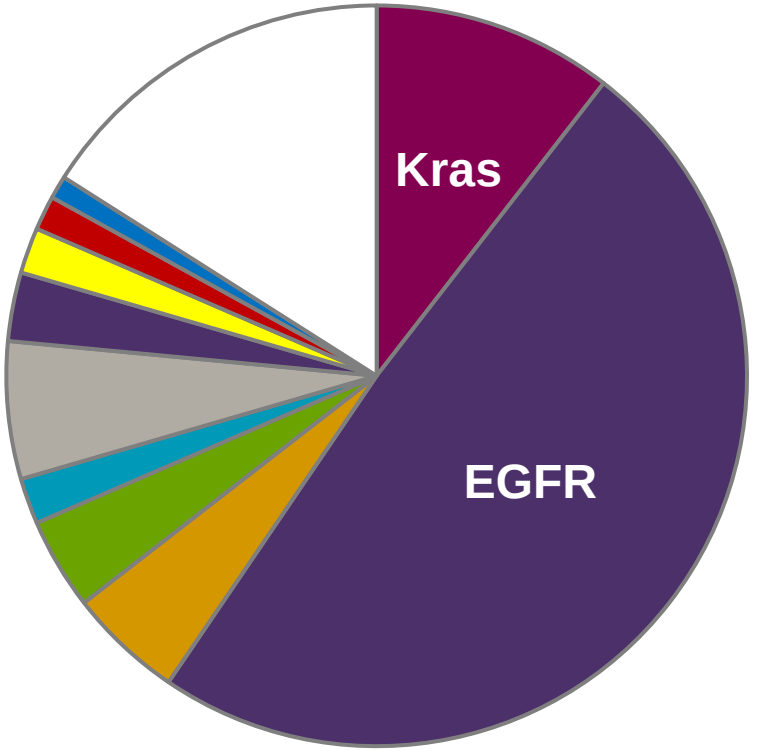
[1] Source: QuintilesIMS:, "Global Oncology Trends 2017."

Example of regional differences: lung cancer
EGFR mutations are more common in SE Asia

Molecular lesions are similar in the two populations
but incidences vary considerably



Caucasian Population



South-East Asian Population

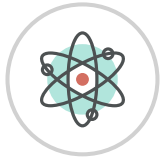
Source: Andrew Mortlock, VP Oncology Projects, AstraZeneca, "Oncology in China", 9 October 2013.

The future of cancer is a balanced, multi-pronged strategy

Baseline Interventions

Surgery

Chemo-therapies



Radio-therapies

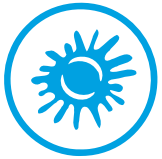
Tumour Microenvironment

Targeting angiogenesis, lymphangiogenesis, etc e.g. vascular endothelial or fibroblast growth factors (VEGFR, FGFR)

Tumour cell signaling and genetic damage

Targeting gene amplification, overexpression, mutations, resistance mechanisms, e.g. epidermal growth factor (EGFR), c-MET, ALK, HER2, etc.

Immuno-oncology



T-cell modulation or redirection, immune micro-environment, etc. e.g. checkpoint inhibitors, CAR-T

Images: mesothelioma.com; Eli Lilly & Company.

Chemistry is our edge

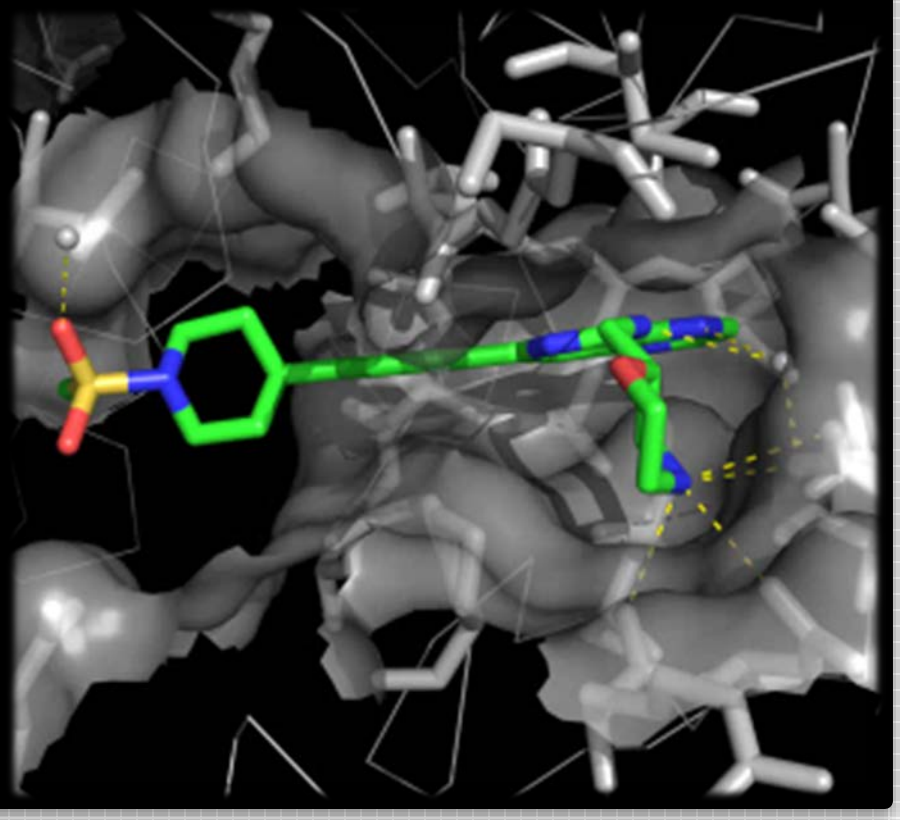
Targeted, selective small molecules

Fragment-based design of new drugs (NCEs).

- **Designed all 8 clinical drug candidates in-house.**
- Use of co-crystal structures.
- Focus on small molecule interactions with tyrosine kinases *(Proteins/enzymes involved in cell signalling)*.

Use of co-crystal structures.

- Focus on small molecule interactions with kinases.
- ✓ Optimise binding to on-target protein, for potency.
- ✓ Minimise binding to off-target proteins for selectivity.



Chemistry is our edge

Targeted, selective small molecules

Focus/discipline designing drugs with superior kinase selectivity.

