CStone Pharmaceuticals
基石藥業
(Incorporated in the Cayman Islands with limited liability)
(**Stock Code: 2616**)

VOLUNTARY ANNOUNCEMENT
CSTONE PRESENTED FIVE LATEST STUDIES AT 2025 AACR ANNUAL MEETING

CStone Pharmaceuticals (the "**Company**" or "**CStone**") is pleased to announce that, from April 25 to 30, 2025, the American Association for Cancer Research (AACR) Annual Meeting was held in Chicago, USA. The Company presented its latest preclinical studies on five internally developed innovative candidates from CStone Pipeline 2.0 in poster session, including the trispecific antibody CS2009 (PD-1/VEGF/CTLA-4 trispecific antibody), the bispecific antibody CS2011 (EGFR/HER3 bispecific antibody), and three novel antibody-drug conjugates (ADCs) developed from CStone's proprietary ADC platform: CS5007 (EGFR/HER3 bispecific ADC), CS5005 (ITGB4 ADC) and CS5006 (SSTR2 ADC).

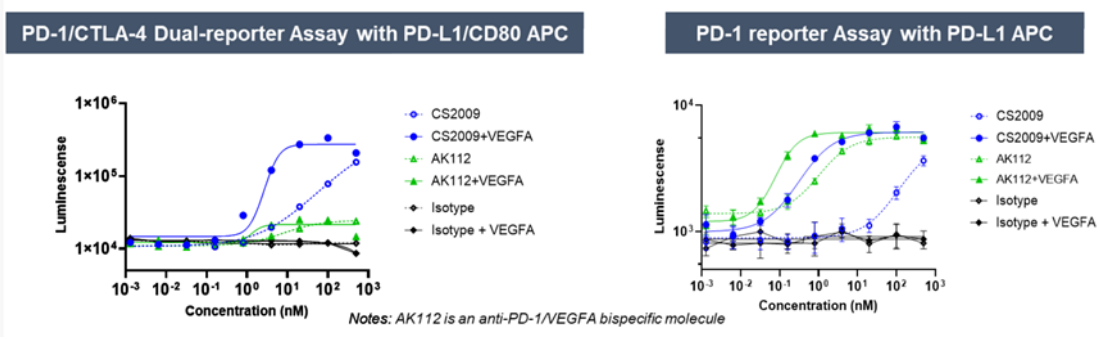
Key Highlights

1. CS2009: a promising trispecific antibody targeting PD-1, VEGFA, and CTLA-4, which demonstrates broad clinical application prospects for solid tumors with the great potential to become the next-generation immune-oncology backbone to replace current anti-PD-(L)1-based therapies.

    - CS2009 exhibited enhanced affinity upon simultaneous PD-1/CTLA-4 engagement. It also enhances anti-tumor efficacy by preferentially targeting PD-1/CTLA-4 double positive T cells in TME.

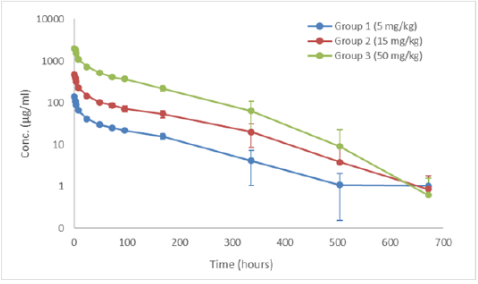
    - CS2009 exhibited a ~150-fold enhancement in checkpoint inhibitory activity on PD-1/CTLA-4 dual-reporter assay through crosslinking with VEGFA dimers. In PD-1 reporter assay, the CS2009/VEGFA combination demonstrated approximately 300-fold greater immune checkpoint activity compared to CS2009 alone. Mixed lymphocyte reaction (MLR) assays evaluating primary T cell activation revealed that crosslinking with VEGFA dimer

significantly increases the activity of CS2009. These findings indicate enhanced activity of CS2009 in VEGFA-enriched TME and minimized peripheral overactivation-induced immune-related toxicity, thereby expanding its therapeutic window.



- CS2009 exhibited comparable pharmacokinetic (PK) profiles to those of monoclonal antibodies.

