R&D UPDATES

October 31, 2025

HKEX: 13, Nasdaq / AIM:HCM

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Agenda

HUTCHMED

Welcome Opening

Michael Shi
Chief Medical Officer & Head of R&D

Antibody-Targeted Therapy Conjugate (ATTC) Platform

- Next-generation ATTC Platform
- Our First Candidate: HMPL-A251
- Our Preliminary Development Strategy

Late-Stage Pipeline Updates

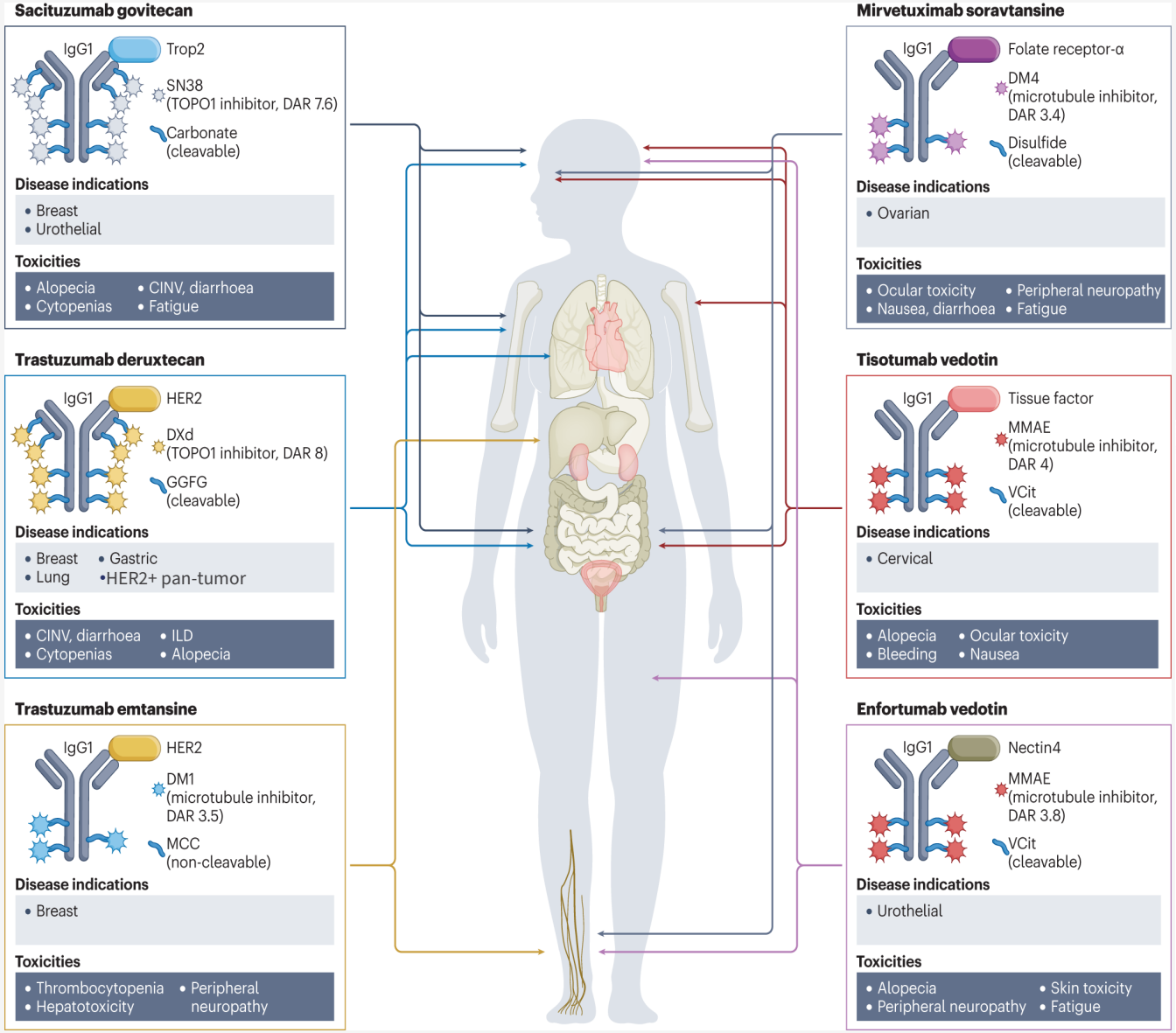
Closing Remarks

Q&A Session

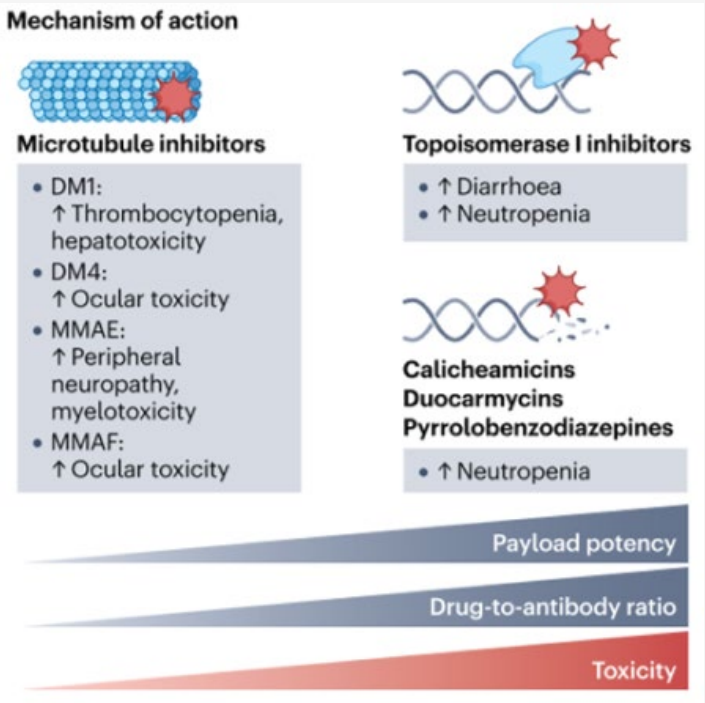
Next-generation Antibody-Targeted Therapy Conjugate (ATTC) Platform

ATTC Platform Overview

Toxin-based ADCs: advantages and challenges

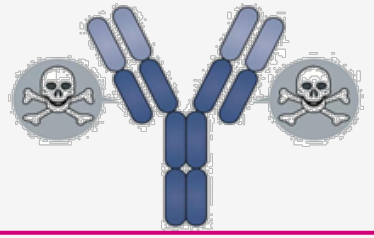


- Despite being designed with the rationale of expanding the therapeutic indices of conventional chemotherapies, most ADCs have a toxicity profile similar to cytotoxic payload.
- Combination of ADCs with chemotherapy presents several challenges related to overlapping toxicities.

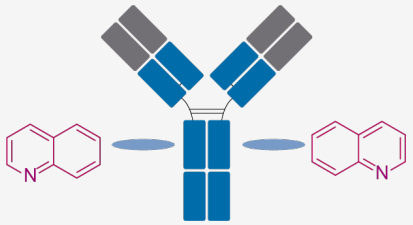


Nat Rev Clin Oncol. 2023, 20(8): 558-576

Traditional ADCs vs. HUTCHMED ATTCs



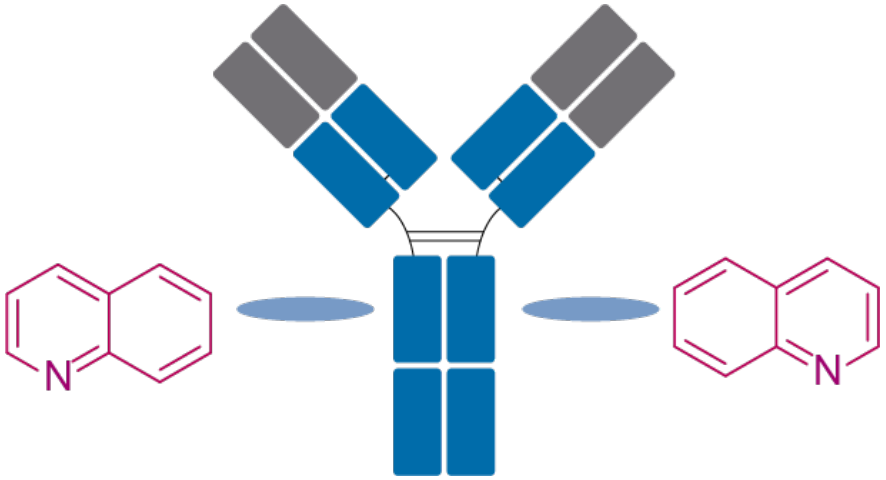
	Traditional Antibody-Drug Conjugates (ADC)	HUTCHMED Antibody-Targeted Therapy Conjugates (ATTC)
How it works	• Cytotoxin payload • Target rapidly dividing cells (mostly cancer cells)	• Target proteins required for cancer growth • Synergistic combination effect with antibody • Ability to combine with IO/chemo-based frontline SOC or other target therapy • Overcome chemo resistance • Can be dosed long term
Side effects	Antibody based toxicities Cytotoxin-related key toxicities[1] • Hematological toxicity • Hepatotoxicity • Gastrointestinal toxicity • Neurotoxicity, ocular toxicity • Interstitial lung disease	Antibody based toxicities Targeted therapy (TT) payload based • Low on-target and off-tumor toxicity • Low compound base toxicity such as liver, QT, etc • Non-genotoxic, low myelotox, amenable for long term use
Limitation	Resistance to chemotherapy, not specific	Resistance to target therapy?
Predictive biomarker / Sensitive population	No/Not clear Patients with genetic drivers do worse	Clear Patients with genetic drivers should benefit most



[1]. Cancers (Basel). 2023 Feb; 15(3): 713

HUTCHMED ATTCs design objectives

Target specific drivers, alleviate chemo-based toxicities, enable combination with frontline chemo-based SoCs.



Antibody and ADC production
High titers, high yields

Stable linkers
High tolerability

Warhead
Targeted therapeutic agents

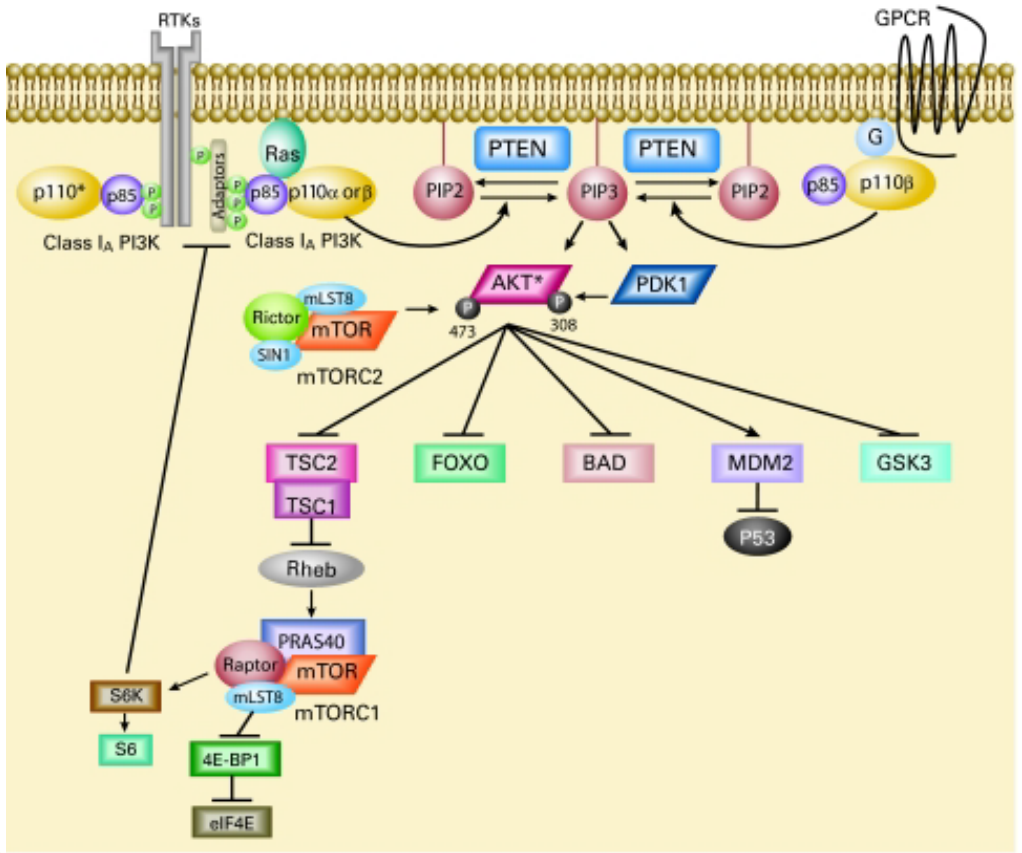
Key attributes of ATTCs

- Targeted therapies target genetic drivers (oncogenes) exist in tumor cells, not in normal cells, leading to lower toxicities.
- Antibody targeted therapy conjugates will lower the free targeted therapy drugs in circulation, further lowering compound or target-based toxicities, such as liver toxicities associated with oral therapies.
- Opportunity to further enhance anti-tumor efficacy through combination effect between the antibody and the targeted therapy.
- Ability to combine with chemo-based frontline SOC or monotherapy as chemo free adjuvant for long term use.

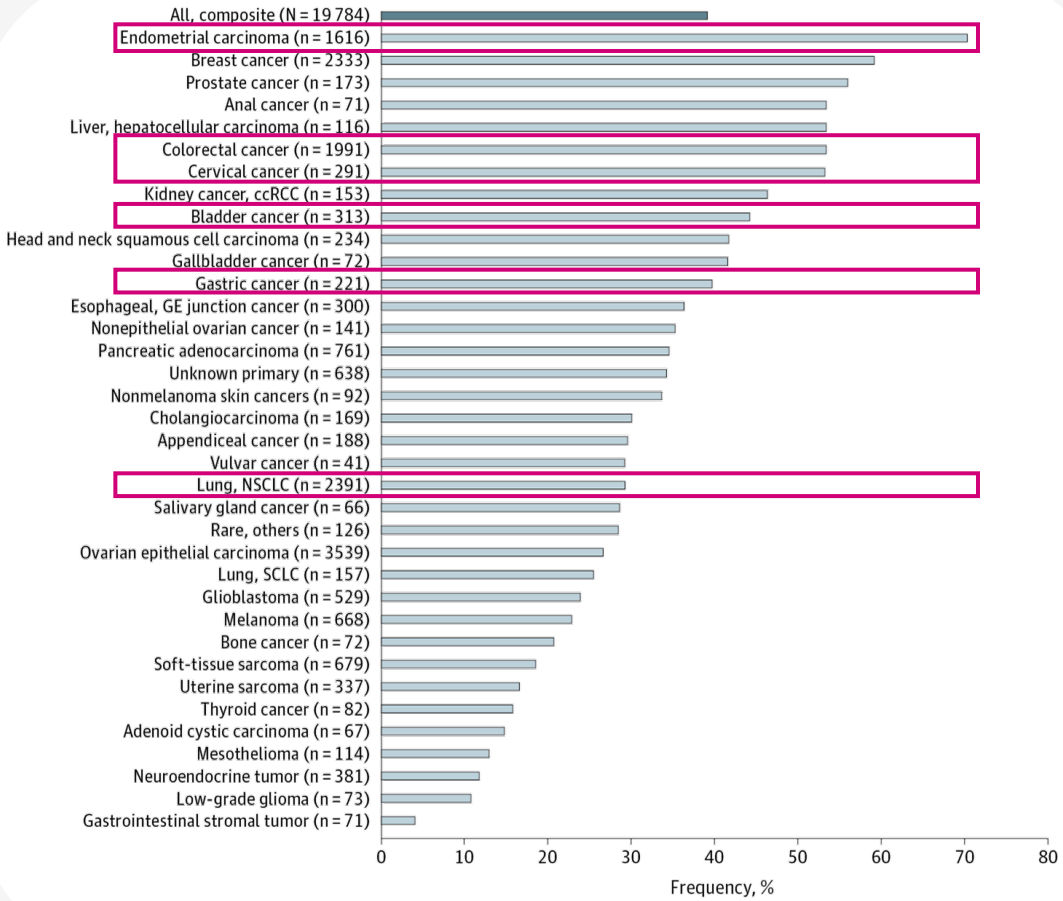
PAM Pathway

PI3K/AKT/mTOR (PAM) pathway is an attractive therapeutic target

PAM signaling pathway controls many physiological functions and cellular processes[1]



PAM pathway alteration is one of the most common events in human cancer (~50% of solid tumor)[2]



PAM pathway alteration: *PIK3CA/AKT1* gain-of-function mutation; PTEN loss of function

[1]. Adapted from J Clin Oncol. 2010;28(6):1075-1083. [2]JAMA Oncol. 2016;2(12):1565-1573

Important to block genomic driver mutations to improve clinical benefit (1/2)

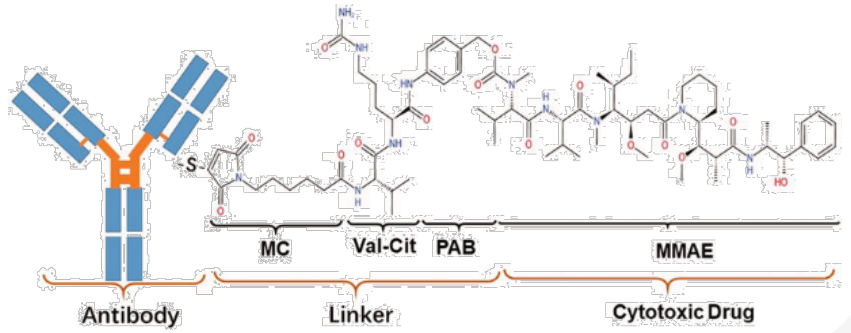
PAM-altered patient populations have a poorer prognosis than non-altered, regardless of their HER2 expression.

Disitamab vedotin (RC48)

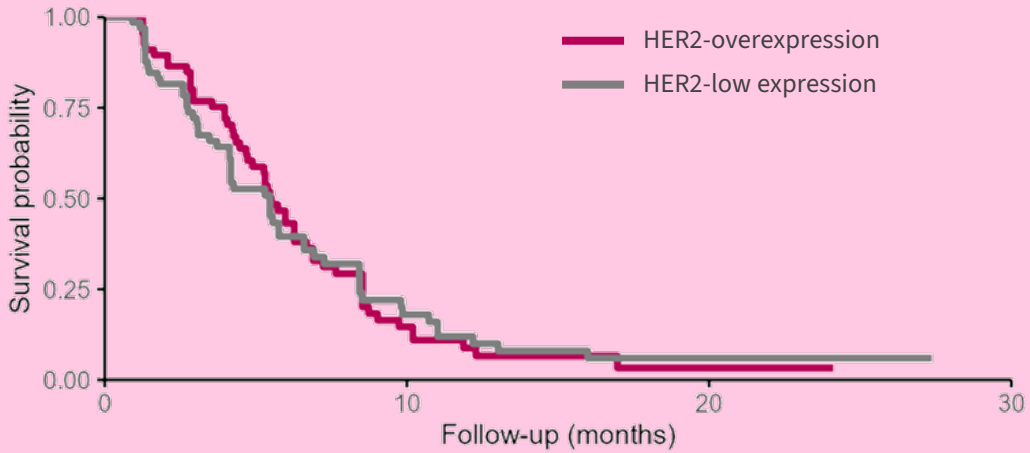
an HER2-directed ADC in breast cancer patients[1,2]

	HER2 positive		HER2 low		
	ITT	PAM-altered		ITT	PAM-altered
ORR	42.9%	34.6%	ORR	33.3%	34.3%
PFS	**5.5m**	**4.5m**	**PFS**	**5.1m**	**3.4m**

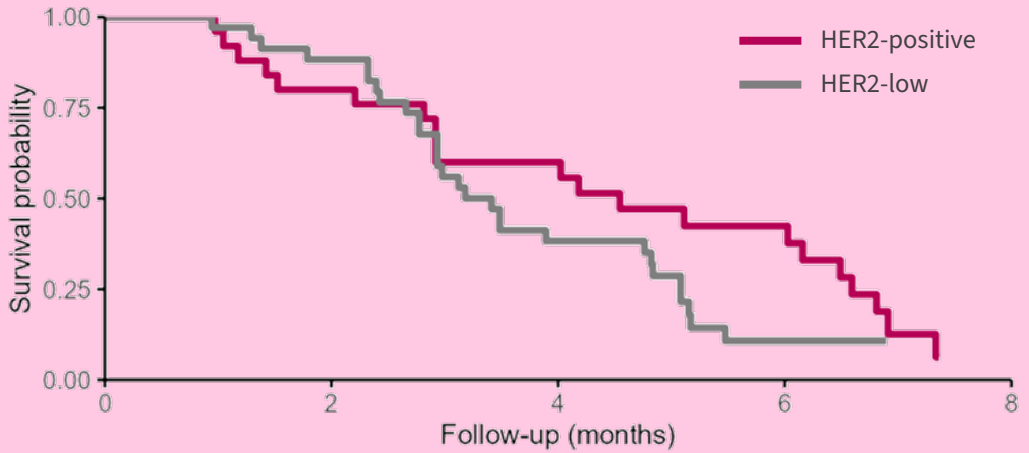
The molecular structure of RC48



RC48 in breast cancer: PAM wildtype and altered[1]



RC48 in breast cancer: with abnormal activation of PAM pathway[2]