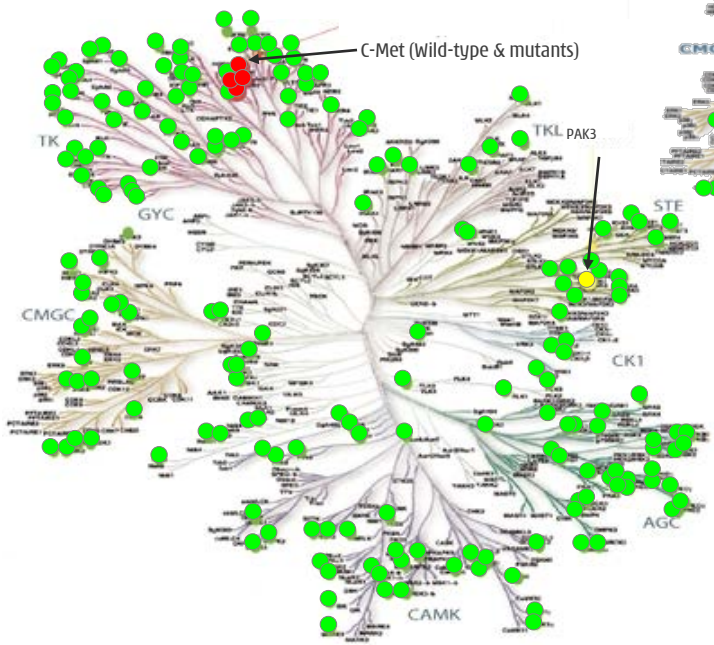
- **Optimise binding to on-target protein.**
- Low/no off-target kinase inhibition → more potent → **better target coverage** with **less toxicity**.
- Combinability - **clean** compounds **allow for combinations** with other tyrosine kinase inhibitors ("TKIs"), immunotherapy & chemotherapy agents.

Screening at 1μM against 253 Kinases

- ›90% inhibition at 1 μM
- 70-90% inhibition at 1 μM
- 40-70% inhibition at 1 μM
- ‹40% % inhibition at 1 μM

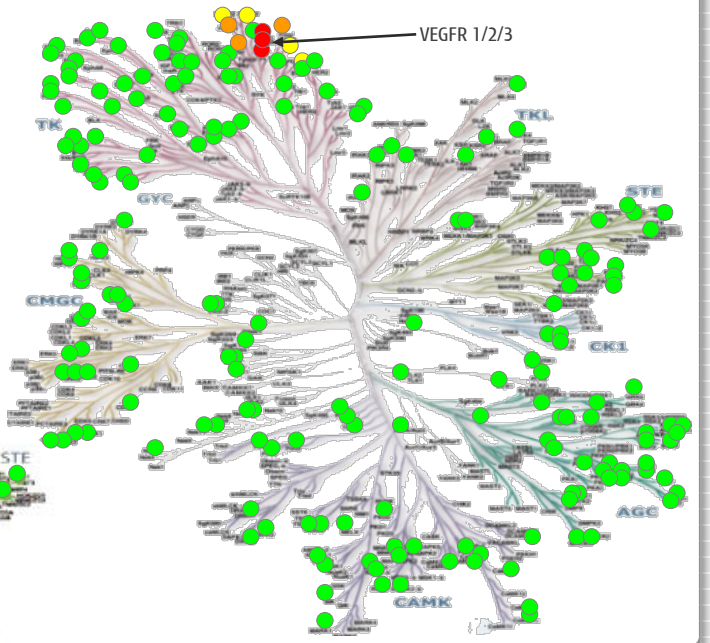
Savolitinib

~1,000 times more selective to c-Met than next kinase (PAK3)



Fruquintinib [2][3]

~250 times more selective to VEGFR3 than next kinase (Ret)



[1] W. Su, et al, 2014 American Association of Cancer Research (note legend yellow = ›50%; green = ‹ 50%; [2] Sun et al., Cancer Biology & Therapy 15:12, 1635--1645; December 2014; [3] Ret is the next "Non-VEGFR" kinase.

Superior selectivity = Better tolerability

More use = prolonged target coverage = better efficacy

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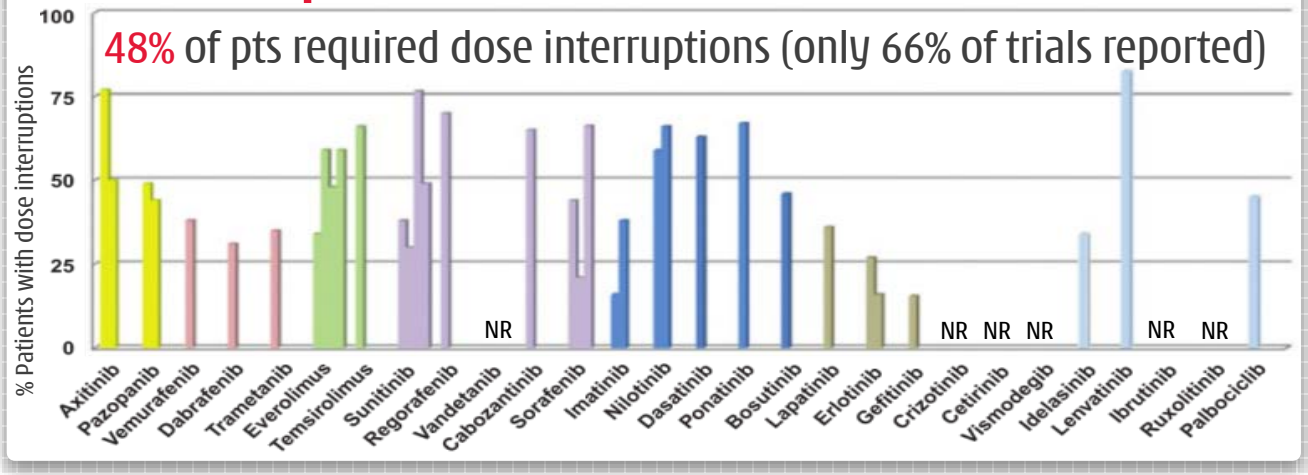
Better tolerability for sustained usage

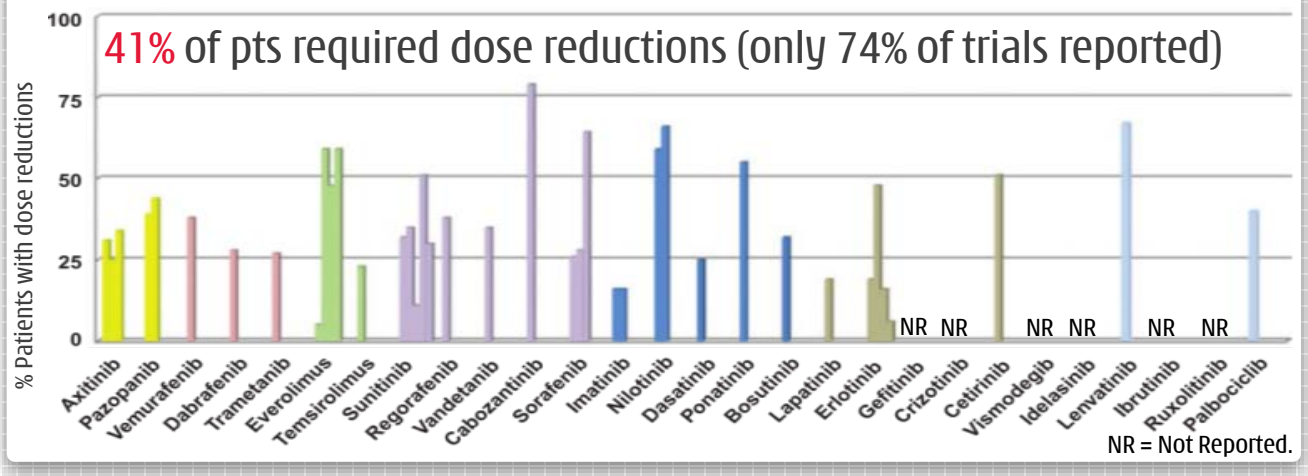
Review of 28 FDA approved small molecule oncology targeted therapies revealed high incidence of toxicity[1]