PK Profiles in Cyno Monkeys following IV Infusion



	CS2009	AK104*
MW (kDa)	200	200
CL (mL/hr/kg)	0.70 (5mpk), 0.57 (15mpk)	1.6 (4mpk), 1.9 (16mpk)
Vd,ss (mL/kg)	79 (5mpk), 75 (15mpk)	92 (4mpk), 113 (16mpk)
$T_{1/2}$ (h)	75.9 (5mpk)	47.9 (4mpk)

Notes: AK104 is an anti-PD-1/CTLA-4 bispecific molecule;
** From AK104 Ph1b study protocol*

- CS2009 demonstrates superb tolerability with the highest non-severely toxic dose (HNSTD)/ the no observed adverse effect level (NOAEL) identified as 100 mg/kg.

- CS2009 global phase I trial is ongoing in Australia with first patient dosed in this March and will soon be expanded to China and the US.

2. CS2011: a potentially best-in-class bispecific antibody with high binding affinity to both EGFR and HER3. It effectively blocks downstream signaling of both targets, thereby inhibiting tumor growth on EGFR/HER3 positive tumor cells, including colorectal cancers (CRC), lung cancers and head and neck squamous cell carcinomas (HNSCC).

- CS2011 targets almost all HER family signaling except HER2 homodimers, addressing tumor heterogeneity effectively.

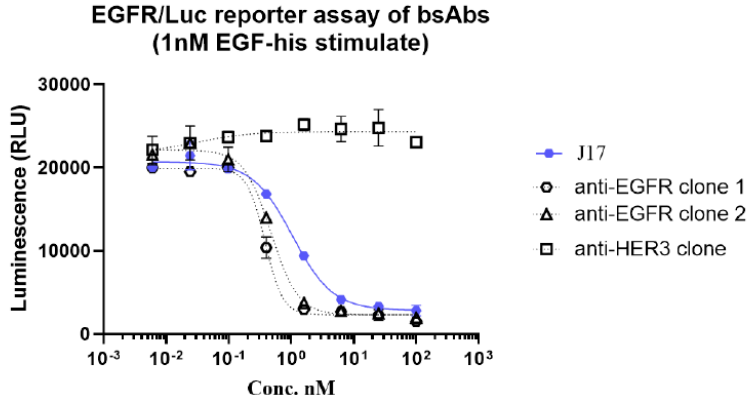
- CS2011 demonstrates potent binding affinity to EGFR and/or HER3 individually and enhanced dual binding affinity to EGFR and HER3 concurrently driven by avidity-based synergy, inhibiting tumor growth by binding to EGFR and/or HER3-positive tumor cells.

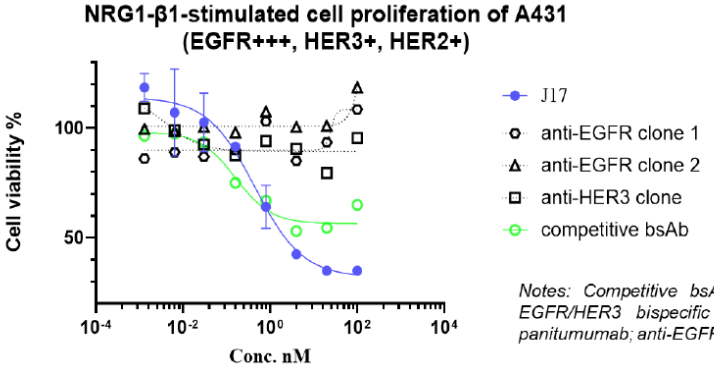
- CS2011 shows superior *in vivo* and *in vitro* anti-tumor activity versus potential major competitors.

  · Compared to anti-EGFR, anti-HER3 and competing bispecific antibody, CS2011

induces faster and deeper internalization in tumor cells across varying EGFR & HER3 expression levels.

