Healthcare

Chinese biopharma releasing promising data at ASCO

OUTPERFORM (Maintain)

China Healthcare Sector

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- **Kelun-Biotech: Promising Ph2 results of SKB264+A167 in 1L NSCLC.** SKB264 (Q3W)+A167 (PD-L1)'s 15.4 months of mPFS in 1L NSCLC was much better than the SoC – 9.0 months mPFS of Keytruda+chemo in KEYNOTE189 and 9.7 months mPFS of tislelizumab+chemo in RATIONALE304. SKB264's Ph3 dose of Q2W could deliver even better efficacy, in our view. SKB264+A167 also showed strong potential in PD-L1 negative NSCLC. Since Trodelvy+Keytruda delivered 13.1 months of mPFS for 1L NSCLC (TPS ≥50%), and Dato-DXd+Keytruda showed an mPFS of 11.1 months in its TROPION-Lung02 trial in 1L NSCLC, both falling short compared to SKB264+A167, we see the BIC potential of SKB264 in NSCLC. SKB264 demonstrated more tolerable safety profiles than its peers, with <1% patients discontinuing SKB264 due to TRAE vs Dato-DXd's 29% and Trodelvy's 17% TEAE-related discontinuation rate. We see the potential of SKB264+ PD-(L)1 to replace the current 1L NSCLC SoC upon the validation in Ph3 trials. We expect Kelun-Biotech and MSD to initiate additional Ph3 trials of SKB264+A167/Keytruda in 1L NSCLC without AGAs (both in PD-L1 TPS>1 and <1), which will provide significant upside for SKB264's global commercial value.
- **Innovent: Promising early signals of IBI389 (CLDN18.2/CD3) and IBI363 (PD-1/IL-2).** The 30.8% ORR of IBI389 (CLDN18.2/CD3) observed in 26 CLDN18.2-positive (expression ≥10% tumours) 3L+ GC patients represents promising early signals, in our view, which are comparable to Keymed/AZ's CLDN18.2 ADC CMG901's 32.6% ORR in 89 CLDN18.2-positive (expression ≥5% tumors) GC pts with median 2 prior lines of treatments. IBI389 has the FIC potential as a CLDN18.2/CD3 bsAb, in our view. IBI363 (PD-1/IL-2) demonstrated much better early efficacy signals than other treatment options in late-line CRC, with an ORR of 12.7% and better tolerance. Recall that in the China FRESCO trial of fruquintinib vs placebo for 3L+ CRC, the ORR was 4.7% vs 0% (1.5% vs 0% in the FRESCO-2 trial), much lower than the 12.7% ORR in IBI363's trial.
- **Hansoh: Leading position in global B7-H3 ADC development with positive signals released.** For heavily pre-treated SCLC patients, HS-20093 (B7-H3 ADC) demonstrated 58.1%/57.1% ORR and 5.6/NA months of mPFS in the 8/10mg/kg dose cohorts, comparable to I-DXd's 52.4% ORR and 5.6 months of mPFS, while free from ILD seen with I-DXd. Following I-DXd, HS-20093 ranks second globally in the B7-H3 ADC development, currently assessed in Ph2 studies, with Ph3 studies in plan. HS-20093 is also in Ph2 studies for broad indications including HNSCC, mCRPC, osteosarcoma, etc, with positive data in heavily-treated R/R osteosarcoma released at ASCO as well. We look forward to further initiation of a Ph3 study of HS-20093 in relapsed SCLC in China, and the initiation of the global trials by GSK.
- **Akeso: Eyes on the readout of AK112's H2H trial in 1L PD-L1+ NSCLC.** AK112+chemo's 0.46 HR in PFS represented a competitive profile for EGFR-TKI resistant NSCLC patients, compared to amivantamab +chemo or sintilimab +bevacizumab +chemo. We are waiting for the results of Summit's global HARMONi-A trial which has co-primary endpoints of OS and PFS. The H2H Ph3 China study of AK112 mono vs Keytruda in 1L PD-L1+ NSCLC met the PFS superiority endpoint, while we look forward to the detailed data release at WCLC in Sep, which will give us better visibility of AK112's global potential in 1L NSCLC.