- Pronounced in drugs with narrow therapeutic index (i.e. efficacious dose at or near max tolerable dose)
- Combination trials even harder: 64% with grade 3-4 toxicities vs. 37% in monotherapy trials

Dose interruptions in Phase III studies



Dose reductions in Phase III studies



NR = Not Reported.

[1] FDA approved btw Jan '02 to Feb '15. Roda D et al. "*Are Doses and Schedules of Small-Molecule Targeted Anticancer Drugs Recommended by Phase I Studies Realistic?*" Clinical Cancer Research 2016 May 1;22(9):2127-32.

Superior selectivity = Better tolerability

More use = prolonged target coverage = better efficacy

1st gen. multi-kinase inhibitors require substantial dose interruptions or reductions.

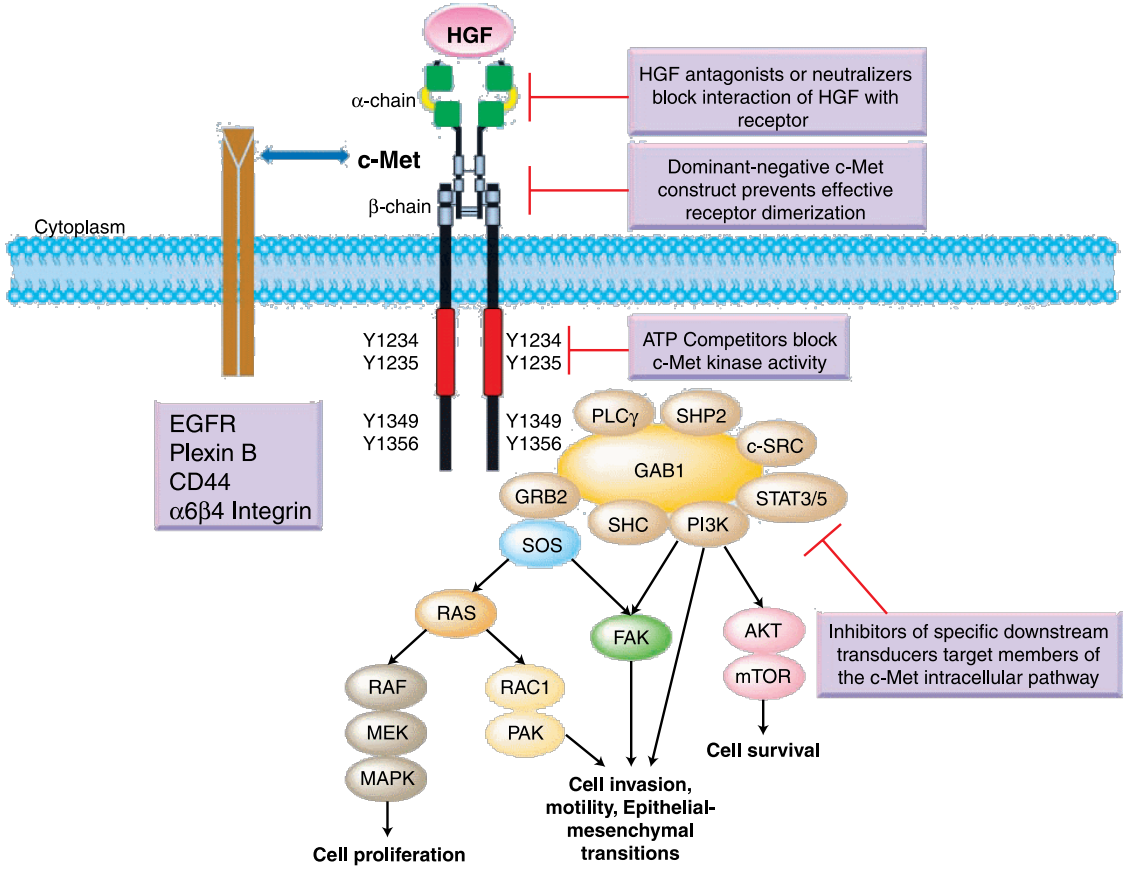
Drug – targets	Phase III Study	Dose Interruptions
Sunitinib – VEGFR1,2,3, PDGFRβ, Flt3, CSF-1R, c-Kit, Ret	1L RCC – vs. pbo	54% vs 39%
Axitinib – VEGFR1,2,3, PDGFRα, c-kit	2L RCC – vs. sorafenib	Dose Mods: 55% vs 62%
Pazopanib – VEGFR1,2,3, c-Kit, Itk, Lck, PDGFRα,β, FGFR, c-Fms	1/2L RCC – vs. pbo	42%
Regorafenib – VEGFR1,2,3, Raf, Ret, PDGFR, c-Kit	3L CRC – vs. pbo	63%
Lenvatinib – VEGFR1,2,3, Ret, PDGFR, c-Kit, FGFR1,2,3,4	DTC – vs. pbo	82% vs 18%
Savolitinib – c-Met (Ph I/Ib/II)	Open-label studies	28%
Fruquintinib – VEGFR1,2,3 (Ph III)	≥3L CRC – vs. pbo	35% vs. 10%
Fruquintinib – VEGFR1,2,3 (Ph II)	3L NSCLC – vs. pbo	13% vs. 0%
Sulfatinib – VEGFR 1,2,3, FGFR1 (Ph I/II)	Open-label studies	34%
Epitinib – EGFR (Ph I/II)	NSCLC w/brain mets	13%

[1] Sources: Prescribing information; Chi-Med data.