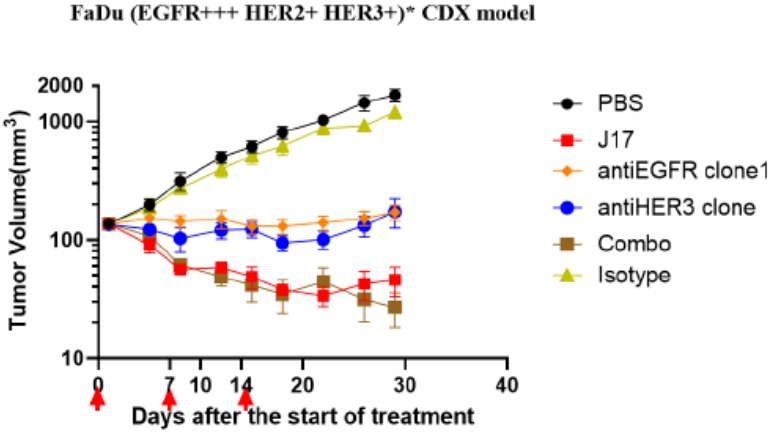
- CS2011 demonstrated potent inhibition of EGFR downstream signaling, comparable to anti-EGFR antibodies, and superior inhibition of HER3-mediated signaling.





Notes: Competitive bsAb was synthetized with published Baili's EGFR/HER3 bispecific antibody, SI-B001; anti-EGFR clone 1, panitumumab; anti-EGFR clone 2, cetuximab; anti-HER3, patritumab.

- CS2011 exhibited robust anti-proliferative activity in tumor cells with diverse EGFR and HER3 expression levels.
- In *in vivo* CDX tumor models, CS2011 demonstrated superior tumor-growth inhibition compared to anti-EGFR or anti-HER3 monoclonal antibodies alone and showed comparable efficacy to their combination treatment.



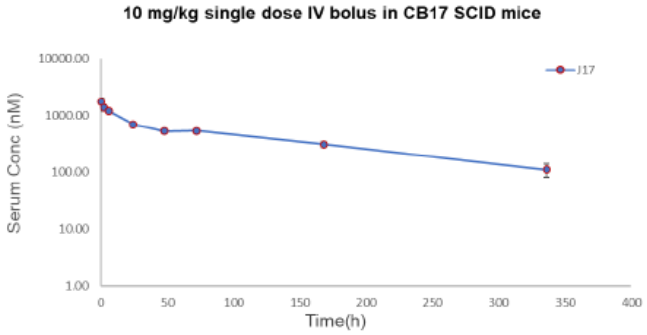
Notes: All mono-therapy groups were given 10 mg/kg or equivalent dose as J17 with 1 week interval 3 times. The combo group was given 5 mg/kg for each antibody.

** The level of antigen expression was determined with FACS.*

anti-EGFR clone 1, panitumumab; anti-HER3, patritumab; Combo group was given anti-EGFR clone 1 and anti-HER3 clone at 5 mg/kg each.

- CS2011 exhibited a PK profile comparable to those of monoclonal antibodies in rodents.

J17 exhibits mAb-like PK in mice, suggesting it is a stable bispecific molecule.



Test Article	Dose	Route	$AUC_{(0-t)}$	C_{max}	Terminal $T_{1/2}$
			nmol/L*h	nmol/L	h
J17	**10 mg/kg**	IV	123959.59	1748.61	121.91

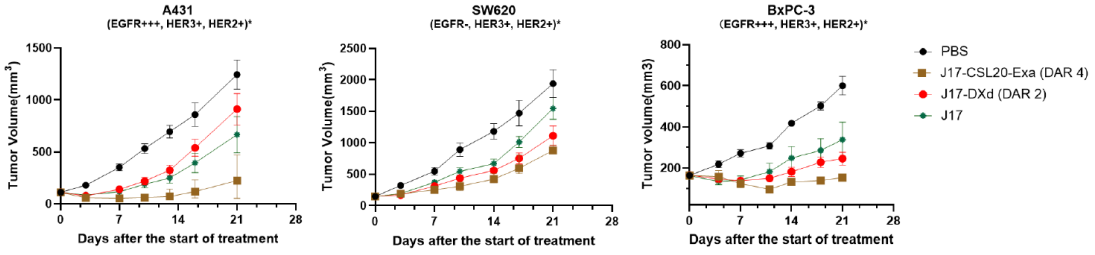
- The patent of CS2011 has been filed in March this year, and its Investigational New Drug (IND) application is expected to be submitted in the near term.

3. CS5007: an EGFR/HER3 dual targeting ADC, composed of EGFR/HER3 bispecific antibody backbone (CS2011), a hydrophilic β-glucuronide linker and a clinically validated topoisomerase I inhibitor, Exatecan. It is positioned as a potential best-in-class candidate for precision oncology.