Valuation Table

			Mkt Cap	TP	Upside/	P/E (x)		P/B (x)		ROE (%)	
Name	Ticker	Rating	(US$mn)	(LC)	Downside	FY25E	FY26E	FY25E	FY26E	FY25E	FY26E
Kelun-Biotech	6990 HK	BUY	5,217.3	246.1	32%	nm	nm	42.8	238.9	(0.6)	(1.4)
Innovent	1801 HK	BUY	7,427.0	55.0	54%	nm	40.5	4.3	3.7	(0.0)	0.1
Hutchmed	13 HK	BUY	3,274.1	34.3	17%	nm	26.7	5.0	4.2	0.0	0.2
Akeso	9926 HK	BUY	4,458.2	59.6	44%	140.2	17.2	7.1	5.0	0.0	0.3
Henlius Biotech	2696 HK	BUY	1,311.0	20.3	8%	15.3	9.9	2.8	2.3	0.2	0.3
RemeGen	9995 HK	BUY	1,773.7	41.7	64%	nm	nm	11.2	12.3	(0.7)	(0.4)

Source: Company data, CMBIGM estimates

Contents

Kelun-Biotech (6990 HK, BUY, TP HK$246.13)

Sacituzumab tirumotecan (SKB264/MK-2870, TROP2 ADC)

SKB264+A167 in 1L NSCLC (Oral abstract)

Data summary:

The initial Ph2 (OptiTROP-Lung01, NCT05351788) results of SKB264+A167 (PD-L1) in 1L NSCLC without actionable genomic alterations (AGAs) were released (link). As of Jan 2024, 40 and 63 pts had been enrolled in cohort 1A (Q3W, SKB264 5mg/kg + A167 1200mg) and cohort 1B (Q2W, SKB264 5mg/kg + A167 900mg). In the two cohorts, 30.0%/33.3%, 32.5%/30.2% and 37.5%/36.5% of pts had PD-L1 expression < 1%, 1%–49% and ≥ 50%, respectively.

In cohort 1A (median follow up of 14.0 months), the ORR was 48.6% (18/37), and mPFS was 15.4 mos (95% CI: 6.7, NE) with 6-mo PFS rate of 69.2%.

In cohort 1B (median follow up of 6.9 months), the ORR was 77.6% (45/58), and mPFS was not reached with 6-mo PFS rate of 84.6%. Additional subgroup analyses of cohort 1B are shown in the table below.

Figure 1: Ph2 outcomes of SKB264+A167 in 1L NSCLC without AGAs

	Cohort 1A Sac-TMT (5 mg/kg Q3W) + KL-A167 (1200 mg Q3W) N = 40	Cohort 1B Sac-TMT (5 mg/kg Q2W) + KL-A167 (900 mg Q2W) N = 63
Median follow-up, mo	14.0	6.9
ORR,[a] n/N (%) [95% CI]	18/37 (48.6) [31.9, 65.6]	45/58 (77.6) [64.7, 87.5]
PR, n (%)	18 (48.6)	45 (77.6)
Confirmed PR, n (%)	16 (43.2)	40 (69.0)
SD, n (%)	17 (45.9)	13 (22.4)
PD, n (%)	2 (5.4)	0
DCR,[b] n/N (%)	35/37 (94.6)	58/58 (100.0)
Median DOR (95% CI), mo	NR (8.3, NE)	NR (6.6, NE)
Median PFS (95% CI), mo	15.4 (6.7, NE)	NR (8.4, NE)
6-mo PFS rate (95% CI), %	69.2 (51.2, 81.6)	84.6 (71.4, 92.1)

Data cutoff date: Jan 02, 2024
[a] Including confirmed PR/CR or response pending confirmation. ORR was calculated based on response evaluable population defined as ≥1 on-study scan.
[b] DCR was defined as BOR of CR + PR + SD ≥6 weeks.

Source: Company data, CMBIGM

Figure 2: Clinical outcomes of cohort 1B

	PD-L1 Expression[a]			Histology	
	TPS <1% N = 21	TPS 1%–49% N = 19	TPS ≥50% N = 23	Non-squamous N = 34	Squamous N = 29
ORR,[b] n/N (%)	12/19 (63.2)	13/16 (81.3)	20/23 (87.0)	24/33 (72.7)	21/25 (84.0)
Confirmed PR, n (%)	11 (57.9)	11 (68.8)	18 (78.3)	21 (63.6)	19 (76.0)
DCR,[c] n/N (%)	19/19 (100.0)	16/16 (100.0)	23/23 (100.0)	33/33 (100.0)	25/25 (100.0)
6-mo PFS rate (95% CI), %	82.2 (54.3, 93.9)	76.6 (41.2, 92.3)	91.3 (69.5, 97.8)	93.8 (77.3, 98.4)	73.5 (49.9, 87.2)

Data cutoff date: Jan 02, 2024.
[a] PD-L1 expression was assessed at a central lab with PD-L1 IHC 22C3 pharmDx.
[b] Including confirmed PR/CR or response pending confirmation. ORR was calculated based on response evaluable population defined as ≥1 on-study scan.
[c] DCR was defined as BOR of CR + PR + SD ≥6 weeks.