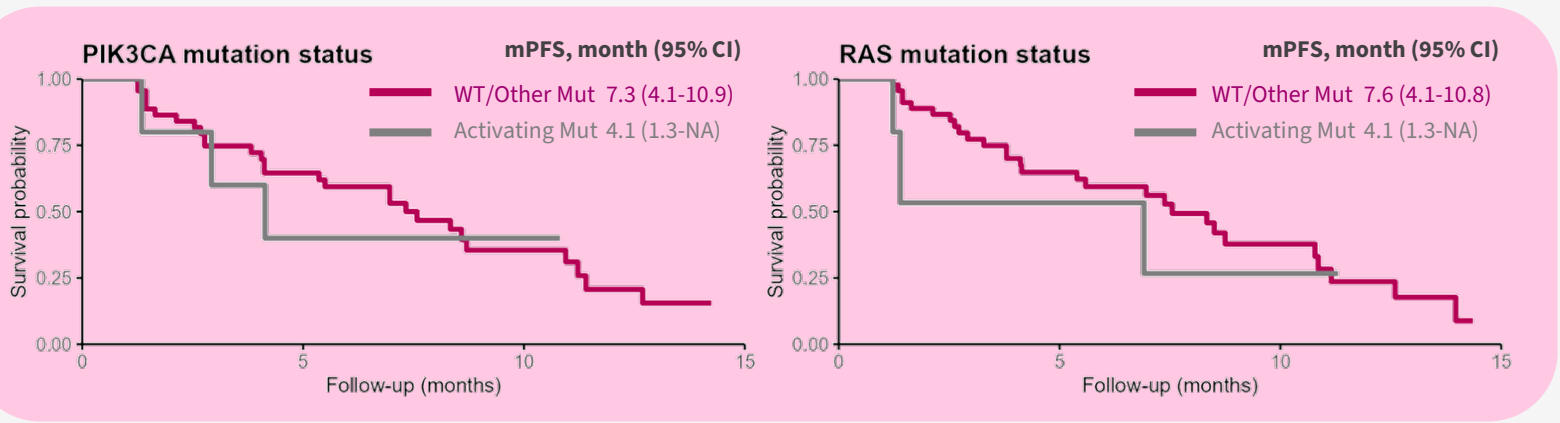
ITT = Intent-to-Treat

[1]. J. Wang et al, Cancer Commun (Lond) 2024 44(7) 833–51; [2] ESMO 2024 #384P

Important to block genomic driver mutations to improve clinical benefit (2/2)

DESTINY-CRC01 flags PIK3CA or RAS-mutant mCRC as a high-need, targetable segment with attractive commercial potential.

		n	ORR (95% CI)	*P* value	Median PFS, months (95% CI)	*P* value	Median OS, months (95% CI)	*P* value
PIK3CA mutation status	WT	46	47.8 (32.9-63.1)	0.674	7.3 (4.1-10.9)	0.324	17.3 (8.8-22.8)	0.360
	Mut	6	33.3 (4.3-77.7)		4.1 (1.3-NA)		11.6 (1.3-NA)	
RAS mutation status	WT	46	47.8 (32.9-63.1)	0.674	7.6 (4.1-10.8)	0.168	17.3 (8.8-24.3)	0.404
	Mut	6	33.3 (4.3-77.7)		4.1 (1.3-NA)		11.6 (4.1-NA)	
HER2 mutation status	WT	44	43.2 (28.3-59.0)	0.447	8.3 (4.1-10.9)	0.407	15.5 (8.8-22.8)	0.917
	Mut	8	62.5 (24.5-91.5)		5.5 (1.4-NA)		15.9 (2.9-NA)	
bTMB status (cutoff = 20)	Low	39	53.8 (37.2-69.9)	0.064	7.6 (4.1-10.8)	0.614	19.9 (12.3-25.3)	0.014
	High	13	23.1 (5.0-53.8)		2.1 (1.3-NA)		7.1 (2.8-15.5)	



- In the T-DXd treated mCRC from the DESTINY-CRC01 study, ORR, PFS and OS tend to be **lower** in the PIK3CA mutant or RAS mutant population than in the wildtype group.
- **This may present an opportunity for targeted agent payloads.**

S. Siena et al, Nat Commun 2024 15 10213; Adapted charts.

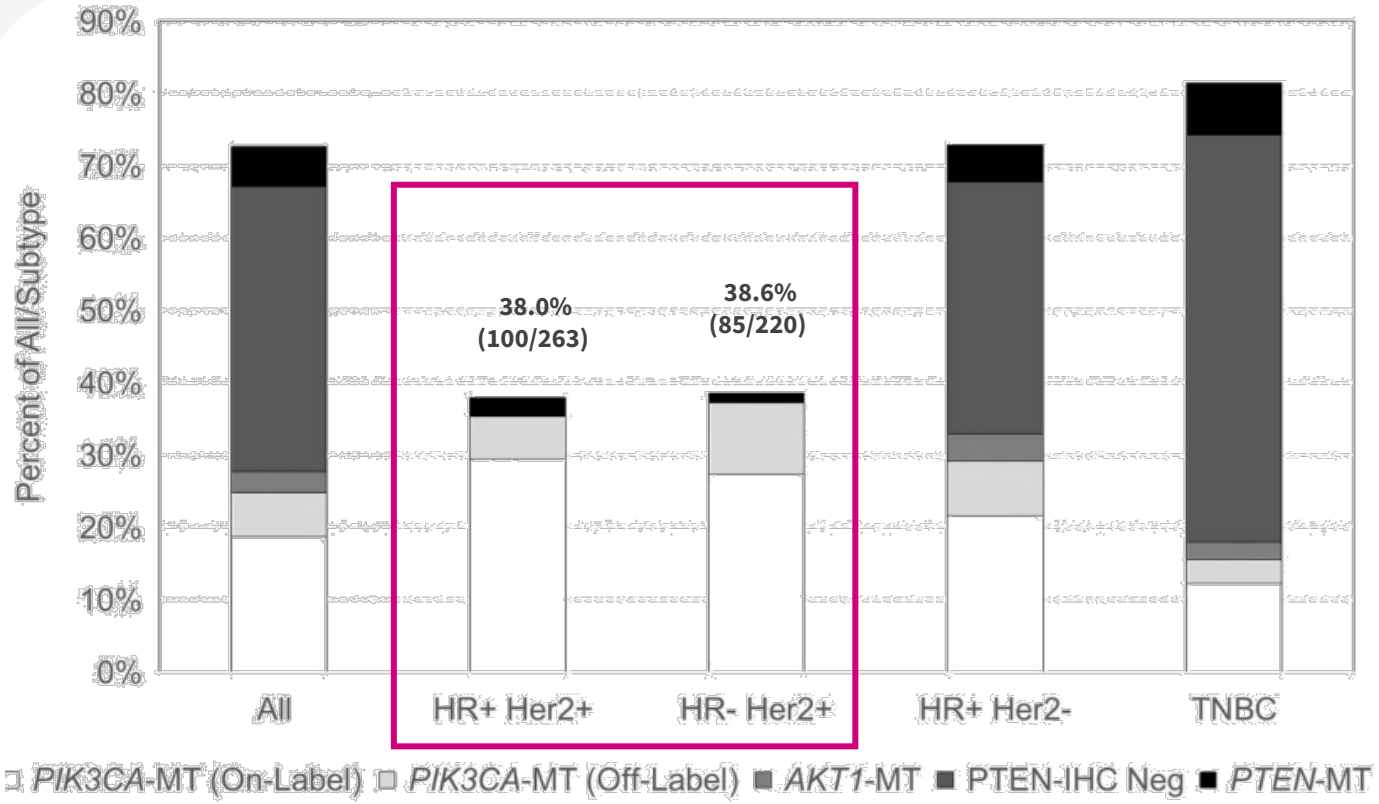
PAM pathway targeted drugs in clinic

- On-target and severe toxicities by PI3K/mTOR inhibition prevent sufficient dose to achieve necessary target inhibition.
- Feedforward and feedback loops between PI3K isoforms, AKT, and mTOR cross-activate uninhibited sub-units, limiting clinical benefit of single node inhibitor.
- **Need to increase the delivery of the PAM pathway inhibitor into tumor cells specifically to maximize their benefit - ATTC strategy.**

PI3K/mTOR		Pan-PI3K		Single node	Today
1st Gen		2nd Gen		3rd Gen	
Programs halted at Phase I/II		**Program halted at Phase III**		**Approved**	**Phase III positive results**
PF-04691502 PKI-402 Dactolisib BGT226 Apitolisib	Picitilisib Omipalisib GSK1059615 Samotolisib	Buparlisib	Taselisib	Everolimus (mTORC1) Alpelisib (P13Kα) Capivasertib (AKT)	Gedatolisib
Too toxic to proceed Poor PK properties		**High toxicity Limited efficacy**		**Tolerable safety profiles No significant OS benefit**	**Need safe, potent pan-PI3K/mTOR inhibitor**

Targeting PI3K/AKT/mTOR (PAM) pathway alteration: a promising approach for breast cancer

High frequent co-occurrence of PAM pathway alterations with HER2 expression in breast cancer[1]



PAM pathway alteration: PIK3CA/AKT1/PTEN mutation, PTEN loss

Gedatolisib
(under development PI3K and mTOR inhibitor)

2L HR+/ HER2-/ PIK3CA wild-type breast cancer phase III study[2]

	Gedatolisib + palbociclib + fulvestrant	Gedatolisib + fulvestrant	fulvestrant
PFS (mo)	9.3	7.4	2.0
TRAE: Stomatitis	69%	57%	0%

3L HER2+ breast cancer phase II study[3]

Gedatolisib + trastuzumab biosimilar

ORR: 43%

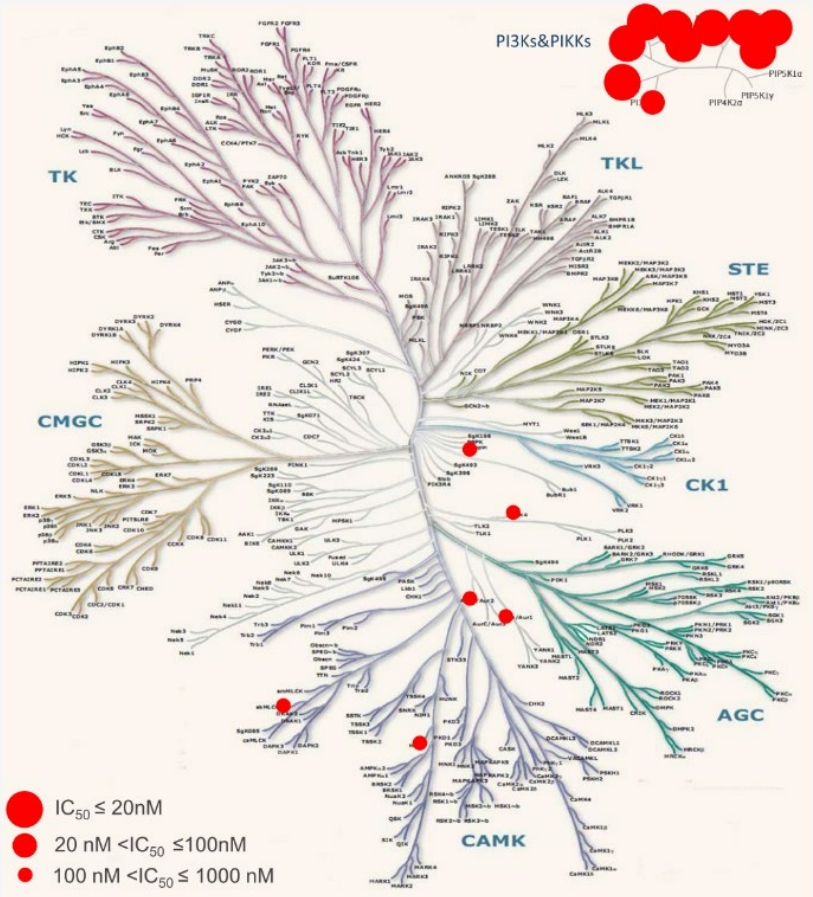
Adverse events: stomatitis (91%)

[1] Front Oncol. 2020;10:1475
[2] Sara Hurvitz,., et al.; Gedatolisib Plus Fulvestrant, With & Without Palbociclib, vs Fulvestrant in Patients With HR+/HER2-/PIK3CA Wild-Type Advanced Breast Cancer: First Results from VIKTORIA-1, ESMO 2025 LBA 17
[3] Ju W K., et al. Phase II study of trastuzumab-pkrb plus gedatolisib in patients with HER2-positive metastatic breast cancer who progressed after 2 or more HER2-directed chemotherapies (KM-10A/KCSG BR18-13). Journal of Clinical Oncology 43(16_suppl):1021-1021

HMPL-A251: *in vitro* profile of payload HM5041609 ("609") (1/3)

A potent PI3K/PIKK inhibitor targeting PAM alterations and potentially synthetic lethality.

Enzyme activity against PI3K and PIKK kinases and selectivity



Kinases		Enzyme activity (IC_{50}, nM)			
		609*	**Gedatolisib*** (PF-05212384)	Dactolisib[1] (NVP-BEZ235)	Buparlisib[5] (NVP-BKM120)
Class I PI3K kinases	PI3Kα	**3**	10	4	52
	PI3Kα (H1047R)	**1**	/	4.6	58
	PI3Kα (E545K)	**0.5**	/	5.7	99
	PI3Kα (E542K)	**0.8**	/	/	/
	PI3Kβ	**7**	23	75	166
	PI3Kγ	**11**	145	5	262
	PI3Kδ	**0.7**	133	7	116
PIKK kinases	mTOR	**3**	20	20.7	4,600
	ATM	**1**	>1000	100[2]	/
	ATR	**13**	>1000	21 (in cell)[3]	/
	DNA-PK	**0.4**	97	1.7[4]	>5,000

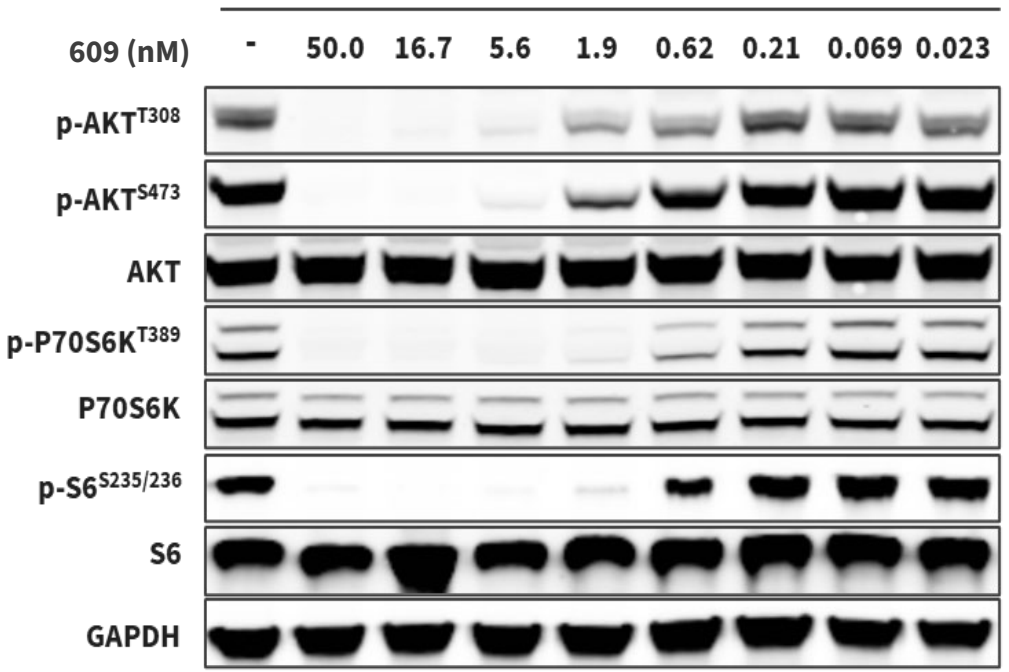
*data generated by Eurofins

[1] Maira SM, et al. Mol Cancer Ther, 2008, 7(7), 1851-1863; [2] Huang C, et al. Mol Pharm. 2021;18(7):2470-2481; [3] Toledo LI, et al. Nat Struct Mol Biol, 2011, 18(6), 721-727; [4] Biol. Pharm. Bull. 32(2) 297—300 (2009)
[5] Burger MT, et al. ACS Med Chem Lett. 2011;2(10):774-779.

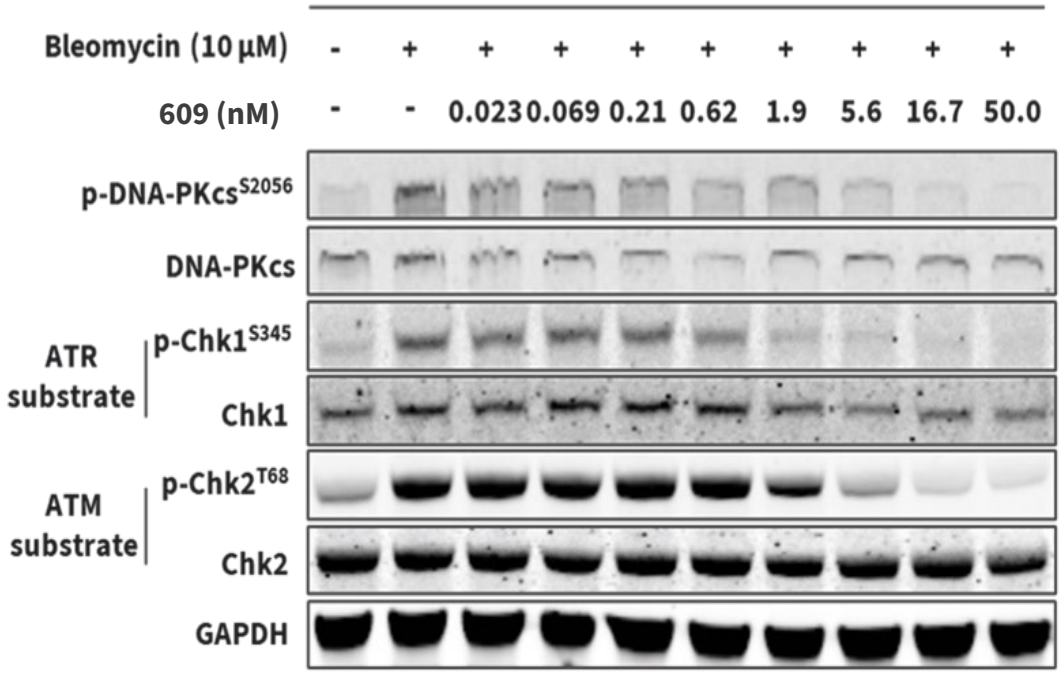
HMPL-A251: *in vitro* profile of payload HM5041609 ("609") (2/3)

A highly potent and selective inhibitor of PI3K & PIKK kinases that suppresses the PI3K and PIKK pathways.

Inhibition of PAM pathways in HCC1954 cells (breast cancer; HER2+; PIK3CA^{1047R})



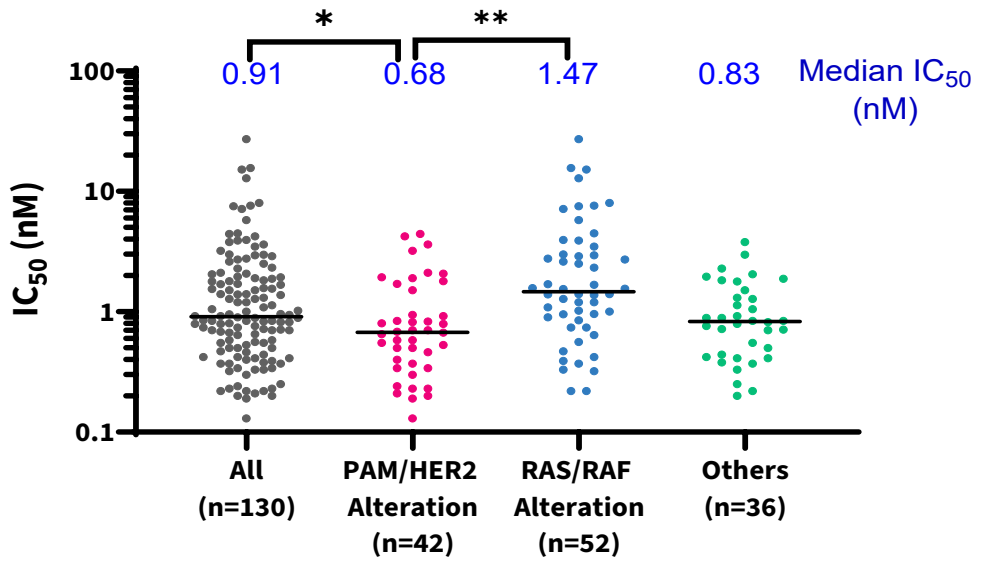
Inhibition of PIKK pathways in HCC1954 cells (breast cancer; HER2+; PIK3CA^{1047R})



HMPL-A251: *in vitro* profile of payload HM5041609 ("609") (3/3)

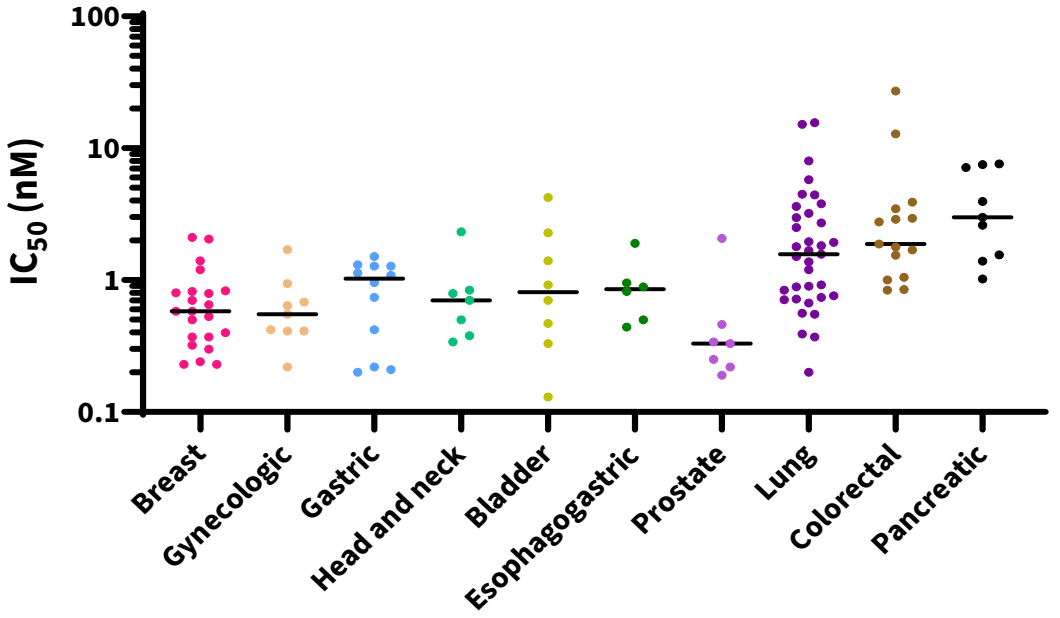
A highly potent and selective inhibitor of PI3K & PIKK kinases with robust anti-tumor activity against a broad panel of tumor cell lines.