- Similar with CS2011, its antibody backbone, CS5007 targets almost all HER family signaling except for HER2 homodimers, addressing tumor heterogeneity effectively and demonstrates high-affinity binding to EGFR single-positive, HER3 single-positive and EGFR/HER3 double positive tumor cells.

- CS5007 triggered high-rate internalization on tumor cells.

- CS5007 demonstrated potent, antigen-dependent cytotoxicity against tumor cells *in vitro* across varying EGFR and HER3 expression levels and showed robust tumor-growth inhibition in CDX models.



Sample ID	A431	SW620	BxPC-3
	Day21 %TGI	Day21 %TGI	Day21 %TGI
J17-CSL20-Exa (DAR 4)	**90%**	**59%**	**102%**
J17-DXd (DAR 2)	29%	46%	82%
J17	51%	22%	60%

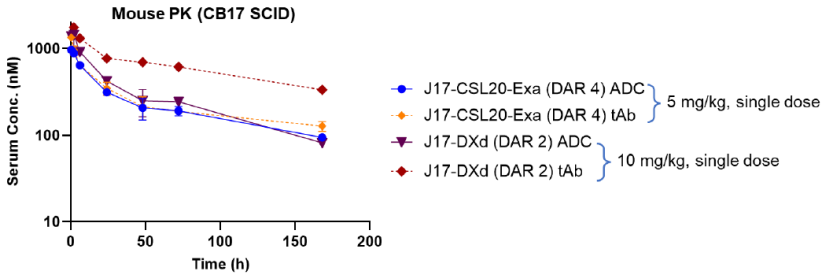
- All groups were given a single dose of 5 mg/kg.
- J17-CSL20-Exa demonstrated effective tumor inhibition.
- In mouse MTD** study on balb/nude mice, J17-CSL20-Exa remained well tolerated at 150 mg/kg.

** The level of antigen expression was determined with FACS.*
*** MTD was defined as the maximum dose that do not cause mortality, serious overt toxicities or >=15% weight loss for more than 24h in any animal.*

- CS5007 exhibited superior *in vitro* stability compared to ADCs conjugated with tetrapeptide and dipeptide linkers. After 7 days of incubation in human/monkey serum, it retained approximately 70% of its drug payload, indicating a minimal release rate.

- CS5007 exhibited comparable PK profile to those ADCs composed of monoclonal antibodies in rodents.

CSL20-Exa-conjugated ADC demonstrated a more favorable PK profile than DXd-conjugated ADC.



Sample ID	AUC0-168h (nM*h)		AUC_{ADC}/AUC_{tAb}	$T_{1/2}$ (h)
	ADC	tAb		ADC
J17-CSL20-Exa (DAR 4)	37288.42	40624.38	91.8%	102.2
J17-DXd (DAR 2) *	23554.33	53026.13	44.4%	64.23

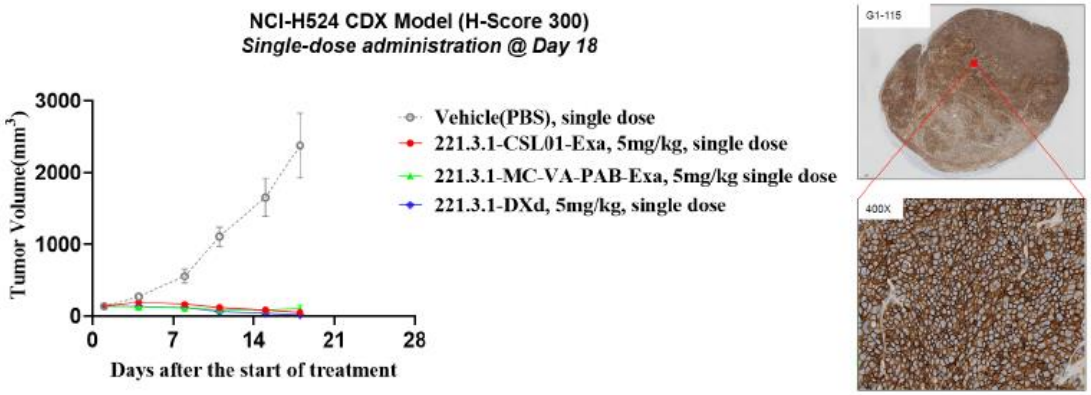
** J17-DXd (DAR 2)'s exposure data was normalized to a dose of 5 mg/kg.*

- The patent of CS5007 has been filed in March 2025. Preclinical findings support its further IND-enabling studies and clinical investigations in various advanced solid tumors.