Source: Company data, CMBIGM

In cohorts 1A/1B, the most common Grade≥3 TRAEs were neutrophil count decreased (30.0%/30.2%), white blood cell count decreased (5.0%/17.5%), anemia (5.0%/15.9%), rash (5.0%/6.3%) and drug eruption (7.5%/0). TRAE leading to discontinuation of SKB264 occurred in 1 patient of cohort 1B due to drug hypersensitivity, and there were no treatment-related deaths.

Figure 3: Overall safety summary

	Cohort 1A Sac-TMT (5 mg/kg Q3W) + KL-A167 (1200 mg Q3W) N = 40 n (%)	Cohort 1B Sac-TMT (5 mg/kg Q2W) + KL-A167 (900 mg Q2W) N = 63 n (%)
TRAEs[a]	38 (95.0)	61 (96.8)
Grade ≥3 TRAEs	17 (42.5)	34 (54.0)
TRAEs leading to sac-TMT dose reduction	7 (17.5)	20 (31.7)
TRAEs leading to treatment interruption	10 (25.0)	32 (50.8)
TRAEs leading to discontinuation of any drug	1 (2.5)	2 (3.2)
TRAEs leading to sac-TMT discontinuation[b]	0	1 (1.6)
Treatment-related SAEs	4 (10.0)	14 (22.2)
TRAEs leading to death	0	0

Data cutoff date: Jan 02, 2024. Median treatment duration in cohorts 1A and 1B was 8.8 months and 7.0 months, respectively.
[a] TRAEs were determined as related to either sac-TMT or KL-A167.
[b] Discontinuation of sac-TMT occurred in only 1 patient in cohort 1B due to drug hypersensitivity.

Source: Company data, CMBIGM

CMBI comments:

Promising efficacy of SKB264+A167 in all subgroups of 1L NSCLC. In cohort 1A (Q3W), the 15.4 months of mPFS was very promising compared with the current SoC of PD-1+chemo for 1L NSCLC. The mPFS of cohort 1B (Q2W) was immature at the follow up, while this higher-dose cohort represented even better results with higher 6-mo PFS rate (84.6% in 1B vs 69.2% in 1A) and higher ORR (77.6% in 1B vs 48.6% in 1A). For 1L nsq-NSCLC, Keytruda+chemo delivered 9.0 months of mPFS in the global trial KEYNOTE-189, and tislelizumab+chemo delivered 9.7 months of mPFS in the China trial RATIONALE304. The 15.4 months of mPFS of SKB264+A167 and the 48.6% ORR in cohort 1A were much better than the SoC. In cohort 1B, the 72.7% ORR of the SKB264+A167 in nsq-NSCLC patients was much better than the 48.3% ORR of Keytruda+chemo and the 57.4% ORR of tislelizumab+chemo, and the 93.8% 6-mo PFS rate could indicate a much longer mPFS. Especially, for patients with PD-L1 TPS<1% in cohort 1B, the ORR was 63.2% and the 6-mo PFS rate was 82.2%, indicating the strong potential of SKB264+A167 in PD-L1 negative NSCLC patients.

Further confirmed SKB264's BIC potential. In Trodelvy's Ph2 EVOKE-02 trial, Trodelvy in combo with Keytruda had an ORR of 67% and mPFS of 13.1 months in PD-L1 TPS ≥50% 1L NSCLC patients (n=30) (link), and 44% ORR in patients with PD-L1 TPS <50% (n=32) (link). SKB264+A167 delivered 87.0% ORR in TPS ≥50% patients, 81.3% ORR in TPS 1-49% patients, and 63.2 ORR in TPS<1% patients, which were much better that Trodelvy's results. Trodelvy+Keytruda's mPFS of 13.1 months in TPS≥50% NSCLC patients could fall short compared to SKB264+A167 which delivered 15.4 months mPFS in cohort 1A regardless of PD-L1 expression, and may expect even longer mPFS in the cohort 1B. In the Ph2 TROPION-Lung02 trial (link), Dato-DXd+Keytruda demonstrated the mPFS of 11.1 months and ORR of 52% in 1L NSCLC, also falling short compared to SKB264+A167. We are confident of SKB264's BIC potential in the global TROP2 ADC space. Additionally, for 2/3L NSCLC, after Trodelvy missed the OS endpoint in the EVOKE-01 trial (link), Dato-DXd also missed the OS endpoint at the final analysis in the TROPION-Lung01 study (link).That said, we think SKB264 will enjoy a better positioning in the global TROP2 ADC market.