World-class chemistry for versatile cancer drugs

Case Study: Savolitinib, A Highly selective c-MET kinase inhibitor

Savolitinib: c-MET genetic alterations drive multiple cancers



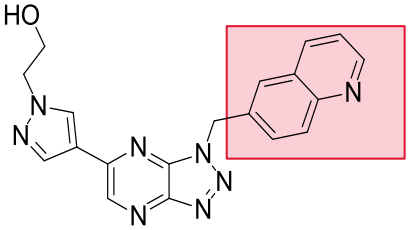
Joseph Paul Eder, et al, *Novel Therapeutic Inhibitors of the c-MET Signaling Pathway in Cancer*, Clin Cancer Res 2009;15(7)

- Aberrant HGF/c-MET pathway activation leads to uncontrolled tumour cell growth, invasion and survival
- Mechanisms of c-MET activation:
  - ↗ c-MET gene amplification
  - ↗ HGF/c-MET over-expression
  - ↗ Mutations
  - ↗ Cross talk with other receptors
- Aberrant HGF/c-MET axis activation detected in multiple major tumour types, including lung, stomach, RCC, CRC and HCC

Savolitinib: designed to be highly selective *and* eliminate serious kidney toxicity

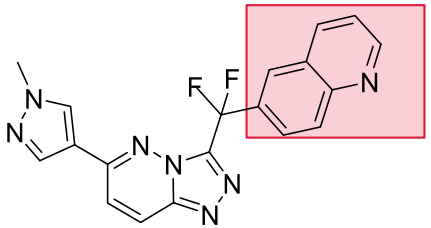
1st generation small molecule C-MET inhibitors encountered human-specific toxicity

2-quinolinone metabolite in humans has dramatically reduced solubility and appeared to crystallise in the kidney resulting in obstructive toxicity.[1]



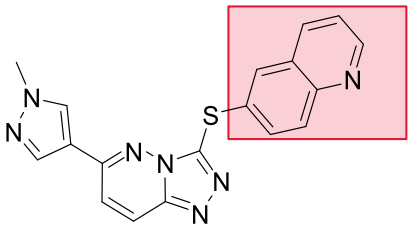
Pfizer

PF-04217903[2]



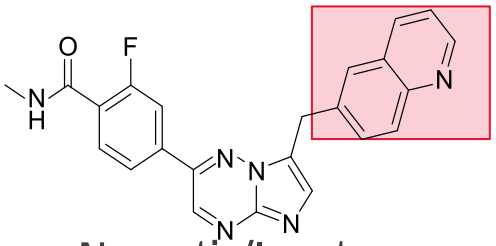
Janssen

JNJ-38877605[3]



Lilly

SGX-523[5]

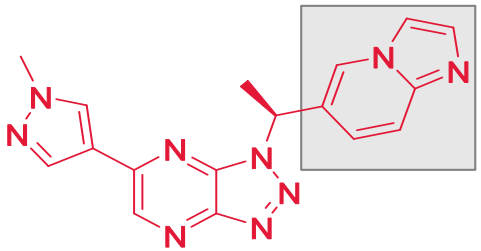


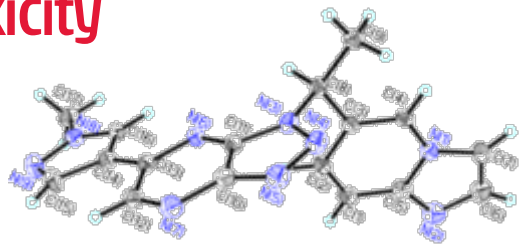
Novartis/Incyte

INC-280[4]

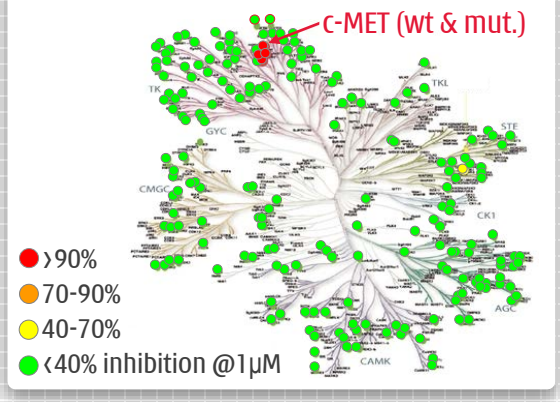
Sources: [1] Diamond, S.; et. al.: Species-specific metabolism of SGX523 by aldehyde oxidase, Drug Metabolism and Disposition, 2010, 38, 1277-85.
[2]-[4] 99th Annual Meeting for American Association for Cancer Research (AACR); 12 - 16 April 2008; San Diego, USA - [2] Zou H, et al, [3] Perera T, et al, [4] Liu X, et al;
[5] Bounaud et al, WO 2008/051808 A2.

Savolitinib: >460 patients treated to-date, no serious renal toxicity





Source: W. Su, et al, 2014 American Association of Cancer Research.



Savolitinib: Phase II study in papillary kidney cancer (PRCC) clear benefit in c-MET+ patients[1]