4. CS5005: a first-in-class, SSTR2-targeting ADC, composed of CStone's proprietary anti-SSTR2 antibody with high affinity and selectivity, hydrophilic β-glucuronide linker, and potent topoisomerase I inhibitor, Exatecan. CS5005 potentially targets various solid tumors, including neuroendocrine tumors (NETs), neuroendocrine carcinomas (NECs), and small cell lung cancer (SCLC) and demonstrates potent antigen-dependent tumor growth inhibition.

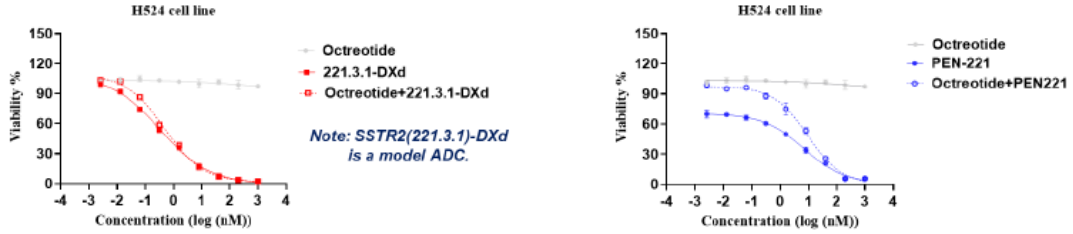
- CS5005 demonstrated high affinity to SSTR2-positive cell lines, inducing high-rate internalization on tumor cells and selectively binding to SSTR2 with minimal interaction with other SSTRs.

- CS5005 demonstrated potent antigen-dependent cytotoxic activity against tumor cells *in vitro* and robust tumor-growth inhibition in CDX tumor model.



- The antitumor activity of CS5005 (SSTR2-DXd) is not compromised by concomitant ligand-

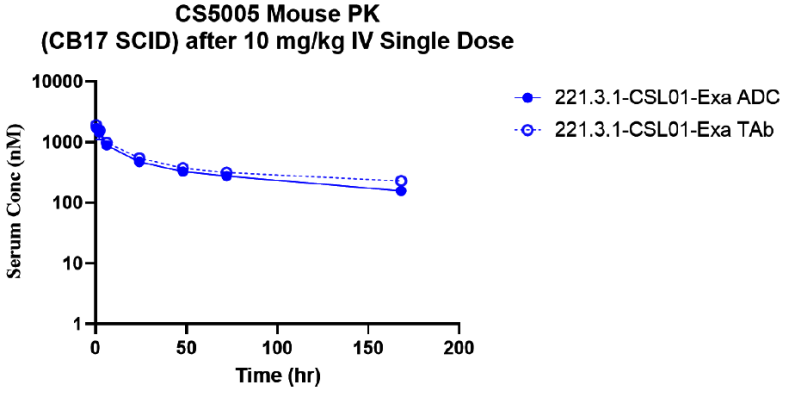
derived treatments (e.g., octreotide, Lutathera®), thereby avoiding drug-drug interference commonly observed with current anti-SSTR2 therapies.



- **KEY FINDINGS** – SSTR2-DXd would avoid drug-drug interference as shown by current anti-SSTR2 therapies
- **No efficacy interference:** SSTR2(221.3.1)-DXd antitumor activity not compromised by octreotide co-treatment while the potency of PEN-221 (octreotide conjugated to DM1) notably lower in the same assay
- **Clinical translation**
  - ✓ No need for washout of first-line treatment of SSA, while Lutathera® requires a 4-week washout
  - ✓ Enable combination therapy with SSAs or Lutathera®