Tolerable safety profile. SKB264 has demonstrated a more tolerable safety profile than its peers. In the SKB264+A167 trial, grade≥3 TRAEs were observed in 54% patients in the cohort 1B. In comparison, tislelizumab+chemo had 63% grade ≥3 TRAEs in the RATIONALE304 trial. In the SKB264+A167 trial, TRAE leading to discontinuation of SKB264 occurred in just 1 patient (<1%) of cohort 1B, and there were no treatment-related deaths. In comparison, TEAEs associated with Dato-DXd discontinuation occurred in 29% of patients (link), much higher than that of SKB264. Additionally, in Dato-DXd's TROPION-Lung02 trial, drug-related ILD was observed in 10% of the patients (2.5% grade 3, link), which again indicated the safety concern of Dato-DXd. Notably, in a pooled analysis of Dato-DXd, with 484 NSCLC patients, 6.8% pts had ILD, among which 2.5% were grade 3-5 and 1.7% were grade 5 (link). In Trodelvy's 1L NSCLC (TPS ≥50%) EVOKE-02 trial, TEAEs leading to discontinuation occurred in 17% patients and 3% treatment-related deaths due to neutropenic sepsis were observed (link).

Regarding neutropenia, SKB264+A167 had 30.2% grade≥3 TRAEs from neutropenia in cohort 1B and 30.0% in cohort 1A. In Trodelvy's Ph3 ASCENT trial in 3L+ TNBC and the Ph3 TROPiCS-02 trial in 3L+ HR+/HER2- BC, the incidence of grade≥3 AEs of neutropenia was 51% (TRAEs) and 53% (TEAEs), leading to an FDA boxing warning of life-threatening neutropenia. In the Ph2 EVOKE-02 trial in 1L NSCLC, Trodelvy+Keytruda recorded 32% of any rate of neutropenia TEAEs (link). We notice that MSD adopted a lower dose in its global Ph3 studies, i.e. 4mg/kg Q2W, which will bring more manageable safety profile, in our view.

Expect wide indication coverage in NSCLC. SKB264+A167 has demonstrated very promising Ph2 efficacy data in 1L NSCLC patients without AGAs, with a consistently tolerable safety profile. We see the potential of SKB264 + PD-(L)1 to replace the current SoC in 1L NSCLC upon the validation in Ph3 trials. Kelun Biotech plans to initiate Ph3 trials in China of SKB264+A167/Keytruda in 1L NSCLC patients without AGAs, both in PD-L1 TPS>1 and <1 groups. We think MSD is also likely to initiate additional global Ph3 trials in the similar settings. Additionally, MSD has already started/registered 5 global Ph3 trials in NSCLC, including 3L EGFR-m NSCLC, 2L EGFR-m NSCLC, 1L sq-NSCLC maintenance after Keytruda+chemo induction, 1L TPS≥50% NSCLC, and adjuvant NSCLC. The potential initiation of Ph3 trials in 1L nsq-NSCLC patients without AGAs will provide significant upside for SKB264's global commercial value, in our view.

Figure 4: SKB264's Ph3 trials conducted by MSD (as of Jun 2024)