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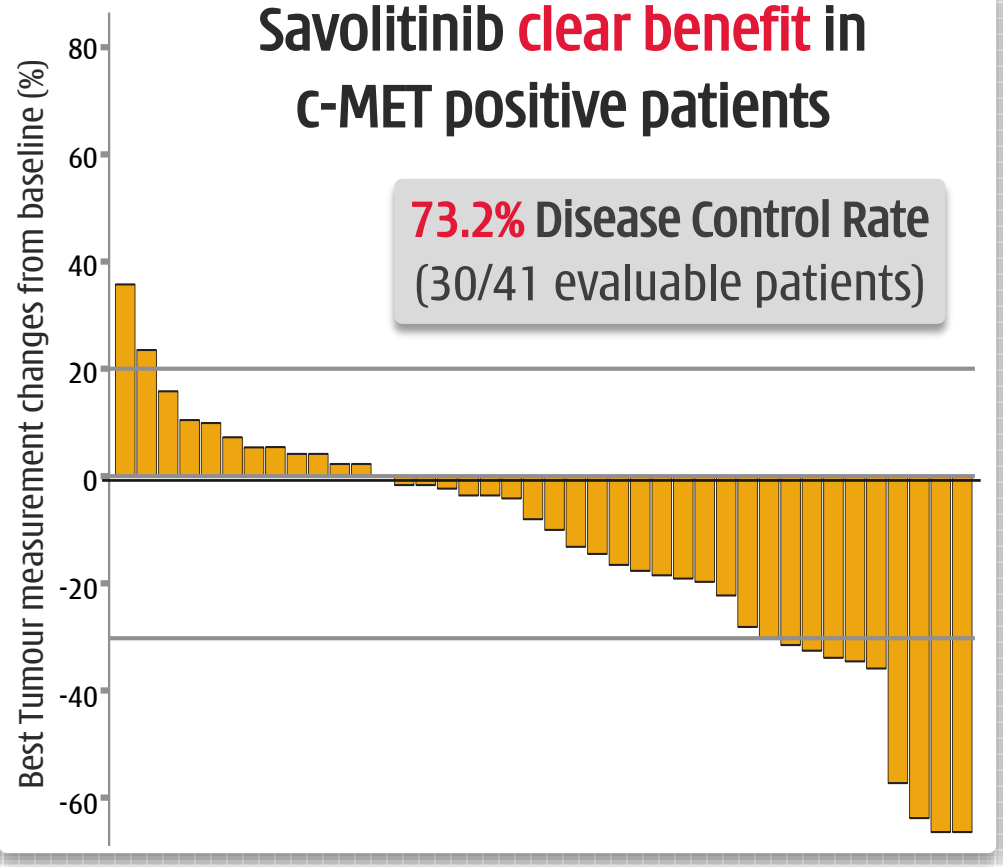
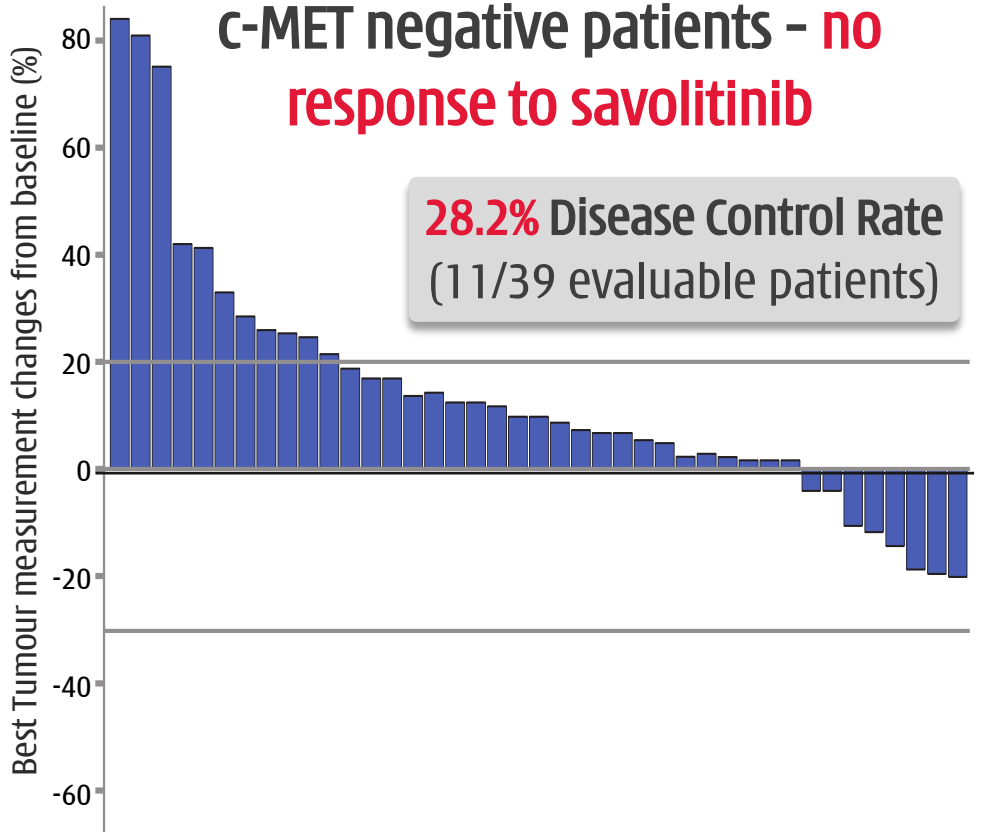
Savolitinib clear benefit in c-MET positive patients



73.2% Disease Control Rate
(30/41 evaluable patients)

c-MET negative patients – no response to savolitinib



28.2% Disease Control Rate
(11/39 evaluable patients)

Savolitinib safe & very well tolerated vs. other RCC TKIs[2]:

Highly tolerable vs. other TKIs:

- ✓ Discontinued: 8% vs. 10~24%.
- ✓ Dose reduction: 13% vs. 44-62%.

Grade 3 & above adverse events (AEs):

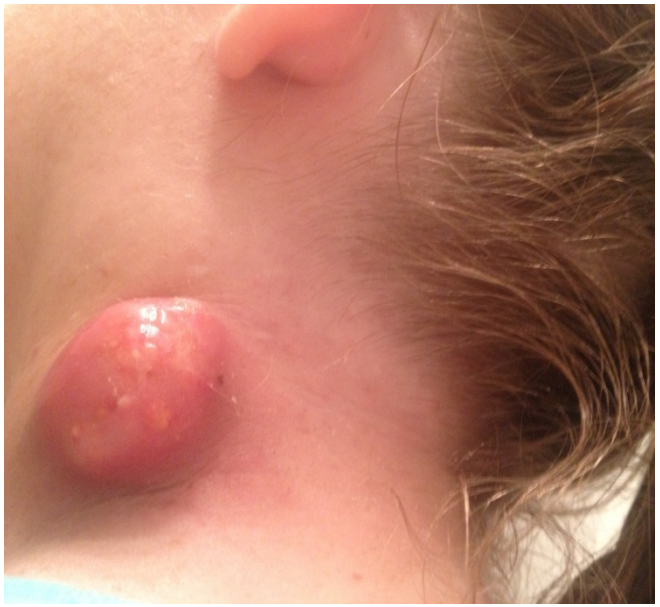
- ✓ Any ≥G3 AE: 19% vs. 58-76%.
- ✓ Specific ≥G3 AEs: 0~2% vs. 6~17%.

[1] Choueiri T et al. A single-arm biomarker-based phase II trial of savolitinib in patients with advanced papillary renal cell cancer (PRCC). J Clin Oncol 35, 2017 (suppl 6S; abstract 436). [2] COMPARZ and METEOR studies: RJ Motzer et al, N Engl J Med 369;8, Aug 22, 2013; TK Choueiri et al, Lancet Oncol.17;7, Jun 5, 2016; RJ Motzer et al, JAMA 295;21 Jun 7, 2006.

Savolitinib: targeting c-MET+ lung cancer

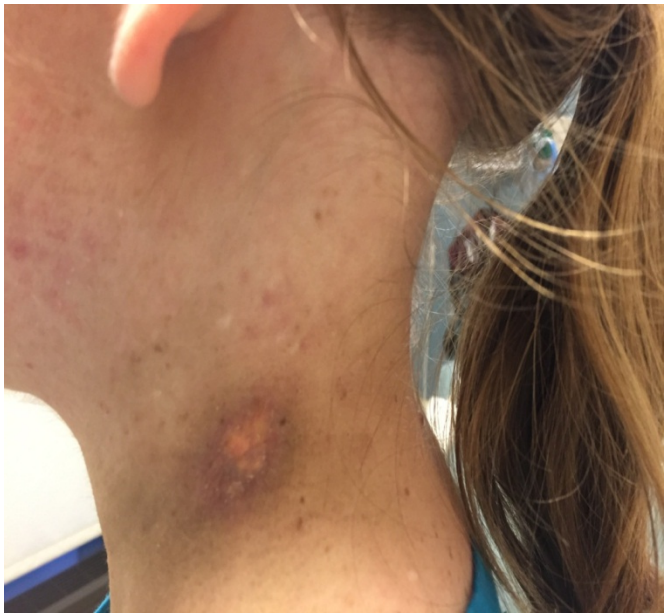
Tumour response to treatment with osimertinib + savolitinib

- 32-year-old female NSCLC patient.
- Rapidly progressing bone & lung metastases. Major solid tumour.
- Primary progression on prior EGFR inhibitor (i.e. Tarceva resistance).
- Brief response to platinum doublet.