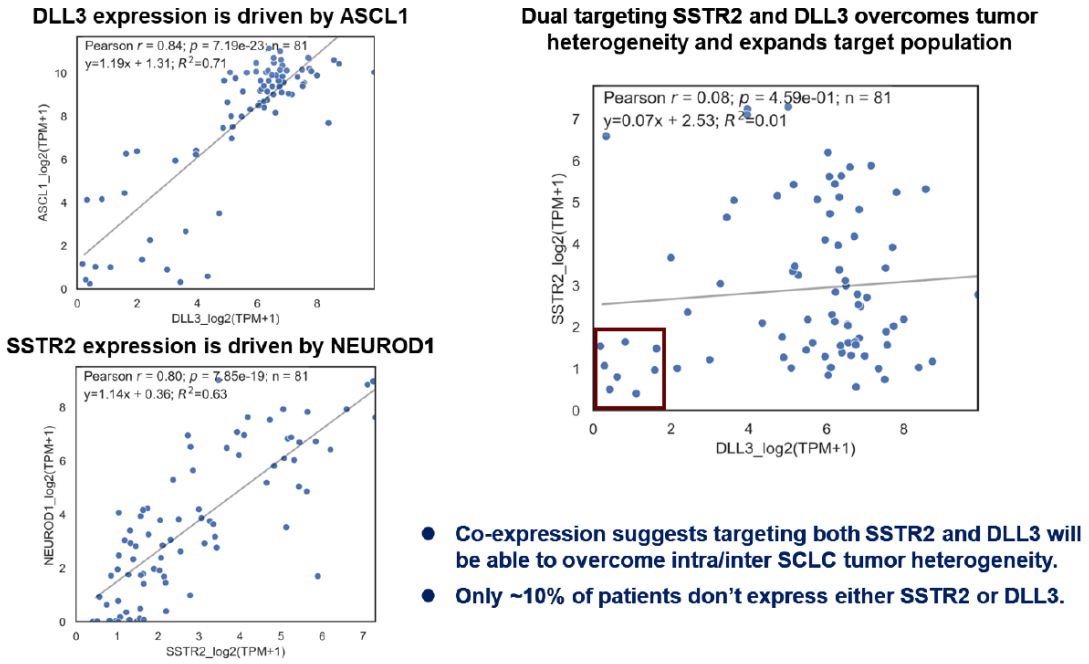
- CS5005 demonstrated superior *in vitro* stability due to its proprietary linker, outperforming ADCs conjugated with well-validated dipeptide and tetrapeptide linkers.

- CS5005 demonstrated superior PK properties in rodents.



Test Article	DAR	$AUC_{0\text{-}168h}$ (nM*h)		AUC_{ADC}/AUC_{TAb}	Cmax (nM)	T1/2 (h)
		ADC	TAb		ADC	ADC
221.3.1-CSL01-Exa	4	54521.11	64729.97	84.2%	1713.22	132.61
221.3.1-MC-VA-PAB-Exa	4	28516.77	34827.12	81.9%	865.12	89.04
221.3.1-DXd	8	40794.43	38668.91	105.5%	1285.77	117.60

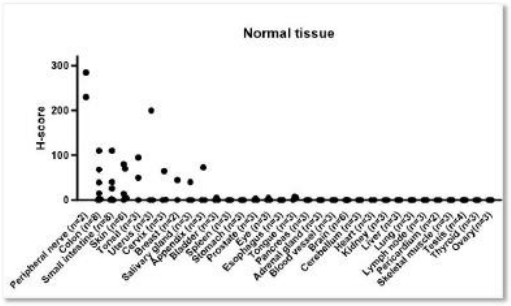
- Bioinformatics analysis of SCLC samples supports DLL3/SSTR2 dual targeting as a strategy to overcome tumor heterogeneity and expand the treatable patient population.

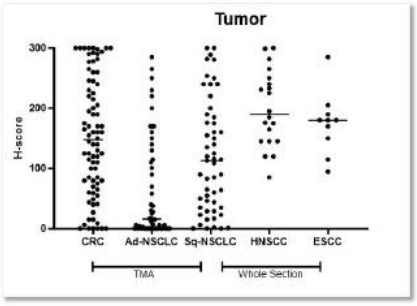


- The patent of de novo antibody has been filed for CS5005 in the first half of 2024. Another preclinical candidate CS5008 (an SSTR2/DLL3 dual targeting ADC) is under development. By simultaneously targeting SSTR2 and DLL3 that frequently co-express in SCLC, NETs, NECs and others, CS5008 aims to overcome tumor heterogeneity, a challenge faced by mono-specific therapies.