Cell growth inhibition of 609 by genotypes



**: p<0.01.

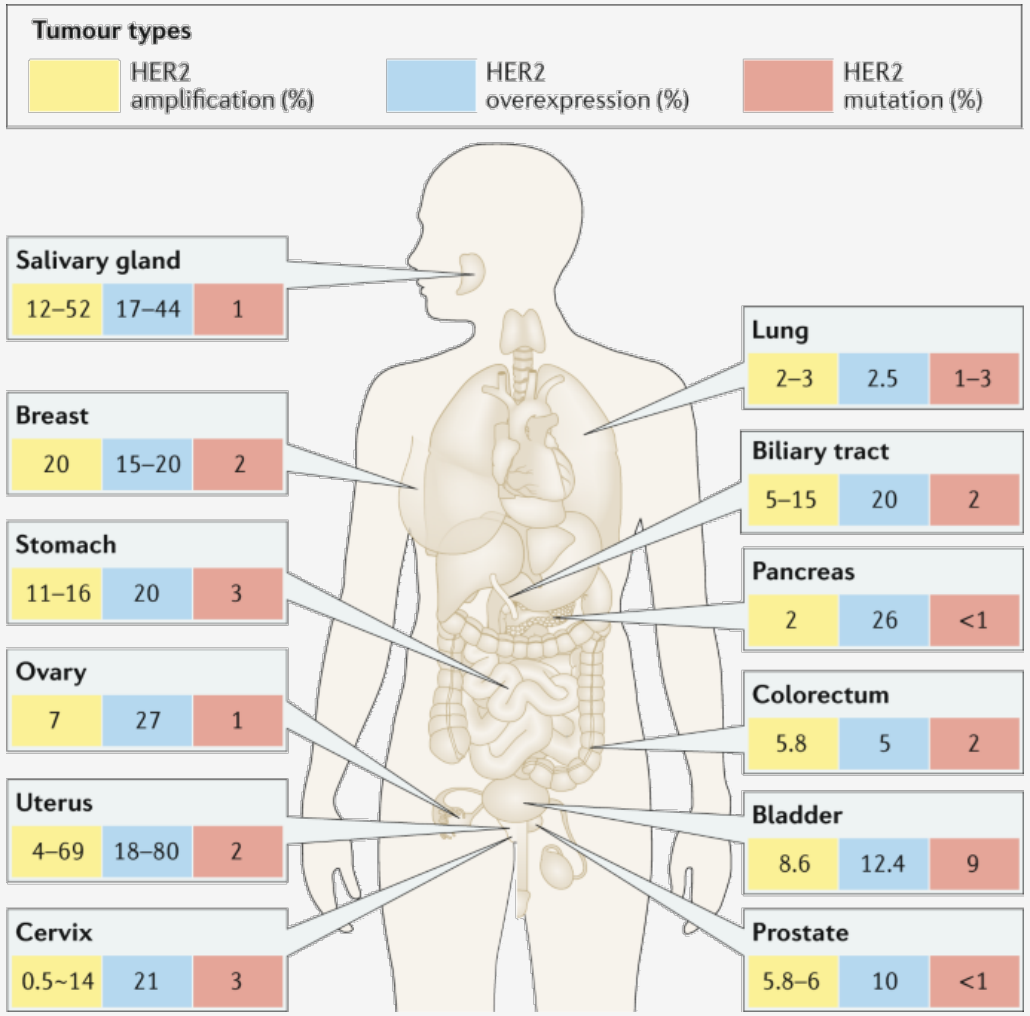
Cell growth inhibition of 609 by tumor types



Anti-HER2 Antibody

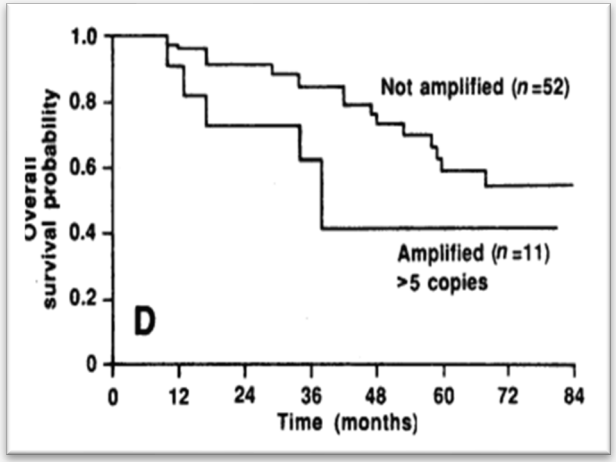
HER2 alterations and poor prognosis in cancer

HER2 alterations found in a variety of cancer types[1]

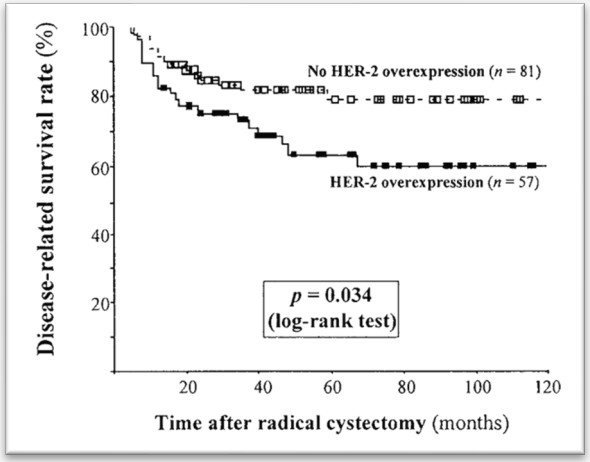


HER2 amplification/overexpression confers worse prognosis

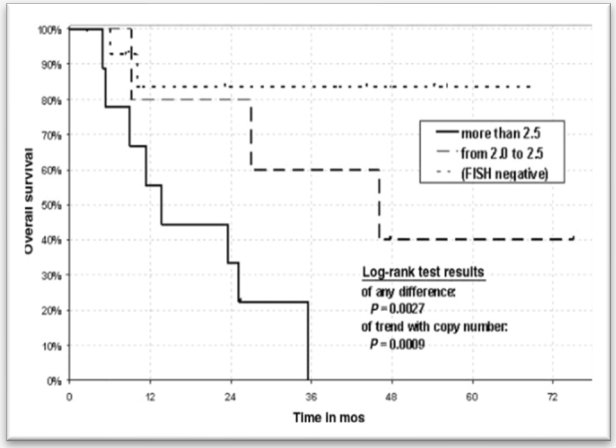
Breast cancer[2]



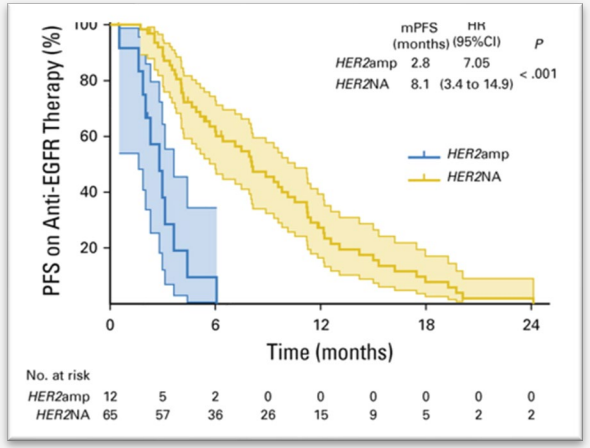
Muscle-invasive bladder cancer[3]



Endometrial carcinoma[4]



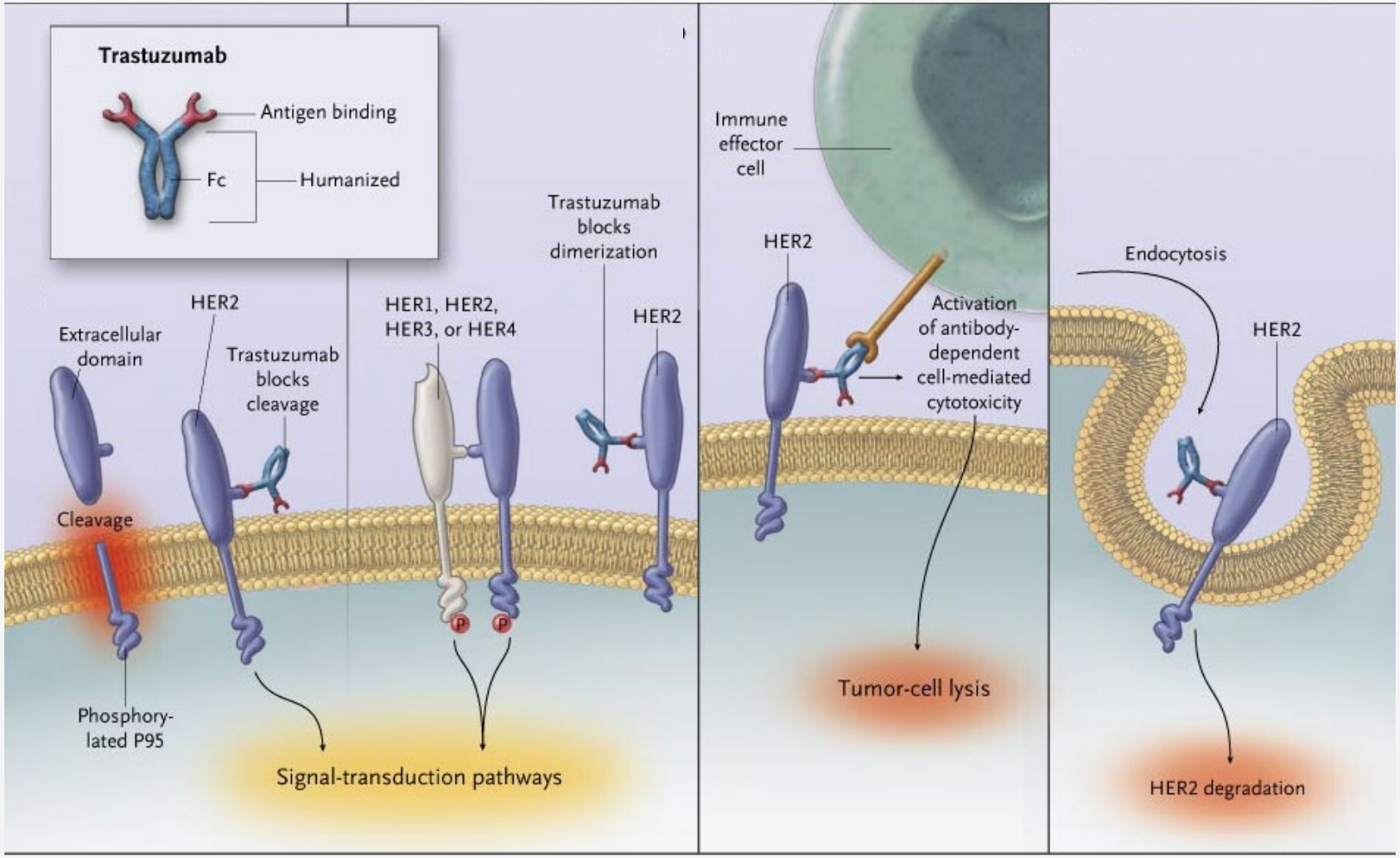
Colorectal cancer[5]



[1]. Nat Rev Clin Oncol. 2020;17(1):33-48. [2]. Science. 1987 Jan 9;235(4785):177-82. [3]. Int. J. Cancer: 102, 514 –518 (2002). [4]. Cancer. 2005;104(7):1391-1397. [5]. JCO Precis Oncol. 2019;3:1-13

Anti-HER2 antibody: mechanism of action

- Anti –HER2 antibody works through multiple mechanisms to inhibit tumor growth, including:
  - Inhibit extracellular domain cleavage and prevent the formation of very active form of HER2, p95HER2;
  - Block dimerization and reduce signaling transduction;
  - Induce antibody-dependent cell-mediated cytotoxicity;
  - Down-regulate receptor through endocytosis.



N Engl J Med. 2007 Jul 5;357(1):39-51

Summary

- HER2 is a well-established therapeutic target and a good tumor-associated antigen, which is overexpressed in a variety of solid tumors.
- PAM pathway is one of the main downstream signaling pathway of HER2.
- PAM pathway alteration confers resistance to trastuzumab-based therapy.
- PAM pathway inhibition synergizes with HER2 antibody to enhance the anti-tumor efficacy.
- **PAMi-based HER2 ADC is expected to enhance the efficacy via the synergy between trastuzumab and PAMi, and improve the safety by specifically deliver PAMi into HER2-positive tumor cells.**

Our First ATTC Candidate: HMPL-A251

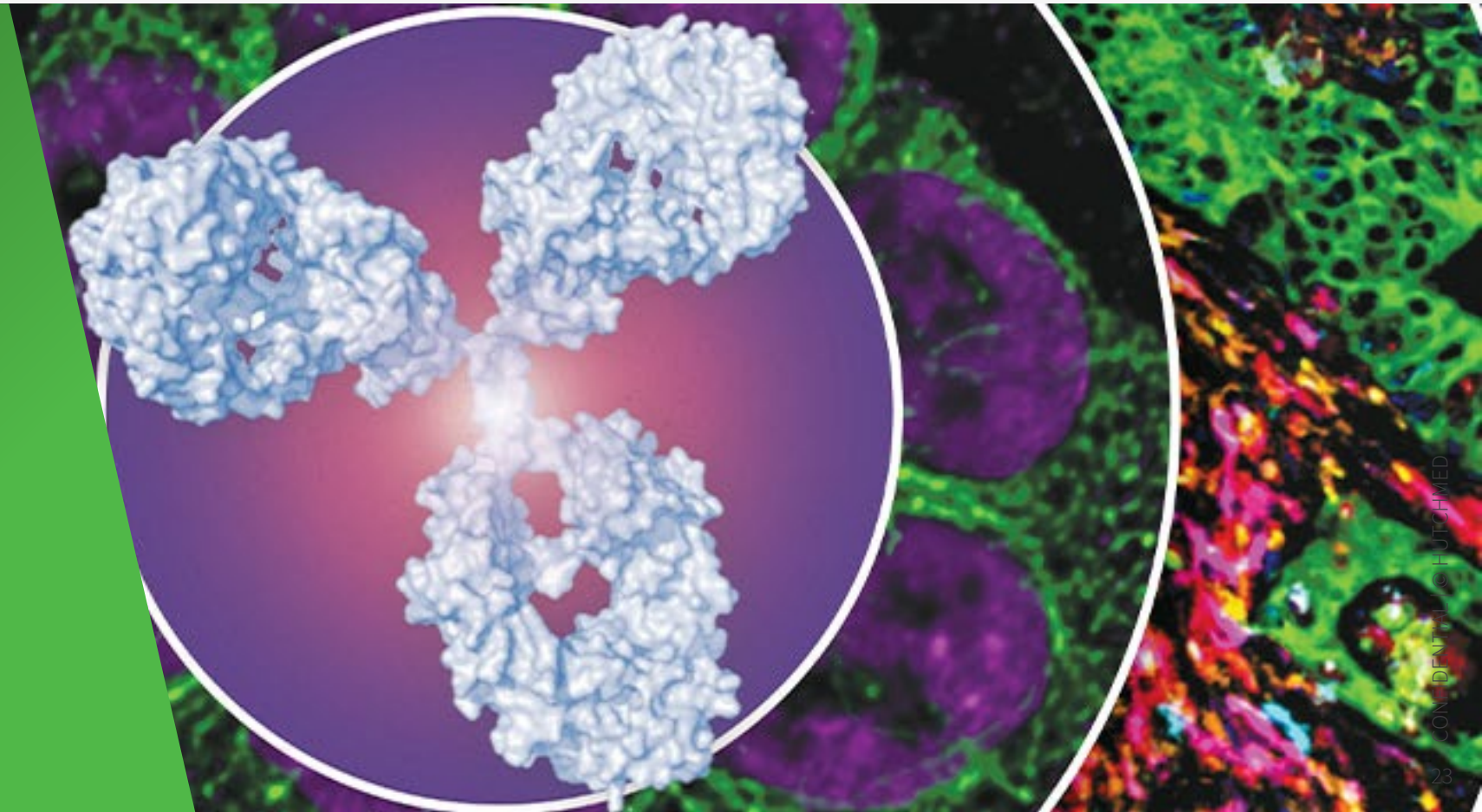
DISCOVERY OF HMPL-A251, A FIRST-IN-CLASS HER2-DIRECTED ANTIBODY-TARGETED THERAPY CONJUGATE (ATTC) WITH A NOVEL PI3K/PIKK INHIBITOR PAYLOAD

Jia Hu, Junqing Liang, Yan Xu, Haibin Yang, Peihua Liu, Yue Liu, Min Cheng, Nelson Ng, Jiahuan Zhu, Fangfang Mao, Xuelei Ge, Wei Zhang, Juntao Yu, Qihang Zhang, Shaohui Shen, Pan Wang, Leilei Wu, Xiaoyan Xu, Na Yang, Yu Cai, Jian Wang, Weihan Zhang, Yongxin Ren, Guangxiu Dai, Michael Shi & Weiguo Su

HUTCHMED

AACR-NCI-EORTC INTERNATIONAL CONFERENCE ON MOLECULAR TARGETS AND CANCER THERAPEUTICS

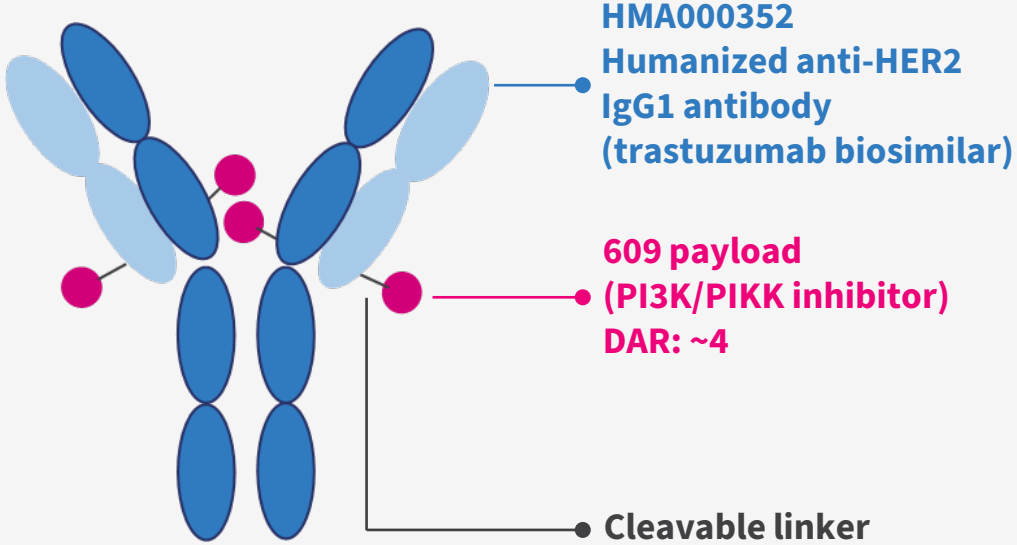
October 22-26, 2025
Hynes Convention Center
Boston, Massachusetts, USA



Introduction

Rationale for a PI3K/PIKK inhibitor conjugated to a HER2-targeted antibody, HMPL-A251.

- Aberrant activation of PI3K-AKT-mTOR pathway (PAM) is associated with poor prognosis and resistance to anti-HER2 therapies[1-2].
- Despite the synergistic effects of dual HER2 and PAM inhibition, systemic toxicity associated with PAM inhibitors limits their clinical application[3], providing the rationale for developing HMPL-A251.