Pre-treatment

High c-MET amplification → responds to osimertinib + savolitinib



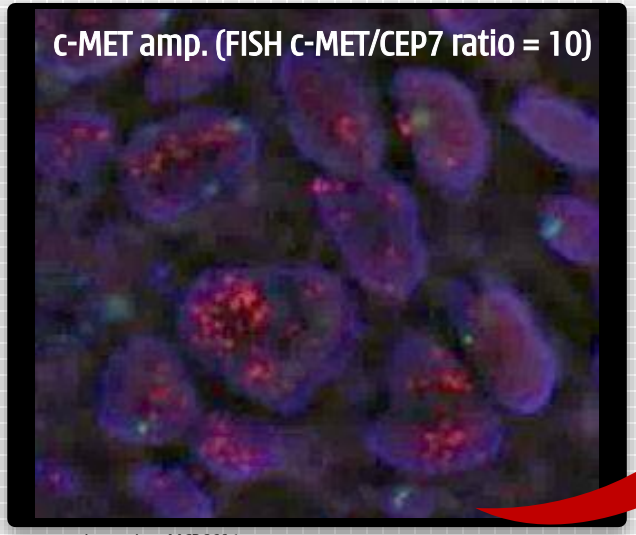
4 weeks later

Oxnard et al J Clin Oncol 33, 2015 (suppl; abstr 2509)

Savolitinib in Gastric Cancer

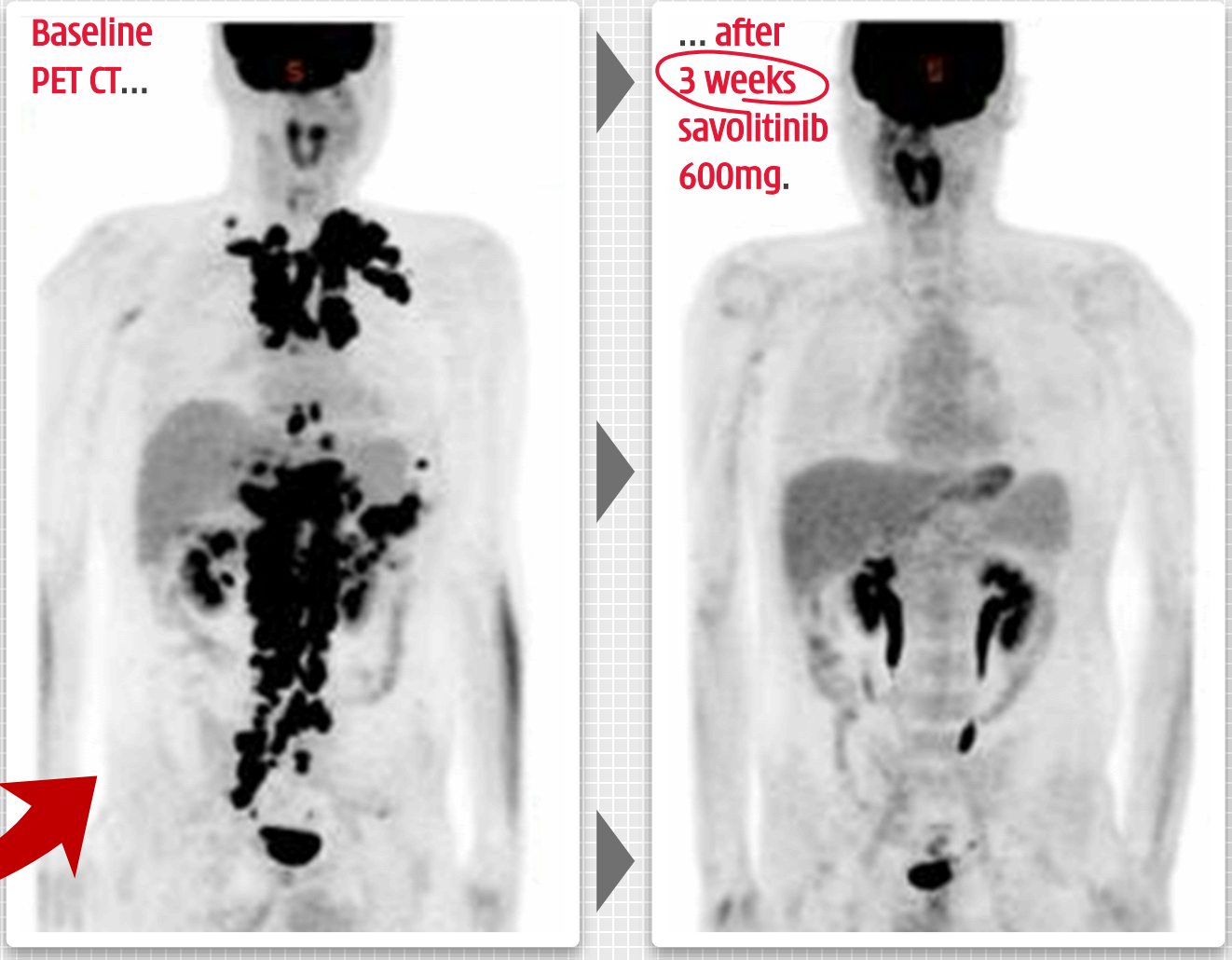
Targeting c-MET gene amplification in PoC trials

- PoC trials ongoing
- Encouraging clinical activity seen in GC patient with c-MET gene amplification
- Durable response observed: one patient in response for >2 years, still on treatment



Jeeyun Lee, AACR 2016.