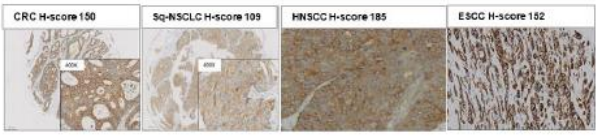
5. CS5006: a first-in-class antibody-drug conjugate (ADC) targeting the novel antigen integrin β4 (ITGB4). ITGB4 is identified to be highly expressed in multiple tumor types, including non-small cell lung cancer (NSCLC), CRC, esophageal squamous cell carcinoma (ESCC) and HNSCC, with rare expression in normal tissues. CS5006 has demonstrated promising therapeutic potential in preclinical studies.

   - Bioinformatics analysis validated high ITGB4 expression in colorectal tumor tissues, supporting ITGB4 as a promising tumor-associated antigen for CRC. Immunohistochemistry (IHC) staining confirmed limited ITGB4 expression in normal tissue but high expression in tumor tissues from patients with CRC, sq-NSCLC, HNSCC and ESCC.

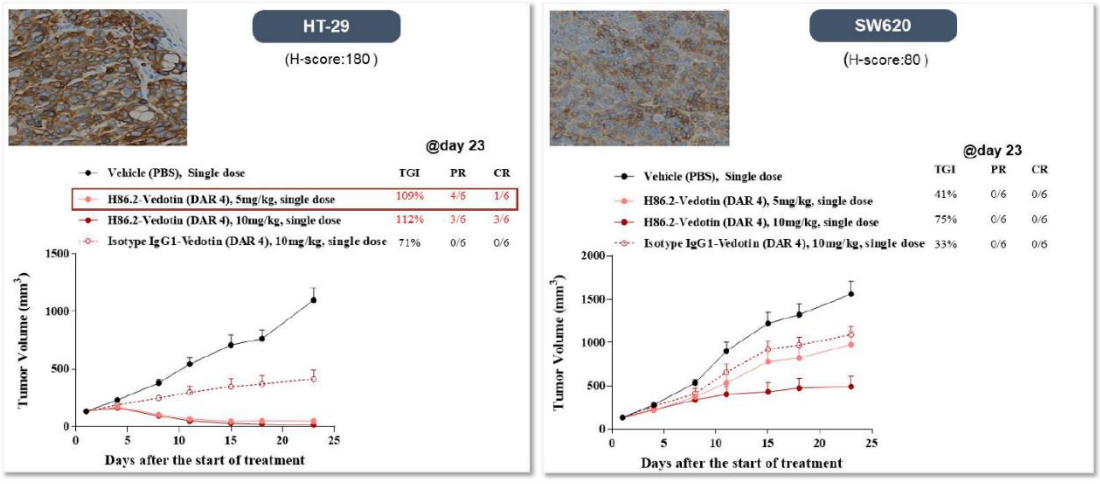




- No detectable ITGB4 expression in life-sustaining organs, e.g., brain, heart, lung, and liver
- High-level expression observed in peripheral nerve, similar to HER2.