- HER2 overexpression are found in a variety of solid tumors[4]
- HER2 overexpression are associated with poor prognosis[5-7] , increased risk of disease recurrence[8], and resistance to anti-cancer treatment[9]

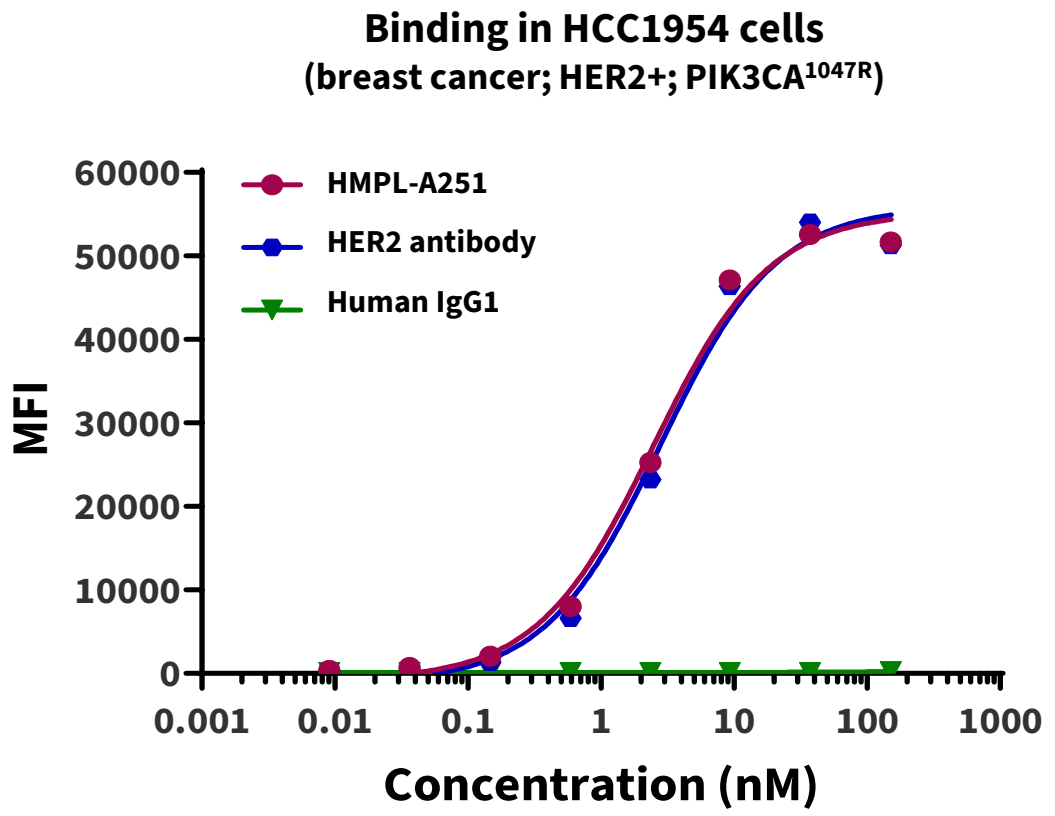
- Highly potent against PI3K and PIKK kinases
- Synergizes with anti-HER2 antibody to improve efficacy
- PIKK inhibition provides potential for combination with chemotherapy
- Bystander effect to kill antigen negative tumor cells

- Stable in human and monkey plasma
- Cleaved by cathepsin B, a protease highly expressed in cancer cells

[1]. Berns K et al. Cancer Cell. 2007;12(4):395-402. [2]. Nagata Y et al. Cancer Cell. 2004;6(2):117-127. [3]. LoRusso PM et al. J Clin Oncol. 2016;34(31):3803-3815. [4]. Oh DY et al. Nat Rev Clin Oncol. 2020;17(1):33-48. [5]. Krüger S et al. Int J Cancer. 2002;102(5):514-518.
[6]. Luo H et al. PLoS One. 2018;13(1):e0191972. [7]. Slamon DJ et al. Science. 1987;235(4785):177-182. [8]. Press MF et al. Cancer Res. 1993;53(20):4960-4970. 9. Raghav K et al. JCO Precis Oncol. 2019; 3:1-13.

Binding of HMPL-A251

HMPL-A251 displayed high binding affinity to HER2-positive breast cancer cell, comparable to the naked antibody.



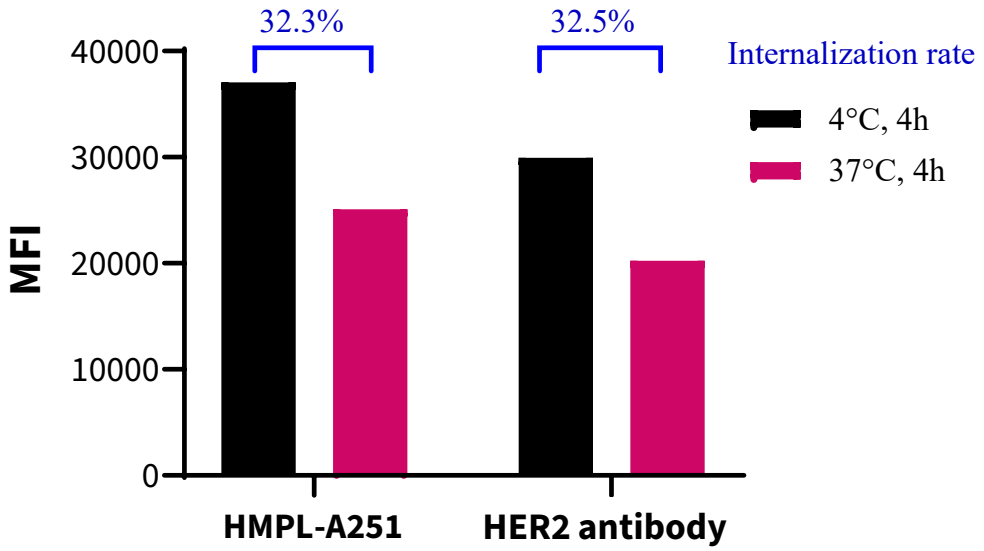
MFI = Median Fluorescence Intensity

Internalization of HMPL-251

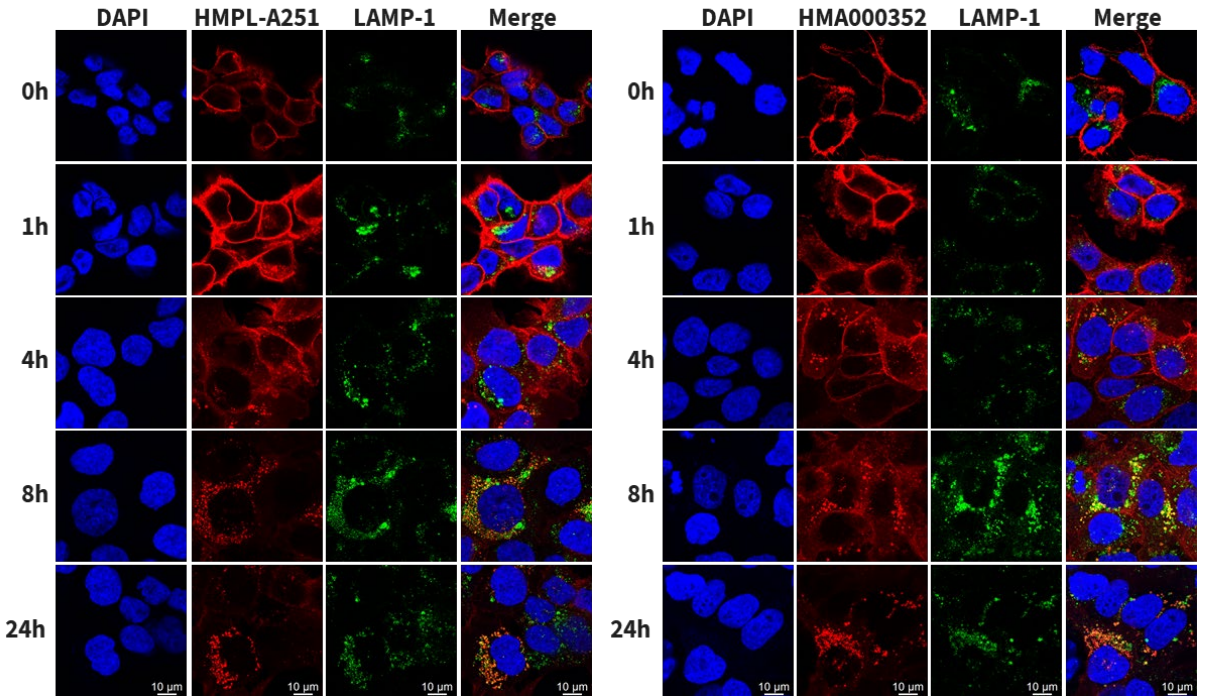
HMPL-A251 displayed efficient internalization to HER2-positive breast cancer cells, comparable to the naked antibody.

Internalization in HCC1954 cell

(breast cancer; HER2+; PIK3CA^{1047R})



Intracellular trafficking

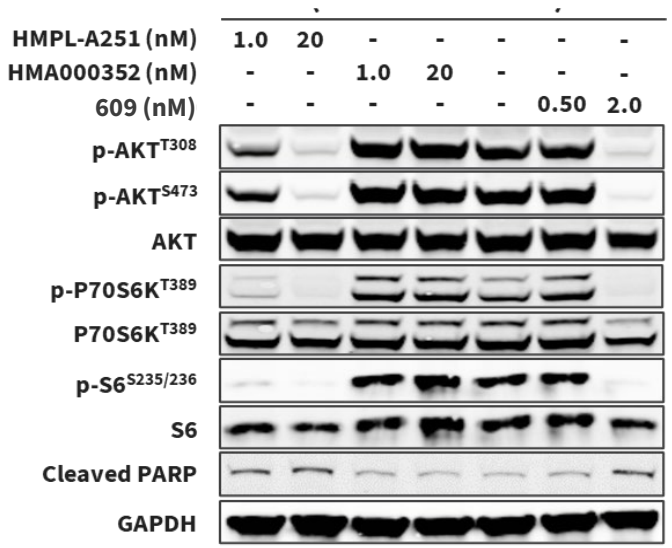


MFI = Median Fluorescence Intensity

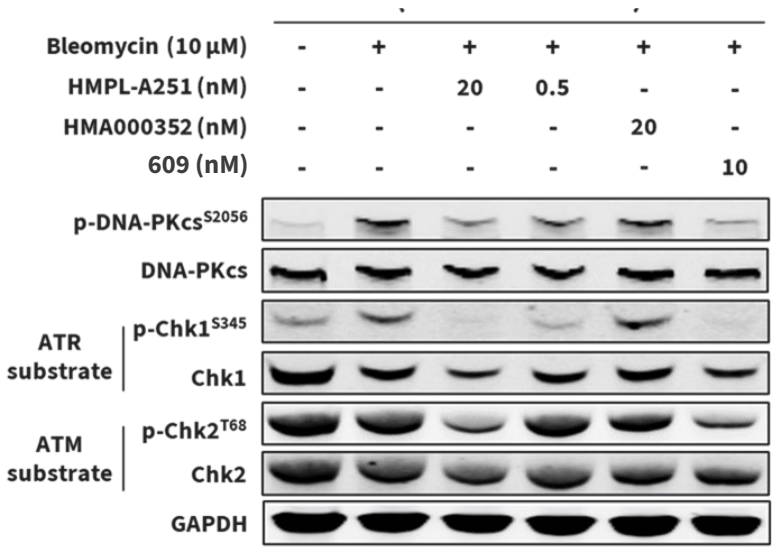
Cellular signaling pathway inhibition of HMPL-A251

HMPL-A251 potently blocked intracellular PAM (PI3K/AKT/mTOR) and PIKK (ATM/ATR/DNA-PK) signaling pathways, leading to subsequent induction of apoptosis and DNA damage.

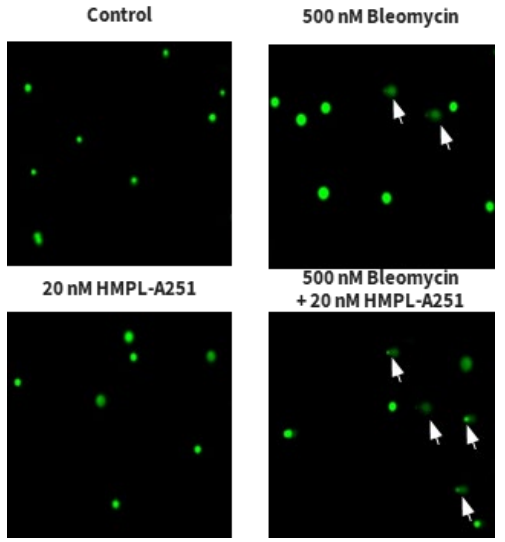
Inhibition of PAM pathway (breast cancer; HER2+; PIK3CA^{1047R})



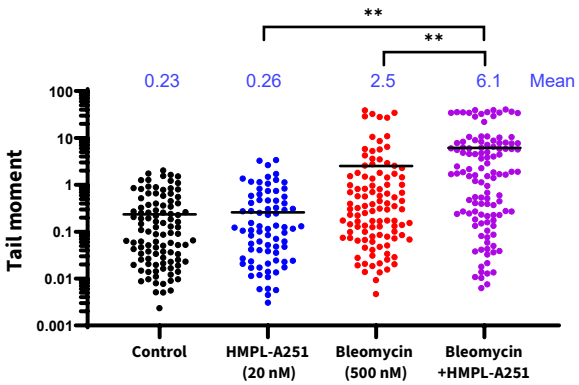
Inhibition of PIKK pathway (breast cancer; HER2+; PIK3CA^{1047R})



DNA damage evaluation



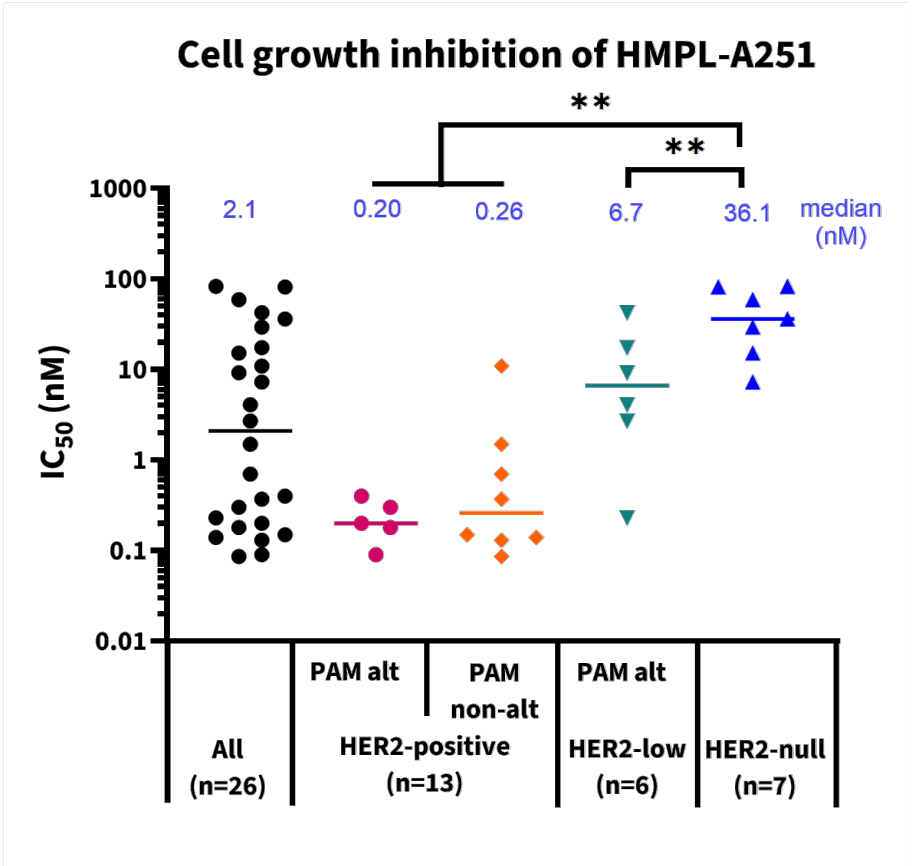
DNA damage in HCC1954 cell by comet assay

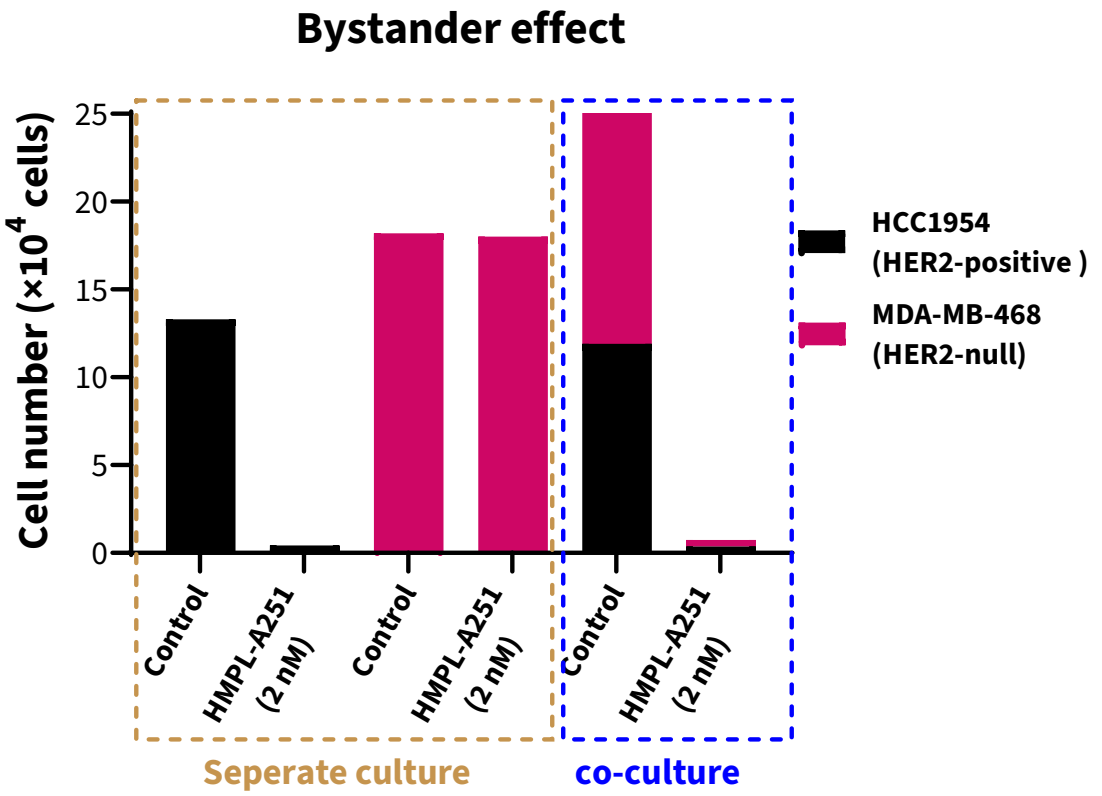


**: p<0.01.

Cell growth inhibition of HMPL-A251

HMPL-A251 exhibited a HER2 expression-dependent cell growth-inhibitory activity with bystander killing effect to overcome HER2 heterogeneity.



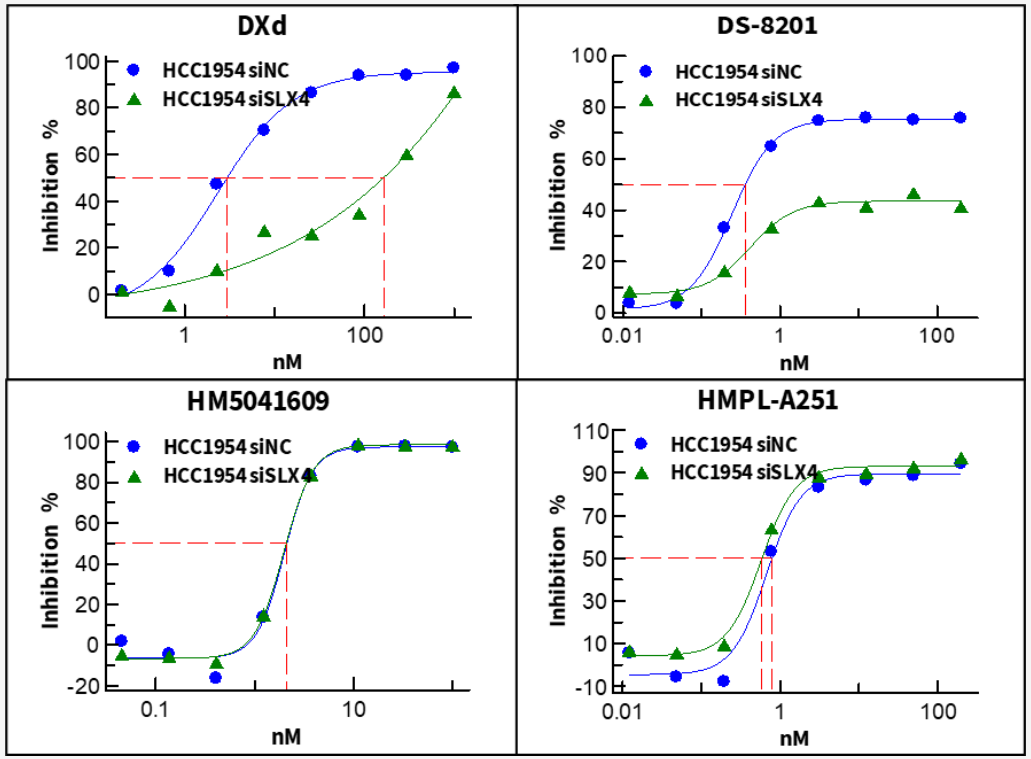


*:p<0.05, **: p<0.01.