VIKTORY trial – 34-year old male; surgery ruled-out; failed 4-cycles XELOX



Our drug candidates in R&D

1st-wave in final clinical trials

2nd-wave in proof-of-concept

Exciting 3rd-wave in research

31 active or completing trials on 8 drug candidates

1st positive pivotal readout – all 4 first wave drug candidates in Ph.III soon

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Program	Target	Partner	Study number/Indication	Latest Status	Line	Target patient	Combo therapy	Site	Preclin.	Ph.I	Proof-of-concept	Pivotal/Ph.III
Savolitinib (AZD6094)	c-Met	AstraZeneca	1. Papillary renal cell carcinoma	Report Ph.II Feb. 2017; **Ph.III started June 2017**	1st	c-Met-driven		Global			*	*
			2. Papillary renal cell carcinoma	NCI Ph.II - savo vs. sunitinib vs. cabozan. vs. crizot.	All	c-Met-driven		US				
			3. Papillary renal cell carcinoma	Ph.Ib enrolling	-	All	**durvalumab** (PD-L1)	UK			*	
			4. Clear cell renal cell carcinoma	Start when Study 3/5 begin Ph.Ib expansion stage	2nd	VEGF TKI refractory		UK			*	
			5. Clear cell renal cell carcinoma	Ph.Ib enrolling	2nd	VEGF TKI refractory	**durvalumab** (PD-L1)	UK			*	
			6. Non-small cell lung cancer	Ph.II expansion enrolling; **Pivotal decision 2017**	2nd	EGFR TKI refractory	**Tagrisso®** (T790M)	Global				
			7. Non-small cell lung cancer	Ph.II enrolling; **Pivotal decision 2017**	3rd	EGFR/T790M TKI	**Tagrisso®** (T790M)	Global				
			8. Non-small cell lung cancer	Ph.II complete; **Pivotal decision 2017**	2nd	EGFR TKI refractory	**Iressa®** (EGFR)	China				
			9. Non-small cell lung cancer	Ph.II enrolling	1st	c-Met-driven		China			*	
			10. Lung cancer	Ph.II enrolling	1st	c-Met-driven		China			*	
			11. Gastric cancer	Ph.Ib enrolling	3rd/All	c-Met+		SK/PRC			*	
			12. Gastric cancer	Ph.Ib enrolling	2nd	c-Met+	**docetaxel** (chemo)	SK			*	
			13. Gastric cancer	Ph.Ib enrolling	2nd	c-Met O/E	**docetaxel** (chemo)	SK			*	
Fruquintinib	VEGFR 1/2/3	Lilly (in China only)	14. Colorectal cancer	**Ph.III met all endpoints; NDA submitted Jun 2017**	3rd	All ✓		China				
			15. Non-small cell lung cancer	**Ph.III enrolling**	3rd	All		China			n/a	*
			16. Non-small cell lung cancer	Ph.II enrolling	1st	All	**Iressa®** (EGFR)	China				*
			17. Caucasian bridging	Ph.I dose escalation start 2017	-	All comers		US				
			18. Gastric cancer	**Ph.III (w/ interim analysis) start 2017**	2nd	All	**paclitaxel** (chemo)	China				*
Sulfatinib	VEGFR/ CSF1R/ FGFR1		19. Pancreatic NET	**Ph.III enrolling**	1st	All		China				*
			20. Non-pancreatic NET	**Ph.III enrolling**	1st	All		China				*
			21. Caucasian bridging	Ph.I dose escalation enrolling	-	All comers		US				
			22. Medullary thyroid ca.	Ph.II enrolling	2nd	Radiotherapy ref.		China				*
			23. Differentiated thyroid ca.	Ph.II enrolling	2nd	Radiotherapy ref.		China				*
			24. Biliary tract cancer	Ph.II enrolling	2nd	Chemo ref.		China				*
Epitinib	EGFRm+		25. Non-small cell lung cancer	**Ph.III start 2017**	1st	EGFRm+ brain mets		China				*
			26. Glioblastoma	Ph.II start 2017	-			China				*

5 pivotal Phase IIIs active or completing, & 3 more to start in 2017 / early 2018

Oncology

Immunology

Notes: * = when an NDA submission is possible based on the receipt of favorable clinical data; Proof-of-concept = Phase Ib/II study (the dashed lines delineate the start and end of Phase Ib); combo = in combination with; brain mets = brain metastasis; VEGFR = vascular endothelial growth factor receptor; TKI = tyrosine kinase inhibitor; EGFR = epidermal growth factor receptor; NET = neuroendocrine tumours; ref = refractory, which means resistant to prior treatment; T790M= EGFR resistance mutation; EGFRm+ = epidermal growth factor receptor activating mutations; EGFR wild-type = epidermal growth factor receptor wild-type; 5ASA = 5-aminosalicyclic acids; chemo = chemotherapy; c-Met+ = c-Met gene amplification; c-Met O/E = c-Met over-expression; FGFR = Fibroblast Growth Factor Receptor ; CSF1R = Colony Stimulating Factor-Receptor 1; NCI = U.S. National Cancer Institute; Aus = Australia; SK = South Korea; PRC = People's Republic of China; UK = United Kingdom; US = United States; Global = >1 country.

2nd-wave of innovation now in proof-of-concept

4 novel 2nd wave drug candidates in Phase Ib/II studies or about to start

Program	Target	Partner	Study number/Indication	Latest Status	Line	Target patient	Combo therapy	Site	Preclin.	Ph.I	Proof-of-concept	Pivotal/Ph.III
Theliatinib	EGFR WT		27. Solid tumours	Ph.I dose escalation enrolling (continuing)	-	All comers		China				*
			28. Esophageal cancer	Ph.Ib expansion enrolling	1st	EGFR WT		China				*
HMPL-523	Syk		29. Rheumatoid arthritis	Ph. I complete; preparing for Ph.II in 2017	-	Methotrexate ref.		Aus				*
			30. Immunology	Ph.I dose escalation start 2017	-	Healthy volunteers		China				*
			31. Hematological cancers	Ph.I enrolling; target complete Ph.I 2017	2nd/3rd	All comers		Aus			*	
			32. Lymphoma	Ph.I dose escalation enrolling	-	All comers		China			*	
HMPL-689	PI3Kδ		33. Hematological cancers	Ph.I dose escalation (PK analysis)	-	Healthy volunteers		Aus				*
			34. Lymphoma	Ph.I dose escalation start 2017	2nd/3rd	All comers		China				*
HMPL-453	FGFR 1/2/3		35. Solid tumours	Ph.I dose escalation	-	All comers		Aus			*	
			36. Solid tumours	Ph.I dose escalation start 2017	-	All comers		China			*	
HM004-6599	NF-κB (TNF-α)	Nestlé Health Science	Ulcerative colitis (Induction)	HMPL-004 reformulation; Re-submit IND 2017	2nd	5ASA refractory		China				*
			Ulcerative colitis (Maintenance)	Await positive Ph.II in Ulcerative Colitis (Induction)	2nd	5ASA refractory		China				*
NSP DC2	TBD	Nestlé Health Science	Immunology	Preclinical complete end 2017				China				*
Multiple	TBD		Oncology	Four small molecule/antibody programs in preclin.				TBD			*	

Oncology

Immunology

~3,100 patients/subjects treated in studies to date on our drug candidates, with over 300 dosed in H1 2017.