Indication	Indication details	Trial ID	Regimen	SKB264 dose	Primary endpoint	Start date	Primary completion date (est)
3L+ EGFR-m NSCLC	Previously treated nsq-NSCLC with EGFR mutations or other genomic alterations (ALK, ROS1, BRAF, NTRK, MET, RET, etc) (pre-treated with TKI, and chemo)	NCT06074588	Mono vs chemo (docetaxel or pemetrexed)	Q2W	PFS，OS	Nov 2023	May 2027
2L EGFR-m NSCLC	post EGFR-TKI nsq-NSCLC (pre-treated with TKI)	NCT06305754	Mono vs chemo (pemetrexed + carboplatin)	Q2W	PFS，OS	Jun 2024 (est)	Sep 2028
1L sq-NSCLC	Maintenance treatment for 1L sq-NSCLC (pts have 4 cycles of prior Keytruda+chemo treatment)	NCT06422143	SKB264+Keytruda vs Keytruda	Q2W	OS	Jul 2024 (est)	Jan 2029
1L NSCLC TPS⩾50%	1L PD-L1 TPS ⩾50% NSCLC	NCT06170788	+ Keytruda vs Keytruda mono	Q2W	OS	Dec 2023	Jan 2028
Adjuvant NSCLC	Adjuvant NSCLC (Stage II, IIIA, IIIB resectable NSCLC not achieving pCR)	NCT06312137	SKB264+Keytruda vs Keytruda	Q2W	DFS	Apr 2024 (est)	Feb 2034
Endometrial carcinoma	Endometrial carcinoma (post chemo and PD(L)-1)	NCT06132958	Mono vs chemo	Q2W	PFS，OS	Dec 2023	Jan 2028
HR+/HER2- BC	HR+/HER2- BC (post endocrine therapies with one in combo with a CDK4/6 inhibitor)	NCT06312176	SKB264 mono vs SKB264+Keytruda vs chemo	Q2W	PFS	Mar 2024 (est)	Jul 2027
TNBC	TNBC (who received neoadjuvant therapy and did not achieve pCR at surgery)	NCT06393374	SKB264+Keytruda vs Keytruda mono or Keytruda + capecitabine	Q2W	iDFS (invasive disease-free survival)	May 2024 (est)	Dec 2030
3L+ GC	3L+ GC	NCT06356311	Mono vs chemo	Q2W	OS	May 2024 (est)	Jan 2027

Source: Company data, CMBIGM.

SKB264 mono in 3L+ TNBC (Clinical Science Symposium)

Data summary:

The results of a Ph3 trial of SKB264 in 3L+ advanced TNBC was released at ASCO meeting (link, OptiTROP-Breast01). Pts were randomised to receive SKB264 mono (n = 130) or chemo (n = 133). 87% had visceral metastases; 26% received prior PD-(L)1; 48% received 3+ prior lines of chemo.

As of Jun 2023, the primary endpoint of PFS was met, with mPFS of 5.7 vs 2.3 months (HR=0.31, P<0.00001). PFS at 6 months was 43.4% vs 11.1%. In the subset of pts with TROP2 expression H-score > 200, the mPFS was 5.8 vs 1.9 months (HR 0.28; 95% CI 0.17 to 0.48). As of Nov 2023, OS was statistically significant in favor of SKB264 (mOS NE vs 9.4 months, HR 0.53, P =0.0005). The ORR was 43.8% vs 12.8%.

Most common grade≥3 TRAEs were neutrophil count decreased (32.3% vs 47.0%), anemia (27.7% vs 6.1%) and white blood cell count decreased (25.4% vs 36.4%).

CMBI comments:

Solid Ph3 results to support the approval in China. In the Ph3 trial, SKB264 demonstrated 43.8% ORR and 5.7 months of mPFS in heavily pre-treated TNBC, consistent with the Ph1/2 results. The results were better than the 35% ORR and 5.6 months mPFS of Trodelvy in Ph3 study, and much better than the 32% ORR and 4.4 months mPFS of Dato-DXd in a Ph1 study. Additionally, SKB264 had lower rate of grade ≥3 TRAEs from neutropenia (32% vs 51%) compared to Trodelvy, with the latter having an FDA boxed warning. Meanwhile, SKB264 has higher rates of leukopenia, anemia and platelet count decrease compared to Trodelvy and Dato-DXd. The Ph3 results of SKB264 in 3L+ TNBC should support its current BLA in China (BLA filed in Dec 2023 with priority review). Kelun-Biotech has started a Ph3 trial of SKB264 in 1L TNBC in China (NCT06279364) in Feb 2024, and MSD has registered a global trial of SKB264 +

Keytruda in TNBC who received neoadjuvant therapy and did not achieve pCR at surgery (NCT06393374).