Anti-tumor activity of HMPL-A251 in DS-8201 resistant model

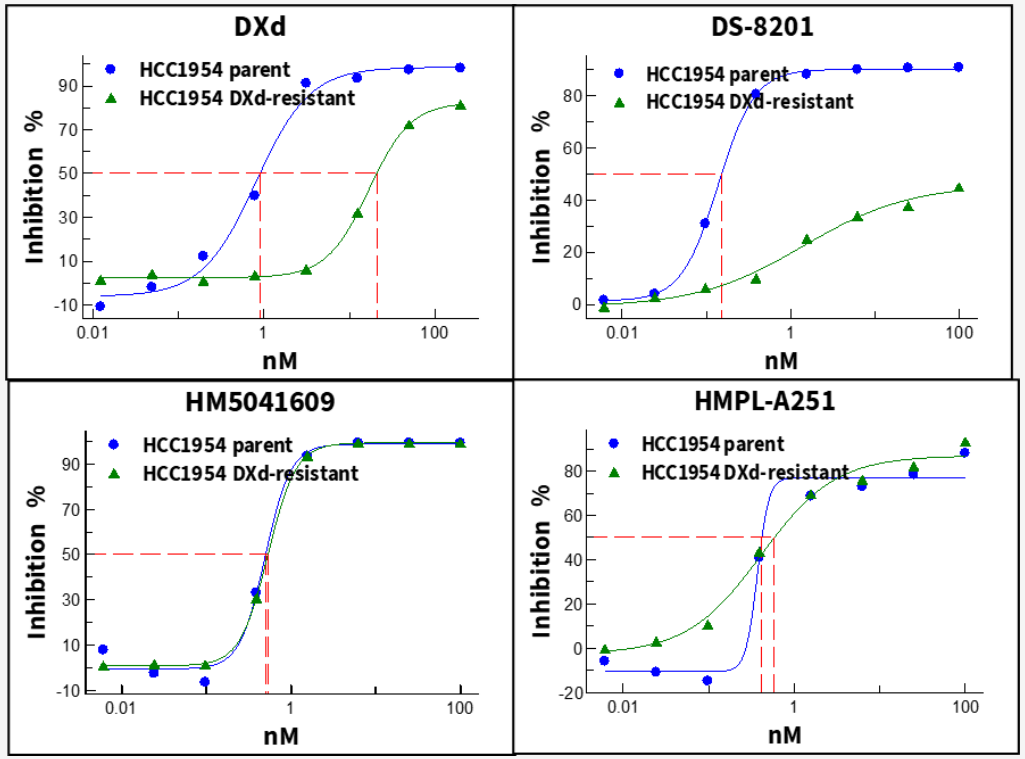
HMPL-A251 can overcome the DXd-mediated resistance to DS-8201.

Dose-response inhibition curves of HCC1954 cells transfected with non-targeting or SLX4-targeted siRNAs



	DXd	DS-8201	609 (PI3K/PIKK)	HMPL-A251
IC_{50} shift	55.3x	>556x	1.0x	0.75x

Dose-response inhibition curves of HCC1954 parent and DXd-induced resistant cells

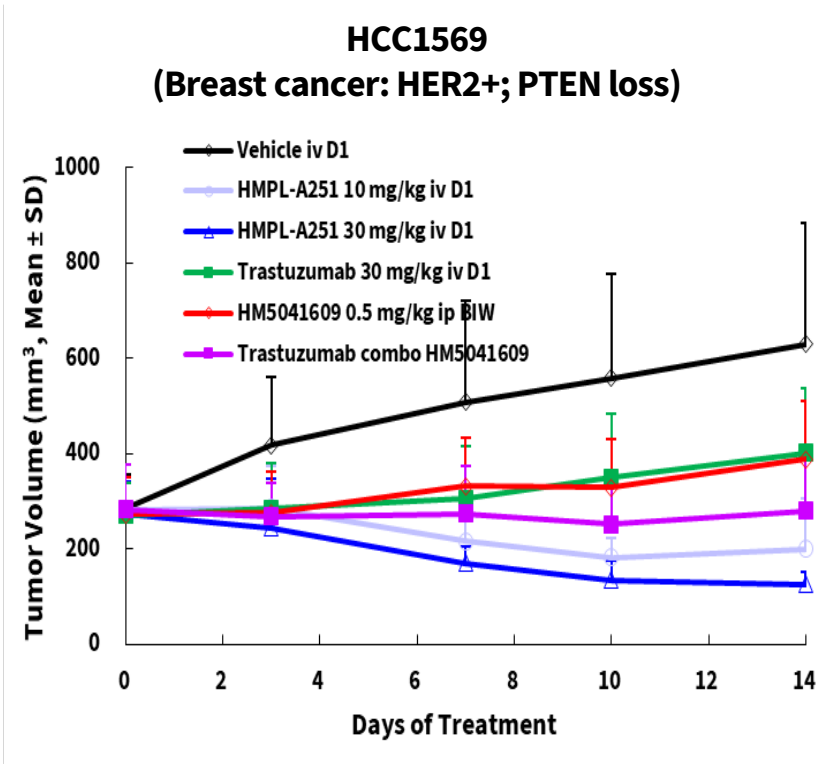


	DXd	DS-8201	609 (PI3K/PIKK)	HMPL-A251
IC_{50} shift	23.2x	>667x	1.1x	1.4x

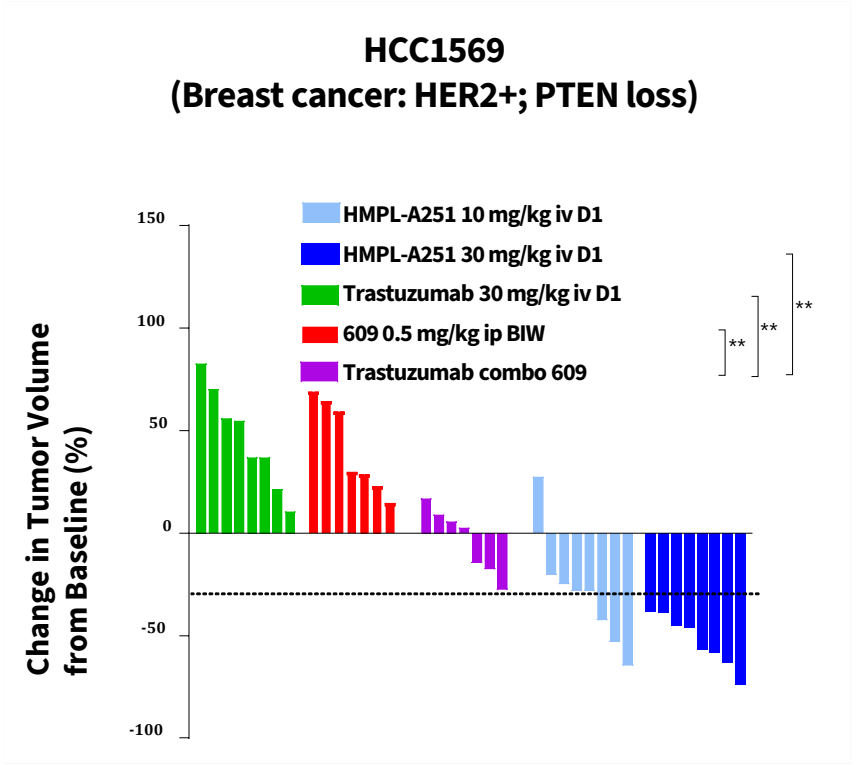
HMPL-A251 vs. antibody + payload combination (1/2)

- **Combination of 609 and trastuzumab produced synergistic anti-tumor.**
- **HMPL-A251 demonstrated stronger anti-tumor activity and better tolerability than antibody and payload combination.**

Tumor Volume



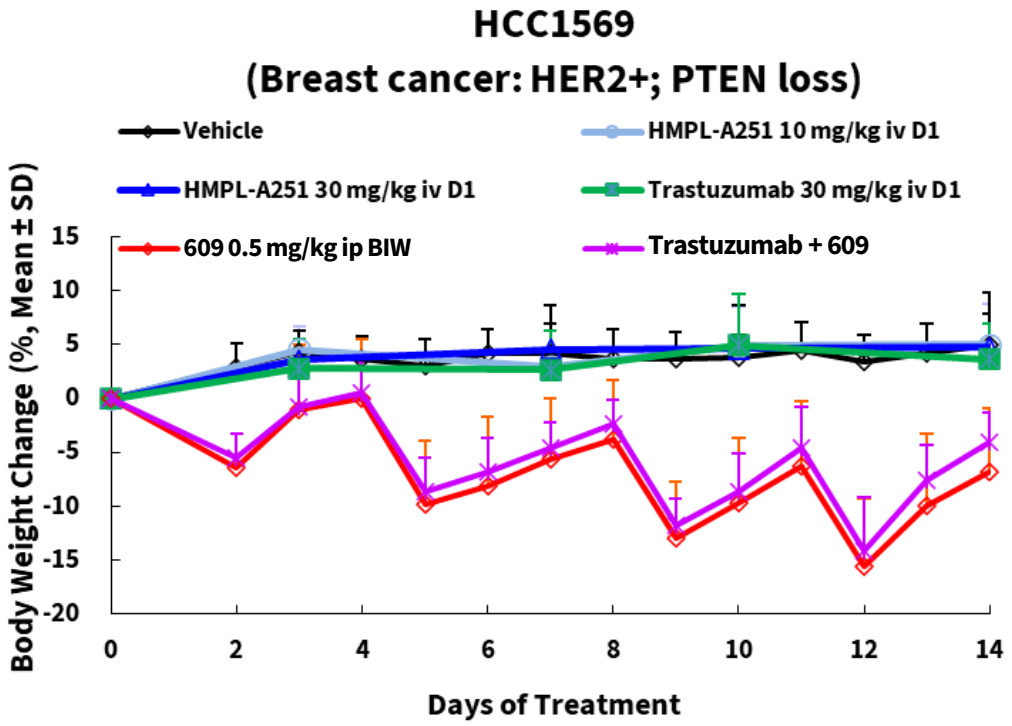
Waterfall Plot of Change in Tumor Size

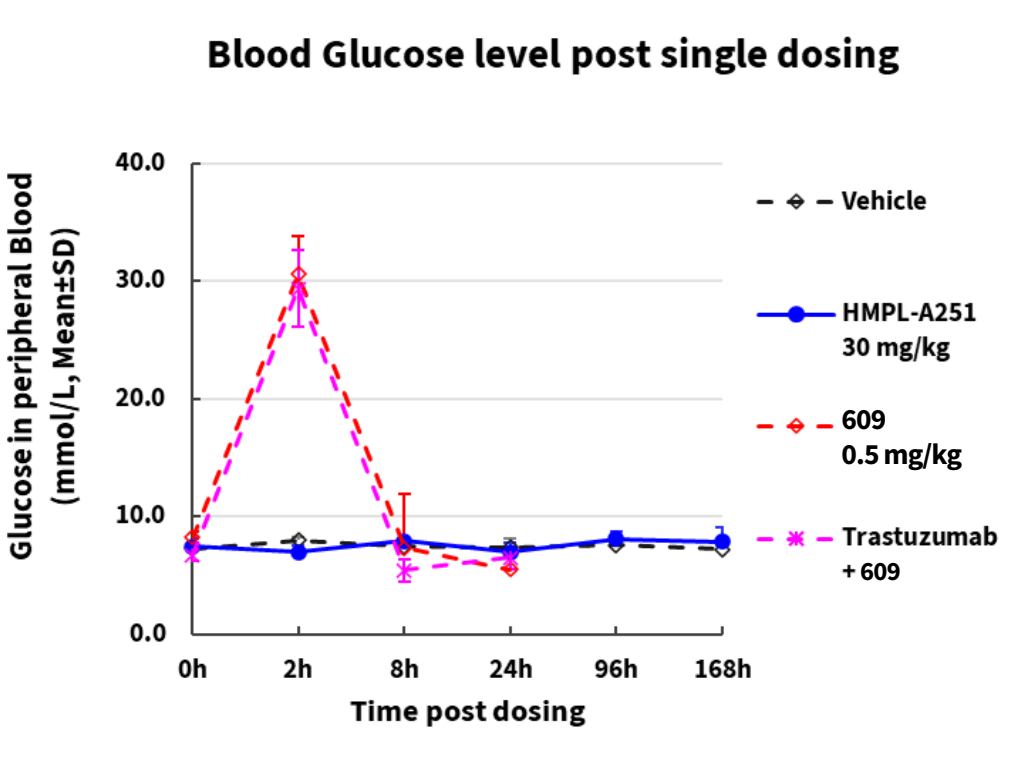


*:p<0.05, **: p<0.01. iv: intravenous; ip: intraperitoneal; D1: day 1; BIW: twice a week

HMPL-A251 vs. antibody + payload combination (2/2)

- **Combination of 609 and trastuzumab caused safety issue as revealed by body weight loss and increase in blood glucose.**
- **HMPL-A251 demonstrated better tolerability than antibody and payload combination.**



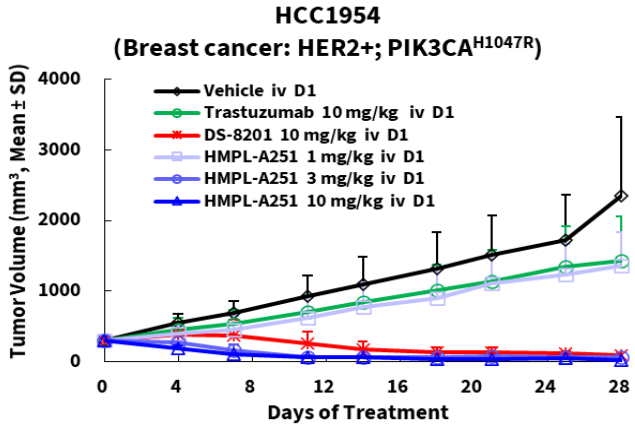


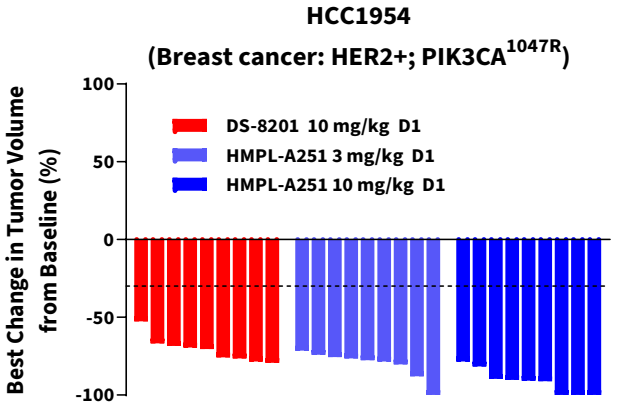
*:p<0.05, **: p<0.01. iv: intravenous; ip: intraperitoneal; D1: day 1; BIW: twice a week

In vivo anti-tumor efficacy of HMPL-A251 (1/3)

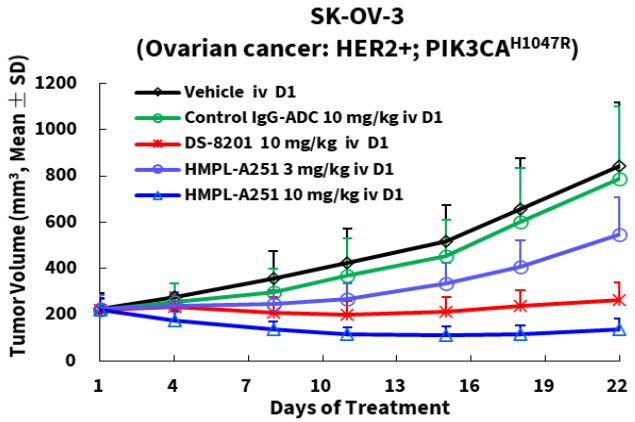
A single intravenous dose of HMPL-A251 demonstrated robust anti-tumor activity in HER2-positive tumor models with PAM alterations, which was comparable or stronger than DS-8201 administered at an equivalent dose.

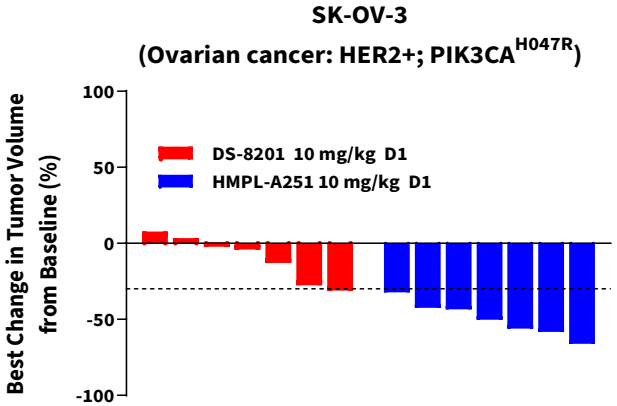
A: HER2+/PAM-altered Breast Cancer Tumor Xenograft (HCC1954)





B: HER2+/PAM-altered Ovarian Cancer Tumor Xenograft (SK-OV-3)



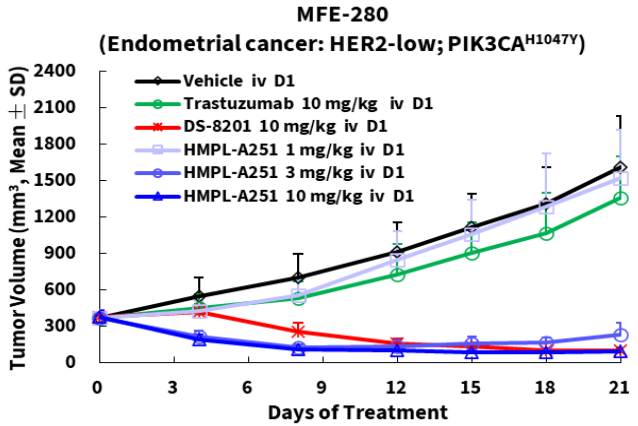


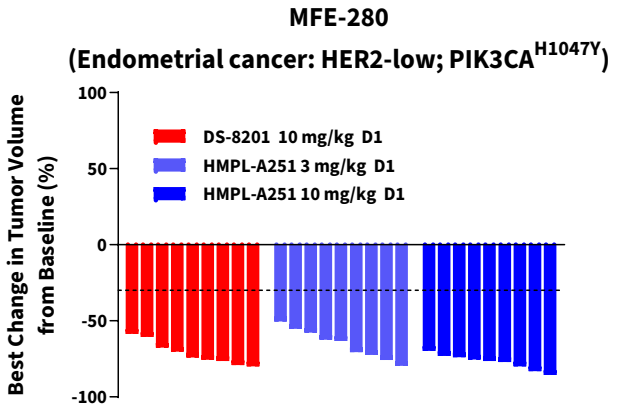
iv: intravenous; D1: day 1; alt: alteration

In vivo anti-tumor efficacy of HMPL-A251 (2/3)

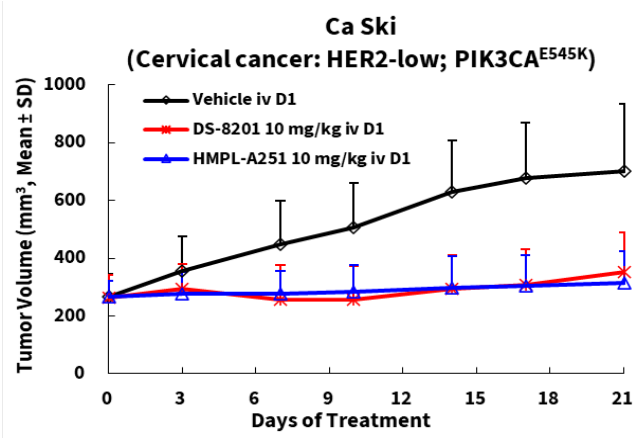
A single intravenous dose of HMPL-A251 demonstrated robust anti-tumor activity in HER2-low tumor models with PAM alterations, which was comparable or stronger than DS-8201 administered at an equivalent dose.