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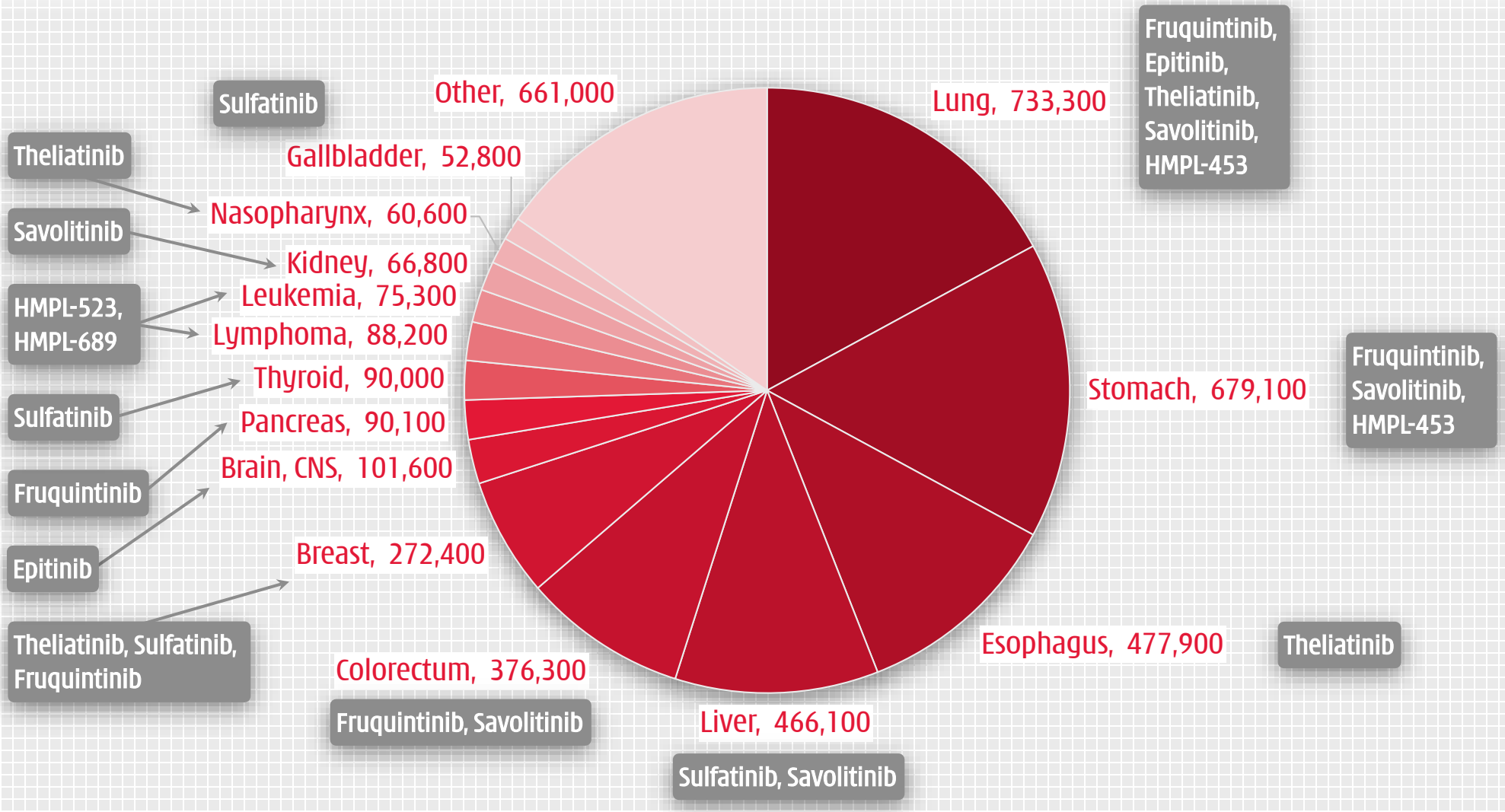
Covering high unmet medical needs in China and around the world

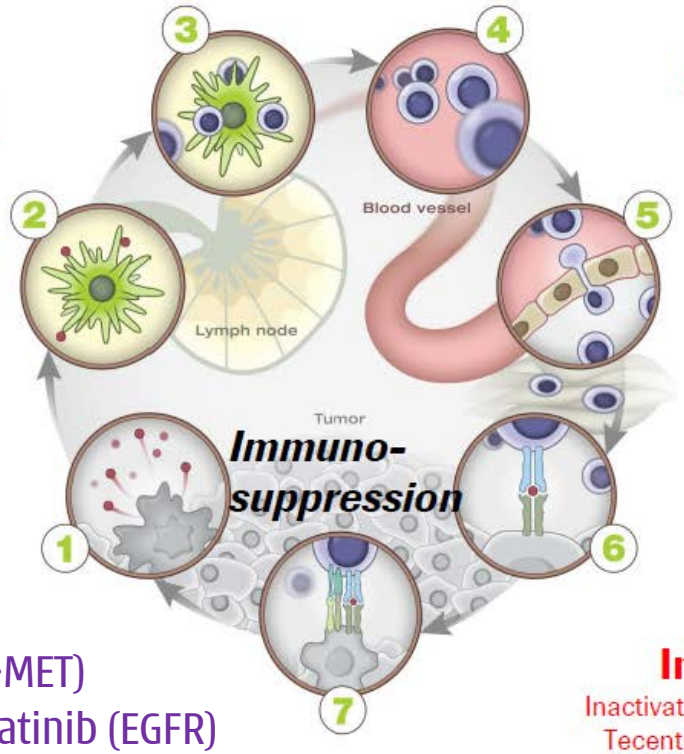


Source: Chen, W., Zheng, R., Baade, P. D., Zhang, S., Zeng, H., Bray, F., Jemal, A., Yu, X. Q. and He, J. (2016), Cancer statistics in China, 2015. CA: A Cancer Journal for Clinicians, 66: 115-132. doi:10.3322/caac.21338.

The 3rd-wave: Immuno-oncology focused, with potential to combine with existing programmes

Immune desert
Insufficient T cell response

Excluded infiltrate
Inadequate T cell homing



Priming & activations
- *aOX40*
- *4-1BB*

Anti-angiogenesis
- VEGFR (fruquintinib)
- VEGFR/FGFR (sulfatinib)
- FGFR (HMPL-453)

Trafficking
- CCRs

- Clinical
- Pre-clinical
- *Italics: antibody*

Antigen release
- Savolitinib (c-MET)
- Epitinib/Theliatinib (EGFR)
- HMPL-453 (FGFR)
- HMPL-523 (Syk)
- HMPL-689 (PI3Kδ)
- ERK, RIP3K, IDH

Inflamed
Inactivated T cell response:
Tecentriq most effective

Negative regulators
- Treg (HMPL-689)
- CSF-1R (sulfatinib)/selective CSF-1R
- IDOi, AhRi
- *TIM3, TCBs*

Derived from Chen DS et al. Oncology Meets Immunology: The Cancer-Immunity Cycle. Immunity , Volume 39 , Issue 1 , 1 - 10.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HUTCHISON CHINA MEDITECH
Thank you