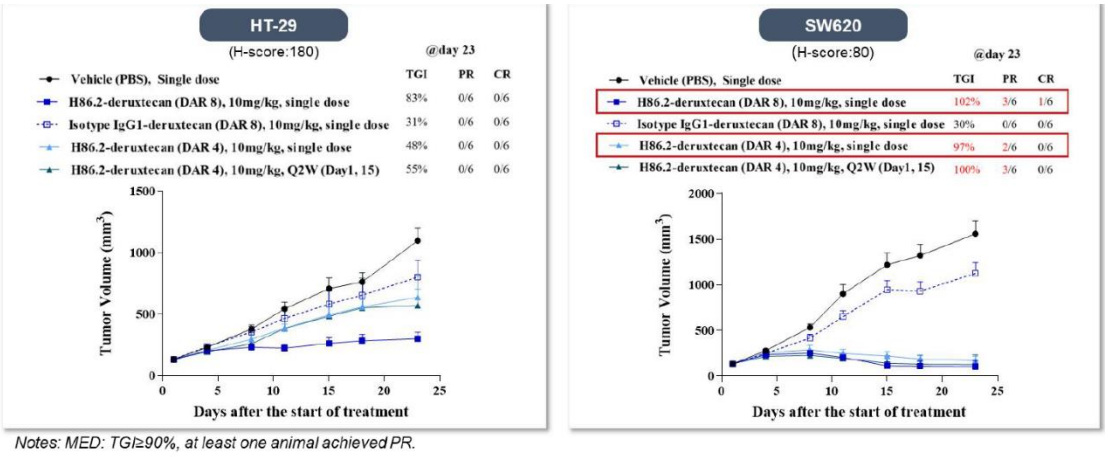


- ITGB4 antibody demonstrated high affinity and internalization rate.
- CS5006 preclinical proof-of-concept models using ITGB4-vedotin and ITGB4-Dxd showed potent antitumor activity in both *in vitro* and *in vivo* studies, along with favorable PK profiles.
  - ITGB4-vedotin exhibited strong antigen-dependent cytotoxicity in ITGB4-positive tumor cell lines *in vitro* and demonstrated potent antigen-dependent tumor inhibition in CDX models *in vivo*.



Notes: MED: TGI≥90%, at least one animal achieved PR.

  - ITGB4-DXd also exhibited potent antigen-dependent cytotoxicity *in vitro* and strong tumor-inhibitory effects *in vivo* CDX tumor models.



Notes: MED: TGI≥90%, at least one animal achieved PR.

- Both ITGB4-vedotin and ITGB4-DXd exhibited favorable PK characteristics.

- The patent of CS5006 has been filed in April 2023.

AACR 2025 Poster Information

Poster Title	**Poster Number**
CS2009: A first-in-class trispecific antibody targeting PD-1, CTLA-4, and VEGFA with potential to be a next-generation backbone therapy with combined checkpoint inhibition and anti-angiogenesis	7299
CS2011: A novel bispecific antibody targeting EGFR and HER3 that demonstrates promising anti-tumor activity in preclinical evaluation	2927
CS5007: A novel EGFR and HER3 dual-targeted antibody-drug conjugate (ADC) with potent antitumor activity in preclinical studies	2954
CS5005: A novel SSTR2-targeted antibody-drug conjugate (ADC) with robust anti-tumor activity in preclinical studies	4751
CS5006: A novel integrin β4-targeted antibody-drug conjugate (ADC) with robust antitumor activity in preclinical studies	2953

About CStone

CStone (HKEX: 2616), established in late 2015, is an innovation-driven biopharmaceutical company focused on the research and development of anti-cancer therapies. Dedicated to addressing patients' unmet medical needs in China and globally, the Company has made significant strides since its inception. To date, the Company has successfully launched 4 innovative drugs and secured approvals for 16 new drug applications (NDAs) covering 9 indications. The Company's pipeline is balanced by 16 promising candidates, featuring potentially first-in-class or best-in-class antibody-drug conjugates (ADCs), multispecific antibodies, immunotherapies and precision medicines. CStone also prides itself on a management team with comprehensive experiences and capabilities that span the entire drug development

spectrum, from preclinical and translational research to clinical development, drug manufacturing, business development, and commercialization.

For more information about CStone, please visit: www.cstonepharma.com.

Cautionary Statement required by Rule 18A.05 of the Listing Rules: THE COMPANY CANNOT GUARANTEE THAT WE MAY BE ABLE TO ULTIMATELY DEVELOP AND MARKET CS2009, CS2011, CS5007, CS5005 and CS5006 SUCCESSFULLY. Shareholders of the Company and potential investors are advised to exercise due care when dealing in the shares of the Company.

Forward Looking Statement

There is no assurance that any forward-looking statements regarding the business development of the Group in this announcement or any of the matters set out herein are attainable, will actually occur or will be realized or are complete or accurate. The financial and other data relating to the Group as disclosed in this announcement has also not been audited or reviewed by its auditors. Shareholders and/or potential investors of the Company are advised to exercise caution when dealing in the securities of the Company and not to place any excessive reliance on the information disclosed herein. Any shareholder or potential investor who is in doubt is advised to seek advice from professional advisors.

By Order of the Board
CStone Pharmaceuticals
Dr. Wei Li
Chairman

Suzhou, the People's Republic of China, May 6, 2025

As at the date of this announcement, the board of directors of the Company comprises Dr. Wei Li as Chairman and non-executive director, Dr. Jianxin Yang as executive director, Mr. Kenneth Walton Hitchner III, Mr. Xianghong Lin and Mr. Edward Hu as non-executive directors, and Dr. Paul Herbert Chew, Mr. Ting Yuk Anthony Wu, Mr. Hongbin Sun and Ms. Yip Betty Ho as independent non-executive directors.