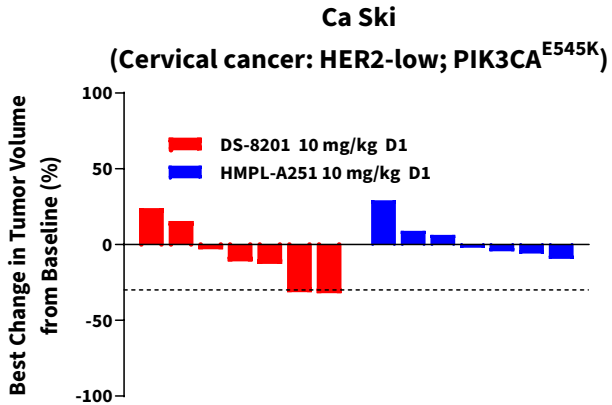
C: HER2-low/PAM-altered Endometrial Cancer Tumor Xenograft (MFE-280)





D: HER2-low/PAM-altered Cervical Cancer Tumor Xenograft (Ca Ski)



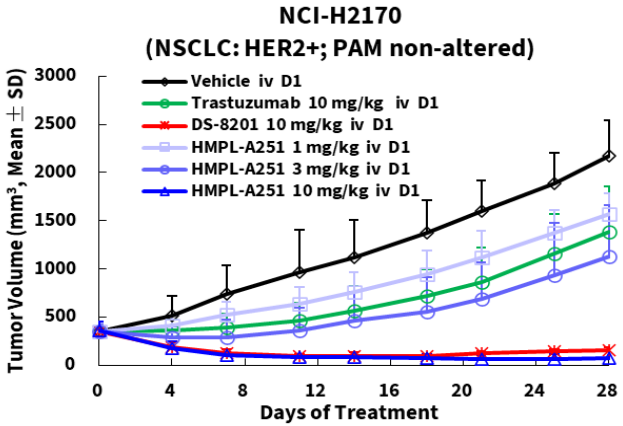


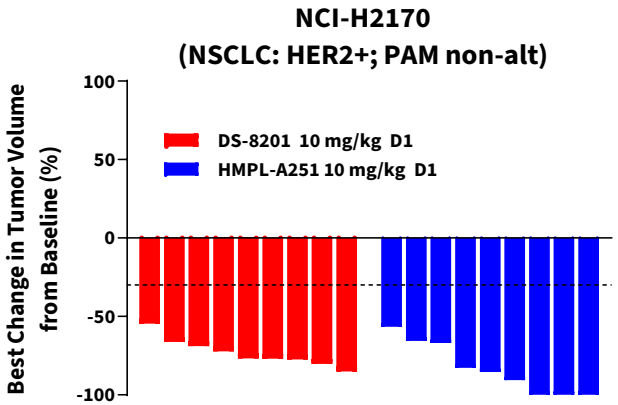
iv: intravenous; D1: day 1; alt: alteration

In vivo anti-tumor efficacy of HMPL-A251 (3/3)

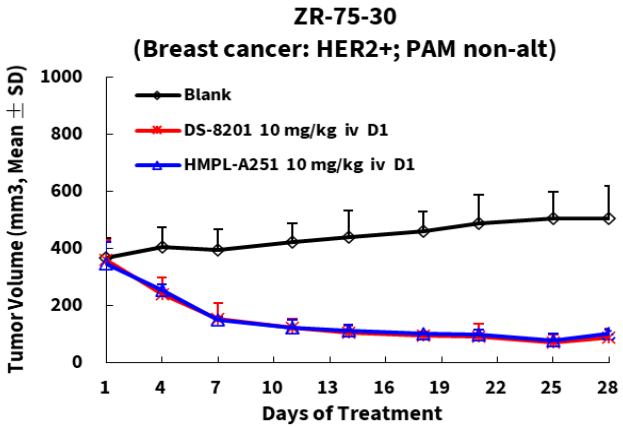
A single intravenous dose of HMPL-A251 demonstrated robust anti-tumor activity in HER2-positive tumor models without PAM alterations, which was comparable or stronger than DS-8201 administered at an equivalent dose.

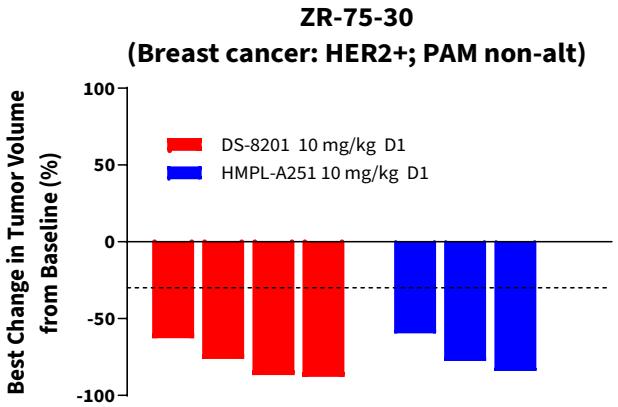
E: HER2+/PAM-non-altered NSCLC Tumor Xenograft (NCI-H2170)





F: HER2+/PAM-non-altered Breast Cancer Tumor Xenograft (ZR-75-30)



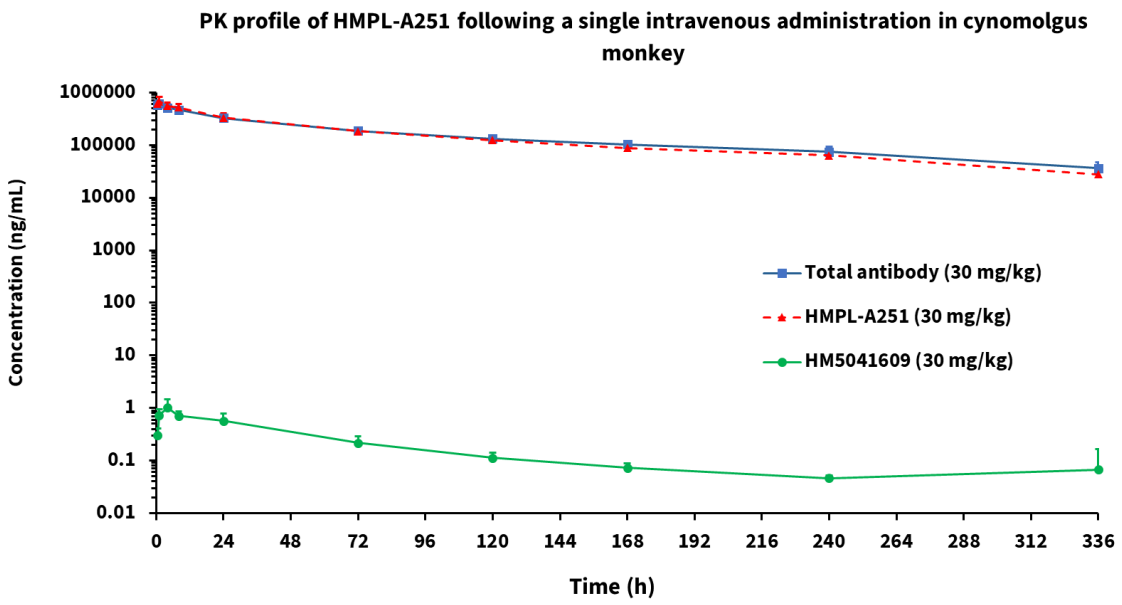


NSCLC: non-small cell lung cancer; iv: intravenous; D1: day 1; alt: alteration

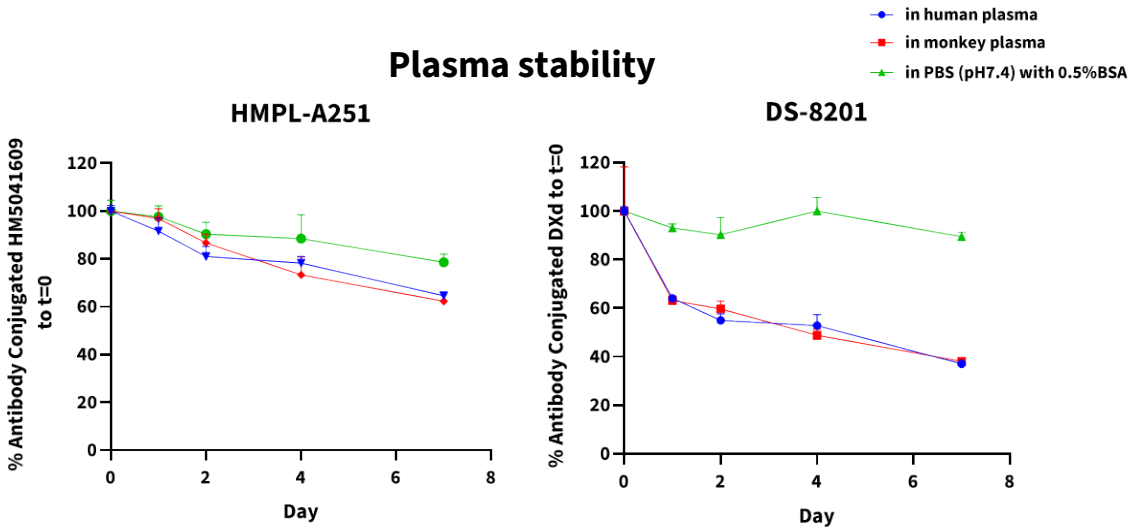
Pharmacokinetic profile of HMPL-A251

- **Following a single intravenous administration in cynomolgus monkeys, HMPL-A251 demonstrated a favorable PK profile with low clearance.**
- **The similar PK profile between HMPL-A251 and total antibody indicated good linker stability during circulation.**

Pharmacokinetics of HMPL-A251 in cynomolgus monkeys

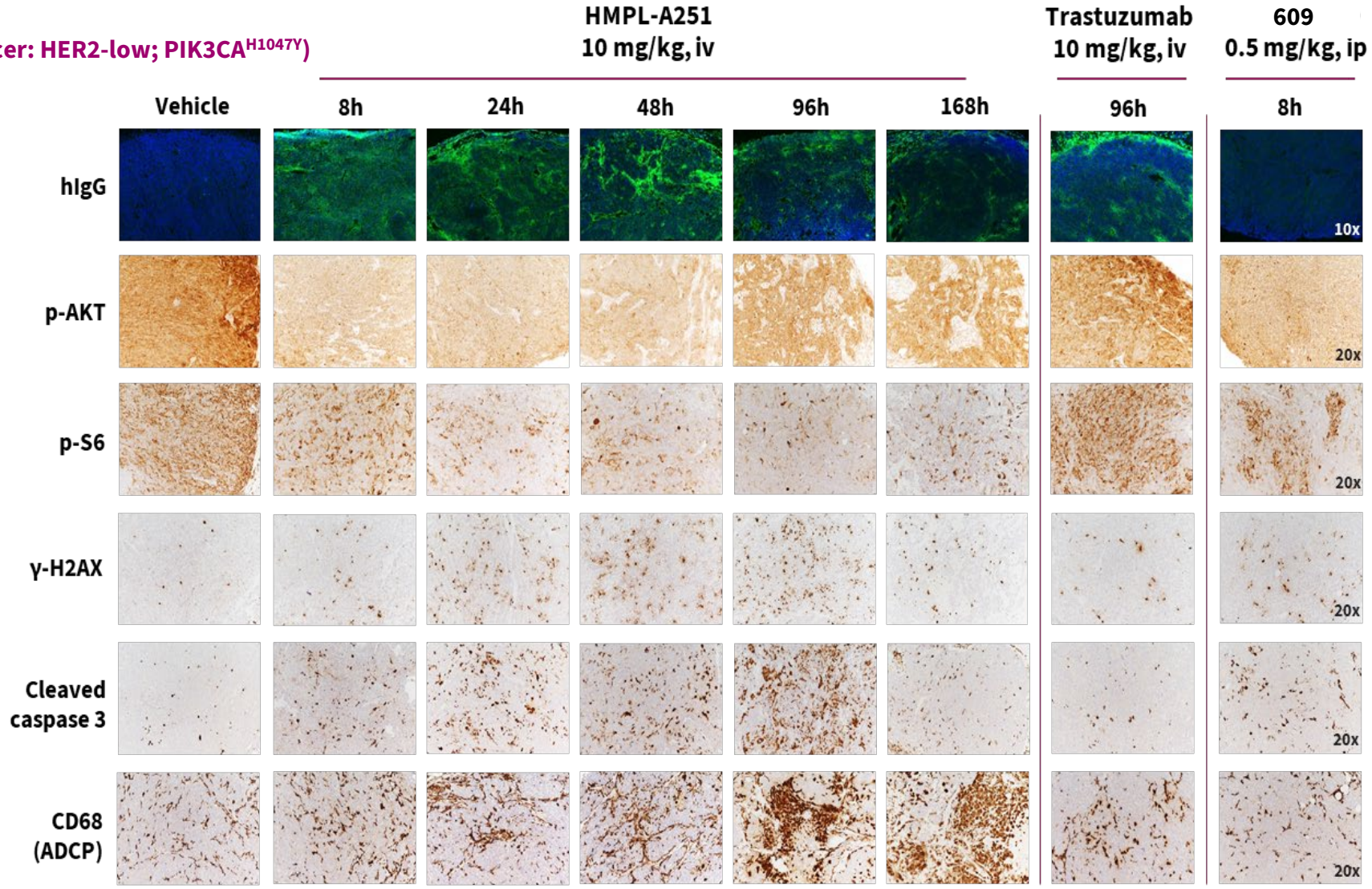


In vitro stability of HMPL-A251 and DS-8201 in plasma



In vivo pharmacodynamic activity of HMPL-A251 (1/2)

MFE-280
(Endometrial Cancer: HER2-low; PIK3CA^{H1047Y})



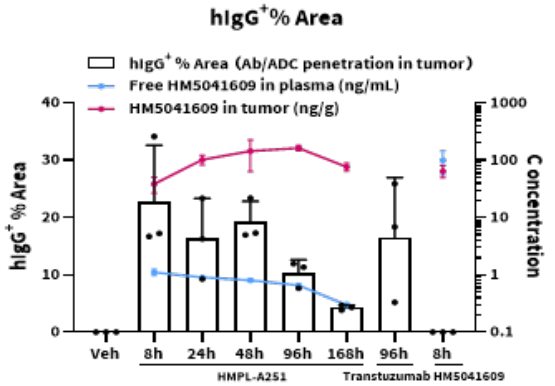
iv: intravenous

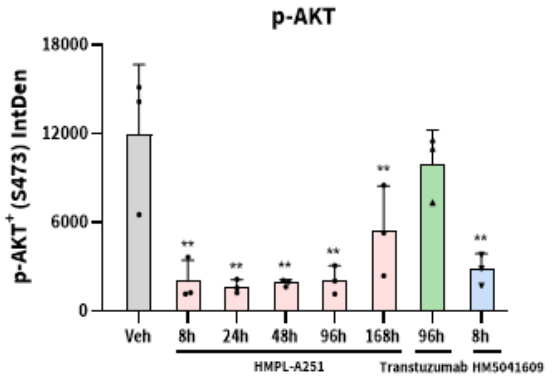
In vivo pharmacodynamic activity of HMPL-A251 (2/2)

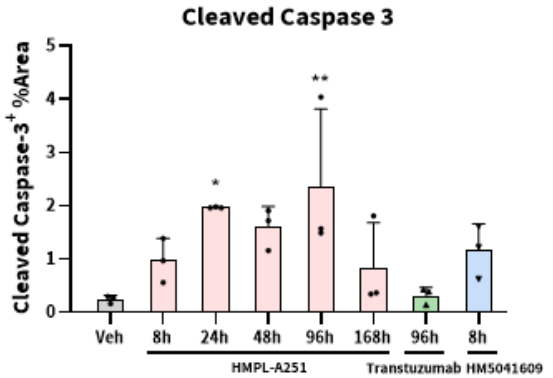
- HMPL-A251 quickly distributed into the tumor, persisted for 168 hours, sustained intra-tumoral payload release with subsequent potent and durable inhibition of PI3K pathway as well as remarkable induction of DNA damage and tumor cell apoptosis.
- Significant accumulation of CD68-positive macrophages observed, suggesting strong ADCP function by HMPL-A251.
- Compared with systemic administration of 609, HMPL-A251 achieved a superior tumor-to-plasma ratio, offering the potential to minimize payload-mediated systemic toxicity.

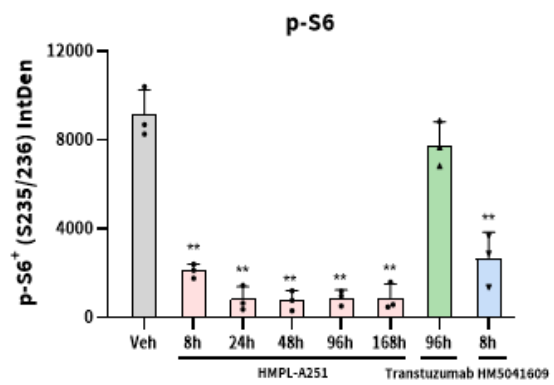
MFE-280

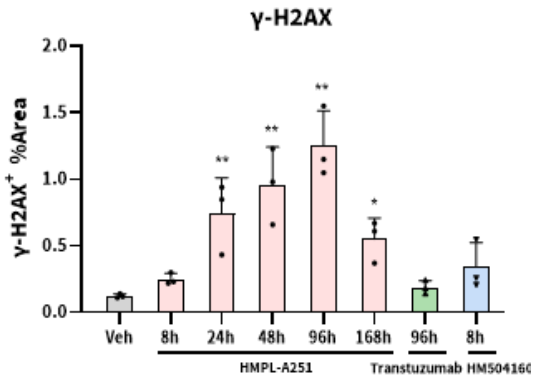
(Endometrial Cancer: HER2-low; PIK3CA^{H1047Y})

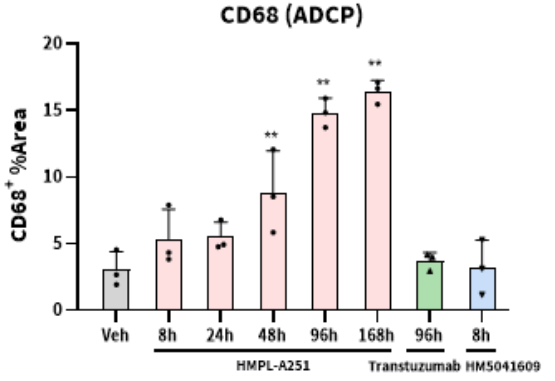












Summary

- **HMPL-A251 is a first-in-class PI3K/PIKK inhibitor conjugated with a HER2 antibody.**
- **HMPL-A251 has demonstrated potent anti-tumor activity in HER2-positive tumor models, with or without PAM alterations, as well as HER2-low tumor models harboring PAM alterations.**
- **HMPL-A251 exhibited favorable pharmacokinetic and safety profiles, warranting further clinical evaluation.**
- **US IND was cleared. China IND was under review. Phase 1 clinical study is expected to start in Q4 2025.**

Preliminary development strategy

Preliminary Global Clinical Development Strategy

A data driven plan for US and China trials

Dose escalation
MTD + RP2D

- Single agent dose escalation
- RP2D ± MTD
- Population:
  - HER2 + or low
  - PAM status will be tested retrospectively

Dose expansion
Define biomarker strategy in various indications

- **HER2 positive and PAM (+)**
- **HER2 positive and PAM (-)**
- **HER2 low and PAM (+)**

Proof of Concept
Safety and efficacy

Solid Tumor A
HER2 positive and PAM +/-
- Mono therapy: ≥2L, inclusive of prior anti-HER2 therapies
- A251 + chemo: 1L or 2L

Solid Tumor B
HER2 positive and PAM +/-
- Mono therapy: ≥2L , inclusive of prior chemo and IO therapies
- A251 + chemo: 1L

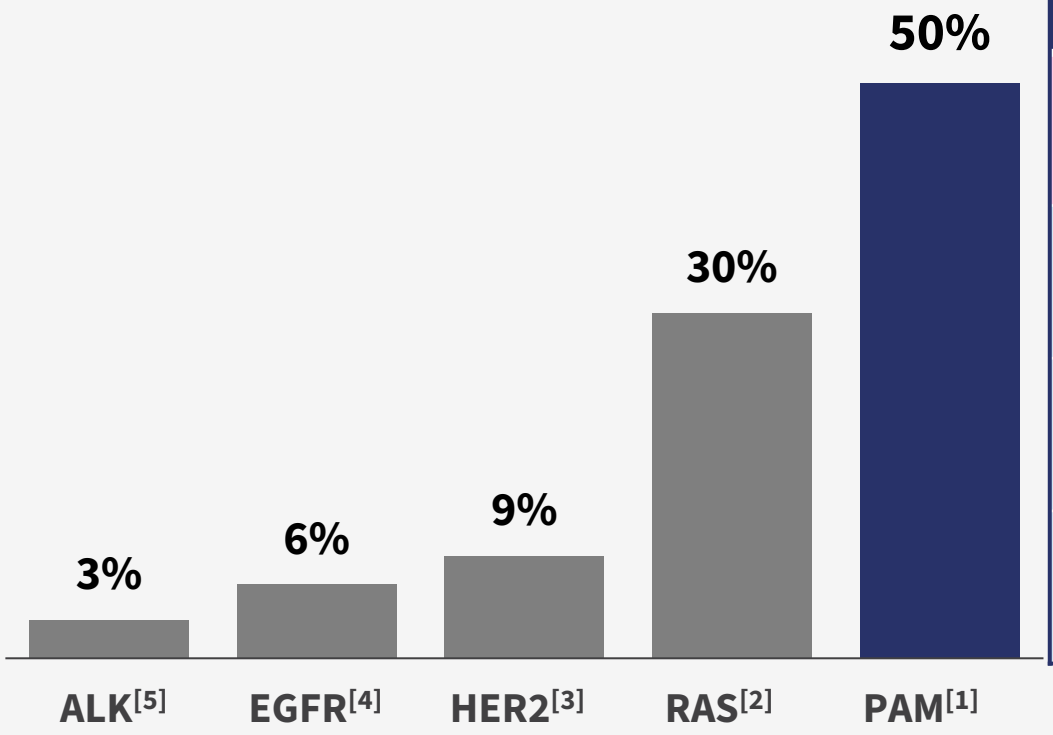
Solid Tumor C
HER2 positive and PAM +/-
- Mono therapy: ≥2L, inclusive of prior chemo and IO therapies
- A251 + chemo: 1L

Solid Tumor A
HER2 low with PAM +
- Mono therapy: ≥2L, inclusive of prior anti-HER2 therapies

Multiple indications with significant market potential

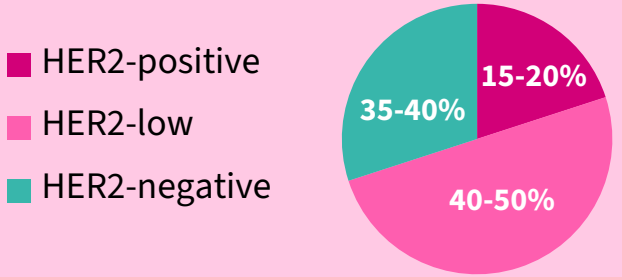
PAM pathway may address a huge unmet medical need.

PAM is the most frequently altered pathway in solid tumors



Major Cancers	US/EU/JP/CN Incidence[6]
Breast Cancer	1,280,984
Prostate Cancer	941,610
Gastric Cancer	646,560
Ovarian cancer	162,404

Bigger Market for HER2+/HER2-low Breast Cancer[7]



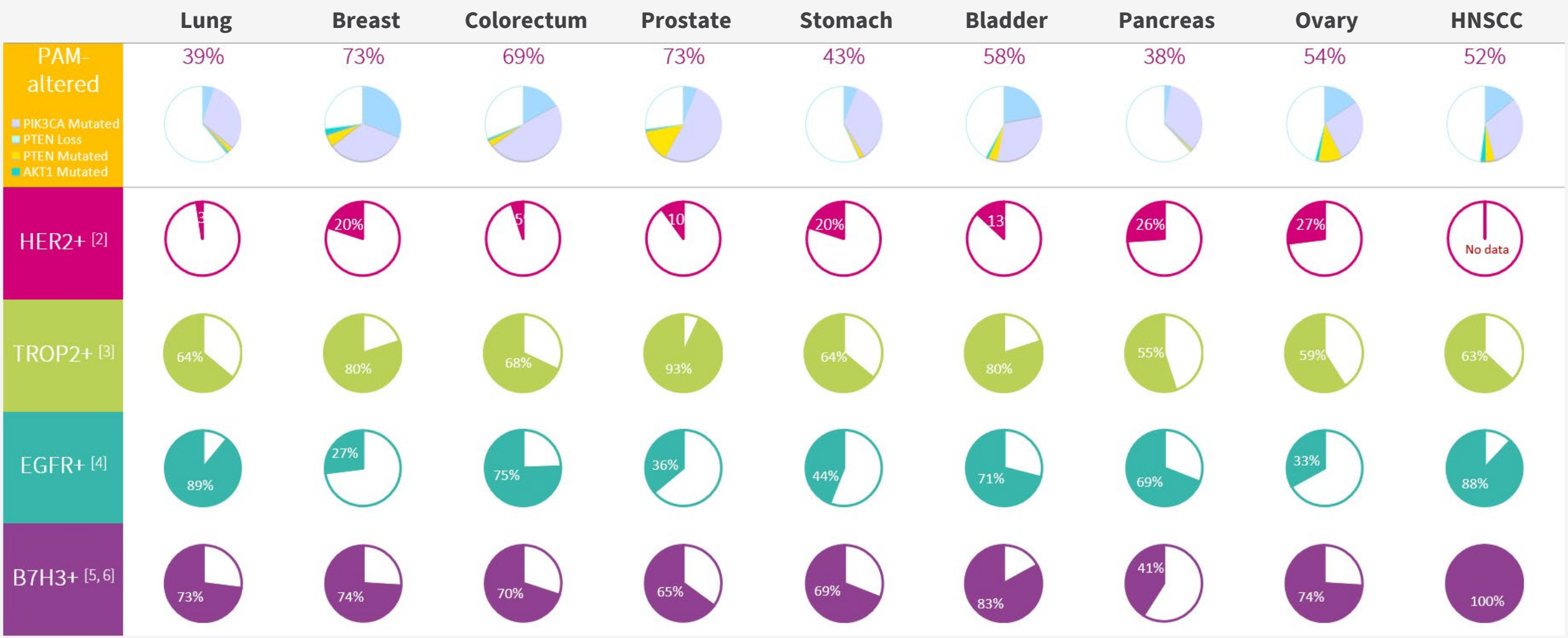
E.g. Market Potential of PAM+ HER2- 2L Breast Cancer[8]

- ~37,000 patients
- US$5 billion

[1] Glaviano, A., et al. (2023). PI3K/AKT/mTOR signaling transduction pathway and targeted therapies in cancer. Molecule Cancer. 2023 Aug 18;22:138. doi: 10.1186/s12943-023-01827-6
[2] Gajendra S.,et al (2016). The value of genomics in dissecting the RAS-network and in guiding therapeutics for RAS-driven cancers. Semin Cell Dev Biol. 2016 Jun 20;58:108–117. doi: 10.1016/j.semcdb.2016.06.012
[3] Jaeyun J., et al (2023). Clinical Implication of HER2 Aberration in Patients With Metastatic Cancer Using Next-Generation Sequencing: A Pan-Tumor Analysis. Precision Oncology, Volume 7. doi.org/10.1200/PO.22.00537
[4] Minkyue S., et al (2025). Epidermal Growth Factor Receptor Aberrations Identified by Next-Generation Sequencing in Patients with Metastatic Cancers. Journal of Korean Cancer Association 2025;57(4):932-941. DOI: https://doi.org/10.4143/crt.2024.564
[5] Aditya S., et al (2023) ALK fusions in the pan-cancer setting: another tumor-agnostic target? Precision Oncology Volume 7, Article number: 101 (2023)
[6] Cancer Today. (2022). Global cancer data visualization tools (GLOBOCAN estimates)
[7] Li Y., et al. (2023). Comprehensive characterization of HER2-low breast cancers: implications in prognosis and treatment. BioMedicine. 2023;91:104571
[8] Celcuity. (2025). Investor Presentation: Detailed Data ESMO, October 20, 2025. Retrieved from https://ir.celcuity.com/wp-content/uploads/2025/10/Celcuity-Investor-Presentation-Detailed-DataESMO10.20.25-Final.pdf

Antibody selection strategy: delivery of and combination with the payload

Antibody-payload tumor signaling synergy; combination with SOC in frontline line intended for all comers.



#, Adenocarcinoma; ##, Squamous cell carcinoma;

[1]. CA Cancer J Clin. 2024 May-Jun;74(3):229-263. [2]. Nat Rev Clin Oncol. 2020;17(1):33-48. [3]. Annu Rev Med. 2024;75:31-48.; [4] Cells 2021, 10, 1206; [5], Cancer Cell. 2017 Apr 10;31(4):501-515.e8.; [6], Cancer Res 2017;77(13 Suppl):Abstract nr 42

HUTCHMED ATTC pipeline

Drug	Target	Payload	Indication	Status	Rights
ATTC 1 **HMPL-A251**	**HER2**	**PI3K/PIKK**	Solid tumors	Phase I initiation H2 2025: China IND filed & US IND approved Pre-clinical	Global
ATTC 2 **HMPL-A580**	**Undisclosed**	**Undisclosed**	Solid tumors	Phase I initiation H1 2026: China & US Pre-clinical	Global
ATTC 3 **HMPL-A830**	**Undisclosed**	**Undisclosed**	Solid tumors	Phase I initiation H2 2026: China & US Pre-clinical	Global

20-minute Break

(Only in Chinese Session)

Late-Stage Pipeline Updates

HUTCHMED diversified and validated late-stage pipeline

Drug	Study	Target Disease	Status
Fruquintinib^^	FRUSICA-1	2L pMMR EMC	China conditional approval in Dec 2024
	FRUSICA-2	2L RCC	China NDA acceptance in Jun 2025; data readout at ESMO 2025
Savolitinib*	SACHI	2L EGFRm MET-amp NSCLC	China NMPA approval in Jun 2025
	SAVANNAH	2/3L EGFRm MET-amp/oe NSCLC	A high, clinically meaningful and durable ORR
	SAFFRON	2/3L EGFRm MET-amp/oe NSCLC	Enrollment target reached (data readout H1 2026)
	SANOVO	1L MET-oe NSCLC	Fully enrolled in Aug 2025
	Registration	3L MET-amp GC	Fully enrolled in Apr 2025 (potential NDA in 2025)
	SAMETA	1L MET-driven PRCC	Fully enrolled
Surufatinib	Phase II/III	1L PDAC	Phase II fully enrolled; data readout H2 2025
Tazemetostat^	Bridging	3L r/r FL	China NMPA approval in Mar 2025
	SYMPHONY-1	2L FL	Ongoing (HUTCHMED conducts the study in China)
Sovleplenib	ESLIM-01	2L ITP	Target re-submission will be in first half of 2026 (China NDA acceptance in 2024)
	ESLIM-02	2L wAIHA	LPI in June 2025 (potential NDA in Q2 2026)
Fanregratinib (HMPL-453)	Registration	2L FGFR2 fusion/rearrangement IHCC	LPI in Feb 2025 (potential NDA by the end of 2025)
Ranosidenib (HMPL-306)	RAPHAEL	2L IDH1/2+ r/r AML	FPI in May 2024

MET-amp = MET amplified; MET-oe = MET overexpressed; LPI = last-patient-in
* In collaboration with AstraZeneca ^ In collaboration with Ipsen ^^ In collaboration with Lilly

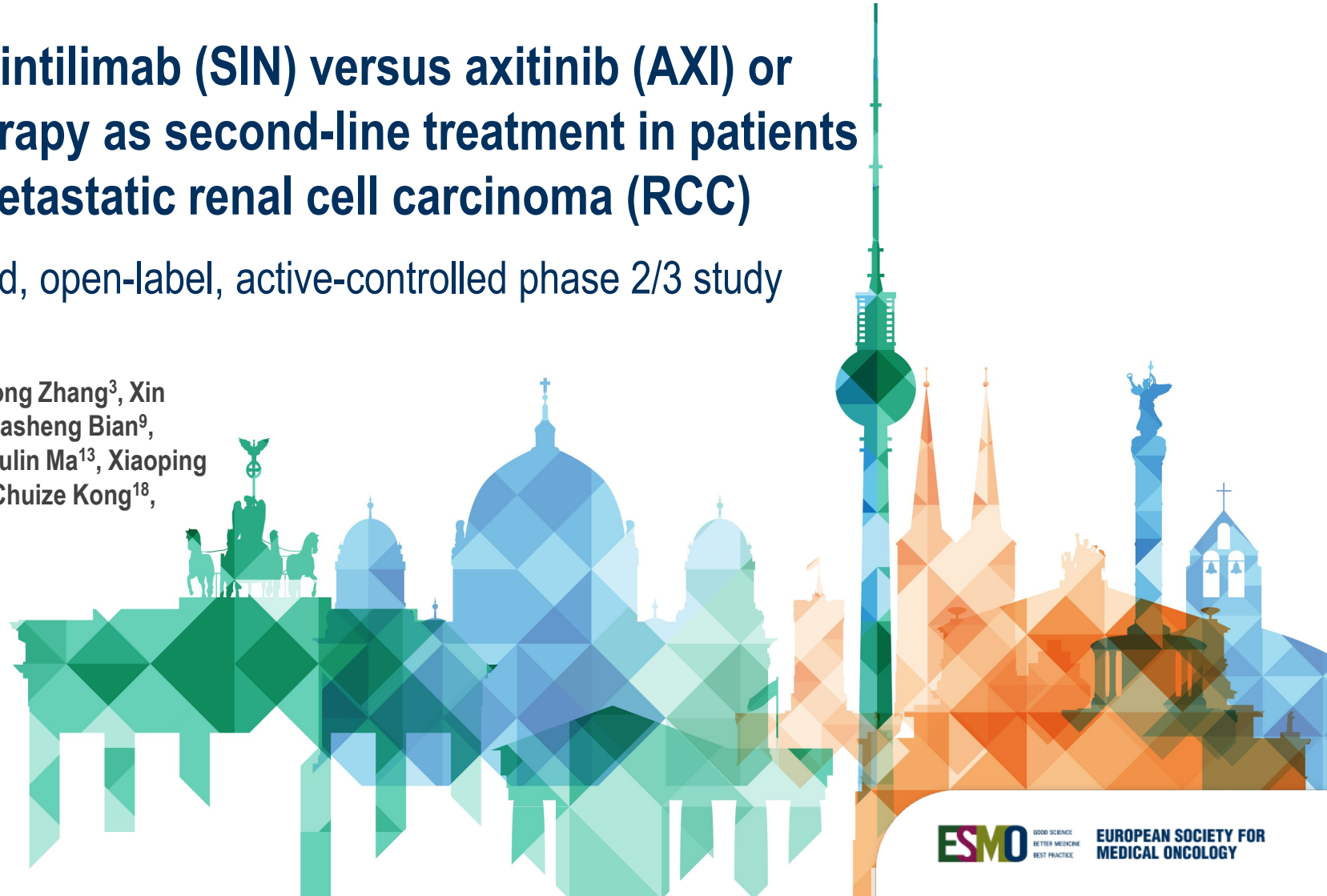
HUTCHMED

BERLIN 2025 ESMO congress

Fruquintinib (FRUQ) plus sintilimab (SIN) versus axitinib (AXI) or everolimus (EVE) monotherapy as second-line treatment in patients with locally advanced or metastatic renal cell carcinoma (RCC)

The phase 3 part of a randomised, open-label, active-controlled phase 2/3 study (FRUSICA-2)

Dingwei Ye[1*], Zhisong He[2], Yuanyuan Qu[1], Xiaodong Zhang[3], Xin Yao[4], Yu Xie[5], Jianming Guo[6], Jing Li[7], Bin Hu[8], Jiasheng Bian[9], Chaozhao Liang[10], Jun Xiao[11], Nianzeng Xing[12], Lulin Ma[13], Xiaoping Zhang[14], Zhenhua Liu[15], Hui Chen[16], Qing Zou[17], Chuize Kong[18], Weiguo Su[19];
on behalf of the FRUSICA-2 investigators



Berlin, Germany 17 Oct 2025

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

FRUSICA-2 study design

HUTCHMED

Key Inclusion Criteria:

- Confirmed locally advanced or metastatic RCC
- Progressed on or intolerant to previous first-line VEGFR-TKI therapy
- Aged 18-75 years
- ECOG PS of 0 or 1

Key Exclusion Criteria:

- Received prior immune-modulatory therapy (except immunotherapy in adjuvant/neoadjuvant therapy without progression within 6 months post-discontinuation)

Randomised 1:1

Fruquintinib (FRUQ) + Sintilimab (SIN) (N=119)

- FRUQ: 5 mg, QD, oral, 2-wk on/ 1-wk off, 21-day/cycle
- SIN: 200 mg, Q3W, IV, 21-day/cycle

Stratification Factors:

- IMDC risk stratification: favourable vs intermediate vs poor
- ECOG PS score: 0 vs 1

(INV's choice of)
Axitinib (AXI) or Everolimus (EVE) (N=115)

- AXI: 5 mg, BID, oral, 21-day/cycle
- EVE: 10 mg, QD, oral, 21-day/cycle

Treatment until progressive disease, death, intolerable toxicity, or other protocol-specified end of treatment criteria

Primary Endpoint

- BIRC-PFS per RECIST 1.1

Secondary Endpoints

- INV-PFS per RECIST 1.1
- ORR, DCR
- DoR, TTR
- OS

Statistical Consideration

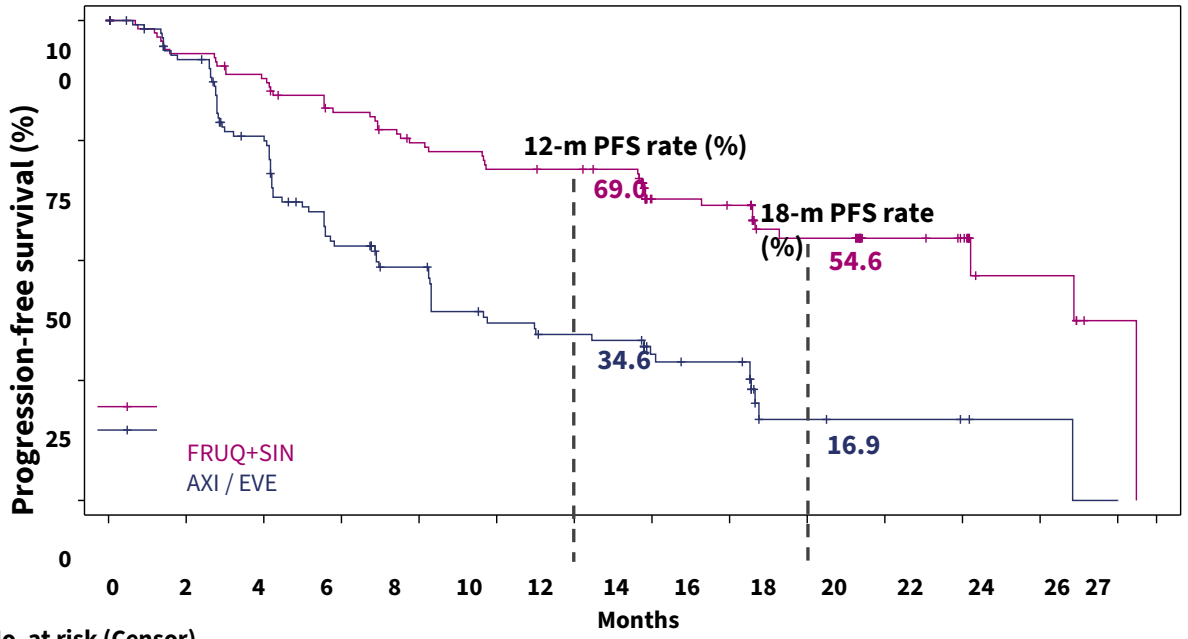
90% power with 146 BIRC-PFS events in ITT population, one sided α=0.025, assuming HR=0.583

The pre-planned final analysis point: one month after achieving 146 INV-PFS events (regardless of strict censoring rules).

FRUQ plus SIN showed significantly improved median PFS

PFS BY BIRC

Median follow-up: 16.56 months

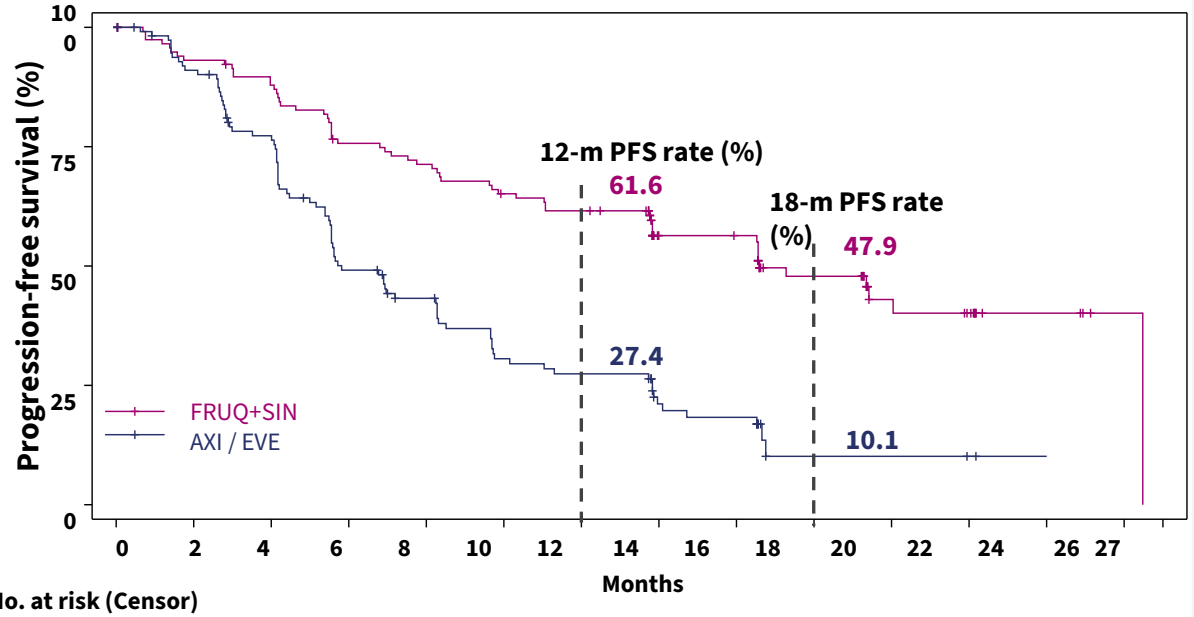


No. at risk (Censor)

FRUQ+SIN	119(0)	108(3)	101(4)	90(7)	81(9)	75(9)	74(10)	48(30)	46(31)	29(44)	17(56)	14(59)	5(67) 1(70)
AXI / EVE	115(0)	100(6)	78(11)	52(14)	43(19)	31(21)	28(22)	19(28)	17(29)	4(37)	3(38)	2(39)	1(40) 0(40)

PFS BY INV

Median follow-up: 16.59 months



No. at risk (Censor)

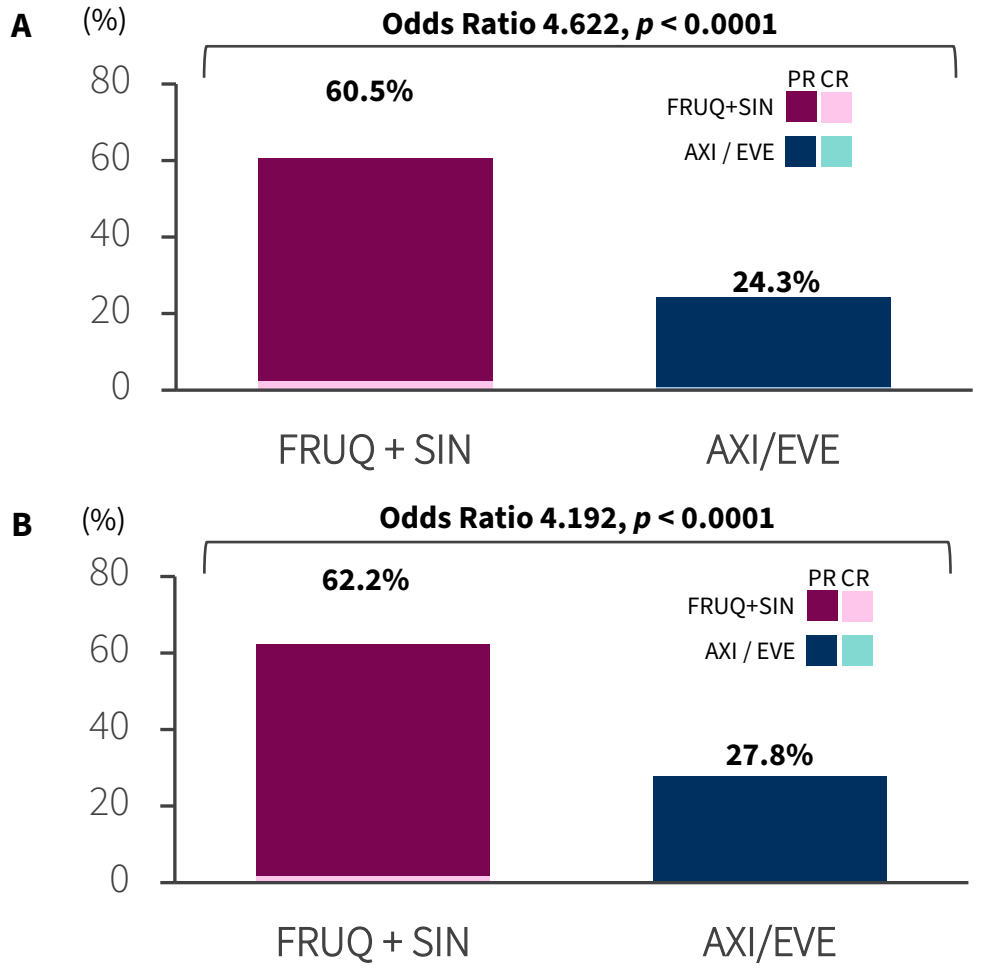
FRUQ+SIN	119(0)	108(3)	101(4)	86(5)	81(5)	73(6)	69(6)	44(26)	43(27)	27(37)	15(47)	12(49)	4(57) 1(60)
AXI / EVE	115(0)	101(4)	83(7)	52(8)	42(12)	29(13)	26(13)	15(19)	13(19)	2(27)	2(27)	1(28)	0(29)

	Event, n (%)	Median (95% CI), months
FRUQ + SIN (N=119)	49 (41.2)	22.21 (16.59, -)
AXI / EVE (N=115)	75 (65.2)	6.90 (5.55, 8.31)
Stratified HR 0.373 (95% CI: 0.256, 0.544); **Stratified log-rank $p < 0.0001$**		

	Event, n (%)	Median (95% CI), months
FRUQ + SIN (N=119)	59 (49.6)	16.59 (13.80, -)
AXI / EVE (N=115)	86 (74.8)	5.82 (5.49, 8.28)
Stratified HR 0.370 (95% CI: 0.260, 0.527); **Stratified log-rank $p < 0.0001$**		

Overall survival data were evolving with data maturity of about 20%

ORR by BIRC (A) and Investigator (B)



	FRUQ + SIN (N=119)	AXI / EVE (N=115)
Per BIRC assessment		
Best overall response, n (%)		
CR	3 (2.5)	1 (0.9)
PR	69 (58.0)	27 (23.5)
SD	34 (28.6)	69 (60.0)
Non-CR/non-PD	2 (1.7)	5 (4.3)
PD	8 (6.7)	9 (7.8)
NE	3 (2.5)	4 (3.5)
ORR (95% CI), %	60.5 (51.13, 69.34)	24.3 (16.83, 33.23)
DCR (95% CI), %	90.8 (84.06, 95.29)	88.7 (81.45, 93.84)
Median DoR (95%CI), months	23.69 (14.46, -)	11.33 (6.90, -)
Media TTR (95%CI), months	2.79 (2.76, 2.86)	2.69 (1.41, 2.83)
Per investigator assessment		
Best overall response, n (%)		
CR	2 (1.7)	0
PR	72 (60.5)	32 (27.8)
SD	34 (28.6)	69 (60.0)
Non-CR/non-PD	0	0
PD	8 (6.7)	10 (8.7)
NE	3 (2.5)	4 (3.5)
ORR (95% CI), %	62.2 (52.84, 70.91)	27.8 (19.87, 36.95)
DCR (95% CI), %	90.8 (84.06, 95.29)	87.8 (80.42, 93.18)
Median DoR (95%CI), months	17.97 (13.83, -)	11.04 (4.17, 12.45)
Median TTR (95%CI), months	2.83 (2.79, 4.14)	2.76 (1.45, 2.83)

Summary

63%

Reduction in risk of disease progression or death with FRUQ plus SIN (by BIRC)

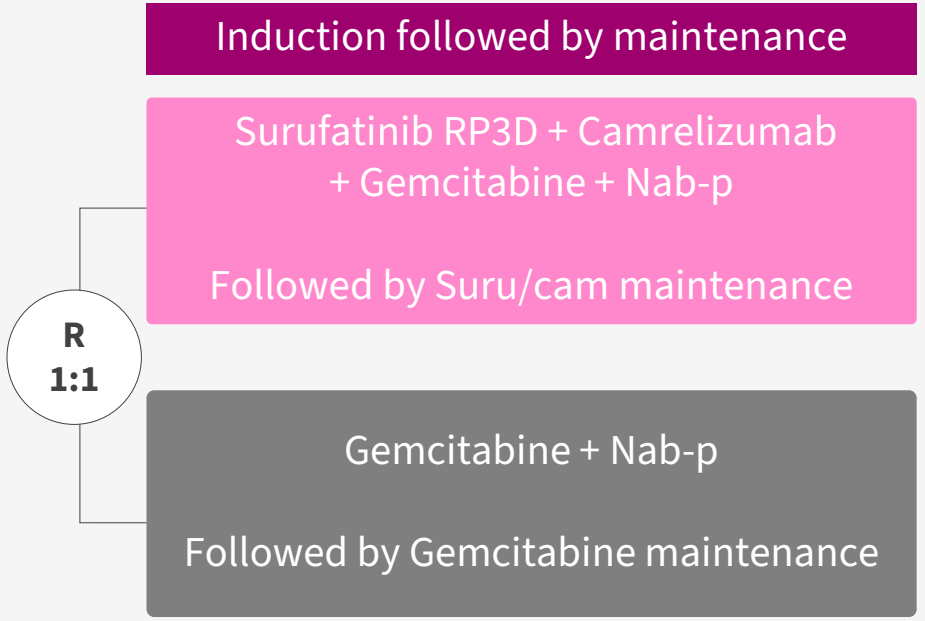
- FRUQ plus SIN demonstrated superior clinical benefits compared with physician's choice of AXI (87.8%) or EVE (12.2%) in advance RCC after first-line VEGFR-TKI
  - ✓ **PFS improvement:** 22.2 vs 6.9 months by BIRC (HR 0.373, $p<0.0001$)
  - ✓ **ORR benefit:** 60.5% vs 24.3% by BIRC (Odds Ratio 4.622, $p<0.0001$)
- The safety profile of FRUQ plus SIN was tolerable, and consistent with known profiles of each individual treatment.

FRUQ plus SIN demonstrated both statistically and clinically meaningful improvement in median PFS, suggesting the combination therapy could be a new second-line treatment for patients with advanced RCC

Surufatinib: 1L PDAC

To be presented at ESMO Asia in Dec.

Multicenter, randomized, open-label, Phase II/III registration study



Phase II
Primary endpoint: ORR
Secondary endpoint: PFS

Phase III
Primary endpoint: OS

Savolitinib: global and China progress driving future growth

7 potential registration studies: 3 global & 4 in China: advancing multiple indications and market opportunities.

H1 2025 achievement

Global — **2/3L TAGRISSO® ref. NSCLC with MET aberration**

ELCC 2025, WCLC 2022

SAVANNAH study:

high, clinically meaningful and durable ORR

ORR: 56% (investigator); 55% (BICR)

China — **METex14 skipping NSCLC**

ELCC 2025, ELCC 2024

Confirmatory Phase IIIb study: 1L and 2L full approval in 2025

China — **2L EGFR TKI ref. NSCLC with MET amplification**

China BTD Priority Review

ASCO 2025

SACHI study:

- **China NMPA approval in Jun 2025**
- Potential for earlier line treatment
- Savolitinib + TAGRISSO® Phase III registration study

Global — **MET-driven Papillary Renal Cell Carcinoma (PRCC)**

SAMETA study:

- Enrollment completed in 2024
- Savolitinib + IMFINZI® vs. SUTENT® vs. IMFINZI®
- Phase III registration study

Ongoing enrollment

Global — **2/3L TAGRISSO® refractory NSCLC with MET aberration**

SAFFRON study:

Savolitinib + TAGRISSO® Phase III registration study

Enrollment target reached

China — **1L EGFRm+ NSCLC with MET overexpression**

SANOVO study:

Enrollment completed in Aug 2025

Savolitinib + TAGRISSO® Phase III registration study

China — **Gastric cancer with MET amplification**

AACR 2023

Potential NDA by end of 2025

Registration cohort FPI Mar 2023

China BTD

BTD = Breakthrough Therapy Designation

Tazemetostat: 3L FL China approval in 2025

- **Tazemetostat in r/r FL with EZH2m.**
- **China is participating global Phase III EZH-302/SYMPHONY-1 (NCT04224493) evaluating TAZ+R2 for r/r FL patients.**

China bridging study
2021-TAZ-00CH1

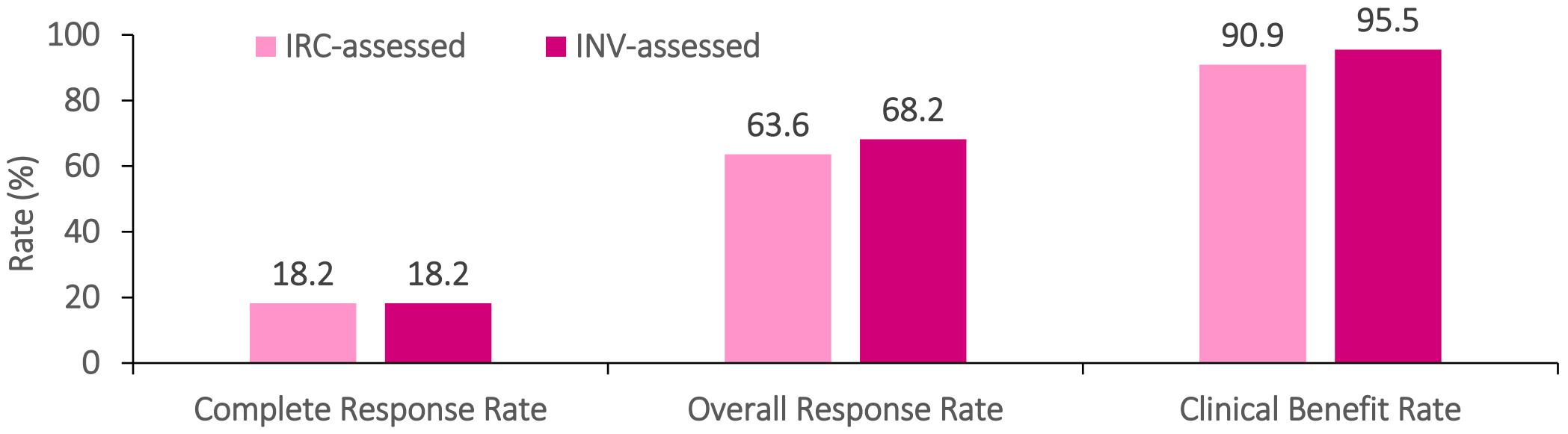
- r/r FL 1-3a
- EZH2 mutation
- ≥ 2 prior systemic therapies, including anti-CD20 therapy

N=22 →

Taz 800mg BID PO →

Primary endpoint
EHA 2025
ORR (EZH2 MT):
- IRC: 63.6%
- Investigator: 68.2%

Approved 2025 March



IRC = Independent Review Committee
J, Cao, et al., A phase 2 study of tazemetostat (TAZ) in Chinese patients (pts) with relapsed or refractory (R/R) follicular lymphoma (FL) harboringenhancer-of-zeste-homolog-2 mutations (EZH2mut); EHA 2025 PF910

Tazemetostat: EZH-302/SYMPHONY-1

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Phase 1b (Stage 1: Safety Run-in)

Dose Escalation Using 3+3 Design[a]

Patients with r/r FL
N≈3–18[a]

TAZ (dose escalation; 3+3 design) + R^2
Enrolled N=44

Phase 1b Dosing		
	Tazemetostat	400 mg, 600 mg, 800 mg orally BID × 28-day cycles
	Rituximab	375 mg/m^2 intravenously on days 1, 8, 15, and 22 of cycle 1, then on day 1 of cycles 2 to 5
	Lenalidomide	20 mg (CrCl ≥60 mL/min) or 10 mg (CrCl <60 mL/min) orally QD on days 1 to 21 every 28 days for 12 cycles

Primary Endpoints
- Safety and tolerability
- TAZ RP3D

Secondary Endpoint
- Safety PK parameters

Phase 3 (Stage 2b)

Patients with r/r FL
N≈568

R
1:1

Arm 1
TAZ RP3D + R^2 → Continue arm 1 treatment for up to 12 cycles or until relapse or intolerability[c] → Continue TAZ as maintenance therapy for up to 2 years

Arm 2
Placebo + R^2 → Continue arm 2 treatment for up to 12 cycles or until relapse or intolerability[c] → Continue placebo as maintenance therapy for up to 2 years

Stratified by *EZH2*m status (MT vs WT), sensitivity to prior treatment (sensitive vs refractory), and number of lines of therapy (1 vs ≥2)

Primary Endpoint
- PFS (by investigator)

Secondary Endpoint
- PFS (by IRC), ORR, DOR, DOCR, DCR, OS, QoL, population PK, safety and tolerability

- Preliminary efficacy analysis was performed on the response-evaluable population
  - Efficacy was reported as best overall response, PFS, and DOR[e]
- The safety population[f] was used for all safety analyses

- [a]Additional patients enrolled to further study safety in the 600- and 800-mg groups. [b]An optional stage 3, for patients with MT *EZH2* FL only, will be executed if the efficacy in stage 2 fails for all patients but is sufficiently promising for patients with MT *EZH2* FL (as assessed in a futility analysis during stage 2). [c]All patients receive treatment in 28-day cycles. [d]The response-evaluable population consists of patients from the intent-to-treat population who had adequate baseline and ≥1 postbaseline tumor assessment, per the International Working Group criteria for non-Hodgkin lymphoma. [e]Per investigator assessment, according to Lugano 2014 response criteria. [f]The safety population is defined as all patients who receive ≥1 dose of study drug
- BID, twice daily; CrCl, creatinine clearance; DCR, disease control rate; DOCR, duration of complete response; DOR, duration of response; FL, follicular lymphoma; IRC, independent radiology committee; MT, mutant; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PO, orally; QD, once daily; QoL, quality of life; R, randomization; R^2, lenalidomide plus rituximab; RP3D, recommended phase 3 dose; r/r, relapsed/refractory; TAZ, tazemetostat; WT, wild-type.

Fanregratinib (HMPL-453): a novel FGFR inhibitor

Completed enrollment in February 2025.

Potential China NDA in 2025.

Cohort 1

- **FGFR2 fusion, inoperable locally advanced ICC**
- **Failure or unwillingness to 1L therapy, or toxicity intolerance**

12 pts → **HMPL-453 150mg QD**

1 Cycle = 21 days

Cohort 2

Cohort 2: Stage I

- Advanced solid tumor
- Failure of standard therapy

Safety-run in 6~9 pts → **HMPL-453 300mg**

2w on/1w off

1 Cycle = 21 days

Safety assessed by SRC

Cohort 2: Stage II

- FGFR2 fusion/rearrangement, inoperable locally advanced or metastatic ICC
- Failure to at least 1L therapy, or toxicity intolerance

SAT pivotal 87pts → **HMPL-453 300mg**

2w on/1w off

1 Cycle = 21 days

SRC will review the safety and efficacy data to decide to expansion

Primary endpoint Pivotal stage ORR(IRC)
Secondary endpoint ORR (INV), DCR, TTR, DoR, PFS, OS
Cohort 2 stage I: Safety

Sovleplenib ESLIM-01 extension study update

- **Target re-submission will be in first half of 2026.**
- **In the future, will look to continue overseas development.**

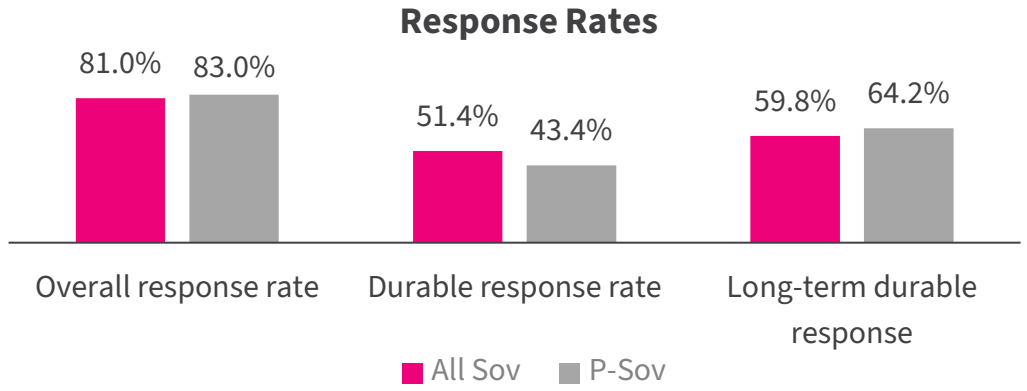
Long-term treatment was effective in increasing and maintaining platelet count with well tolerated safety

A Follow-on, open-label sub-study[1]
(Total N=179: 126 initial + 53 P-Sov crossover)

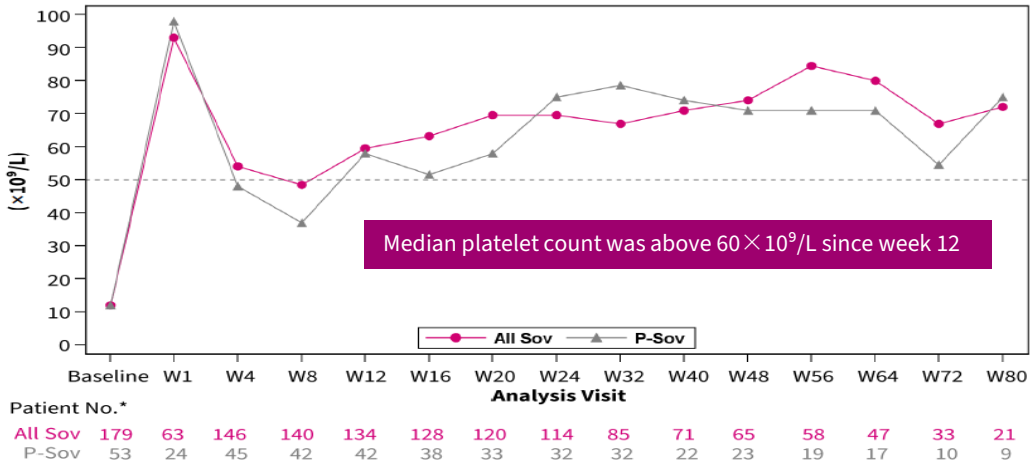
- Overall response: 81.0%; durable response: 51.4%

  ESLIM-01 at EHA:
  overall response 70.6%; durable response 48.4%

- Median cumulative duration of platelet count ≥50×10^9/L: 38.9 weeks
- Use of rescue therapy: 22.9%
- Well tolerated, with a safety profile consistent with previous studies and no new safety signals were identified



Median Platelet Count During Treatment



Note: * the number of patients with platelet counts value at the related visits

[1] Hu, Y. (2024, December 8). Long-Term Sovleplenib Treatment of Adults with Primary Immune Thrombocytopenia in China [Conference presentation]. 2024 ASH Annual Meeting, Abstract #2558

Warm antibody autoimmune hemolytic anemia (wAIHA) ESLIM-02 Phase II demonstrated encouraging results

- **Completed enrollment in June 2025.**
- **Potential China NDA in Q2 2026.**

Efficacy	Definition	Week 0-8 (Double blind)		Week 8-24 (Open label)	Week 0-24 (Double blind + Open label)
		Sovleplenib (n=16)	Placebo (n=5)	Cross-over from placebo (n=5)	All sovleplenib (n=21)
Overall response, n (%)	Hb ≥100 g/L with an increase of ≥20 g/L from baseline	7 (43.8)	0	3 (60.0)	14 (66.7)
Durable response, n (%)	Hb ≥ 100 g/L with an increase of ≥20 g/L from baseline on 3 consecutive visits with at least 7 days interval	3 (18.8)	0	2 (40.0)	10 (47.6)

Lancet Haematology. 2024 Aug;11(8):e567-e579

Closing Remarks

HUTCHMED today and beyond…

(In US$)

- FRUZAQLA® : H1 2025 up +**25%** to $162.8m
- ORPATHYS®: 2nd potential global commercial success
- ELUNATE®: new indication (EMC) approved

Potential events next 12-months:

- SAFFRON recruitment completion
- Surufatinib PDAC Phase II readout
- Fanregratinib NDA submission
- Savo GC NDA submissions
- Fruquintinib RCC NMPA approval
- SAMETA and SAFFRON Phase III readout

Antibody-Targeted Therapy Conjugate (ATTC) platform with multiple selective, efficacious and tolerable drug candidates

- ✓ First candidate US + China clinical trial initiation in H2 2025
- In-licensing and out-licensing options

Profitable, ~$2.7bn market cap, $1.4bn cash

Q&A

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