Figure 5: Cross-trial comparison of ADC drugs for late-line TNBC

Drug	SKB264		Trodelvy	Dato-DXd
Company	Kelun-Biotech		Gilead	Daiichi Sankyo / AstraZeneca
Trial ID	NCT05347134	NCT04152499	ASCENT	TROPION-PanTumor01
Trial stage	Ph3	Ph1/2	Ph3	Ph1
Regimen	SKB264 vs chemo	SKB264, single arm	Trodelvy vs chemo	Dato-DXd, single arm
Primary endpoint	PFS		PFS	Safety
n (efficacy evaluable)	130 vs 133	59	468 (235 vs 233) pts without brain metastases	44
Baseline	87% had visceral metastases; 26% received prior PD-(L)1; 48% received 3+ prior lines of chemo	88% pts had >=3 prior treatment	All >= 2 prior treatment	Median of 3 prior treatment (range 1-10)
Median follow-up		22.8 months	17.7 months	16.6 months
PFS (month)	5.7 vs 2.3 HR=0.31, P<0.00001	5.7	5.6 vs 1.7 HR=0.41, P<0.001	4.4
OS (month)		16.8	12.1 vs 6.7 HR=0.48, P<0.001	13.5
ORR	43.8% vs 12.8%	42.4%	35% vs 5%	32%
CR		--	--	2%
mDoR (month)		11.5	6.3 vs 3.6	16.8
Key Grade>=3 TRAEs				
diarrhea		*0*	*11% vs 1%*	*0*
stomatitis		--	--	*11%*
decreased neutrophil count (neutropenia)	*32.3% vs 47.0%*	*25.4%*	*51% vs 33%*	*2.3%*
platelet count decreased		*16.9%*	*1.2% vs 2.7%*	--
leukopenia (decreased in total white blood cell)	*25.4% vs 36.4%*	*23.7%*	*10% vs 5%*	*0*
anemia	*27.7% vs 6.1%*	*22%*	*8% vs 5%*	*2%*
ILD		0%	1 case with grade 3 ILD in Trodelvy arm	0% (2% discontinued due to pneumonitis, not ILD)
AE leading to dose reduction		15.2%	--	18%
AE leading to discontinuation		6.8%	5% vs 5%	2% (due to pneumonitis)
Approval status	BLA accepted in Dec 2023 in China		Approved in China (3L+ TNBC) and the US (3L+ TNBC)	Not approved yet
Source	Link	Link	Link1 Link2	Link1, Link2, Link3

Source: Company data, CMBIGM.

Innovent (1801 HK, BUY, TP HK$55.00)

IBI389 (CLDN18.2/CD3)

IBI389 in GC (Rapid Oral Abstract)

Data summary:

IBI389 is an anti-CLDN18.2/CD3 bispecific antibody that induces immune synapse formations by linking CD3 molecules in T-cell receptor complexes and CLDN18.2 antigens on the membrane of tumor cells. Preliminary Ph1 results of IBI389 in patients with advanced solid tumors (GC and PDAC) were reported (link). Eligible pts with advanced solid tumors who failed or were intolerant to standard treatments were enrolled. Selected dose levels were expanded in pts with advanced GC and PDAC.

As of Jan 2024, a total of 114 pts were enrolled (G/GEJ C: 32.5%, PDAC: 57.9%, stage IV: 81.6%).

In all pts, grade≥3 TEAEs occurred in 66.7% pts, and grade ≥3 TRAEs occurred in 55.3% pts. The most common grade ≥3 TRAEs were gamma-glutamyl transferase increased (21.9%), lymphocyte count decreased (13.2%) and nausea (4.4%). Cytokine release syndrome (CRS) related adverse events occurred in 65 (57.0%) pts including 1 (0.9%) pts with grade 3 CRS and no grade 4 or 5 CRS. TEAEs leading to dose interruption and treatment discontinuation occurred in 44 (38.6%) and 8 (7.0%) pts.

Preliminary efficacy of IBI389 was observed in pts with CLDN18.2 expression ≥10% (immunohistochemistry 2+/3+). In 26 GC pts with previous treatments ≥2 lines receiving IBI389 at various dose levels (n=26), 8 pts had PR – ORR of 30.8%.

CMBI comments:

Promising early signals of IBI389 for CLDN18.2-positive GC patients. The 30.8% ORR of IBI389 (CLDN18.2/CD3) observed in 26 CLDN18.2-positive (expression ≥10% tumors) patients who had at least 2 prior treatments represents promising early signals, in our view. The results are comparable to Keymed/AZ's CLDN18.2 ADC CMG901's 32.6% ORR in 89 CLDN18.2-positive (expression ≥5% tumors) GC pts with median 2 prior lines of treatments (link). CLDN18.2 represents a promising immunology therapeutic target, and Innovent's IBI389 has the potential to be a FIC CLDN18.2/CD3 bsAb.

IBI389 in PDAC (Clinical Science Symposium)

Data summary:

In PDAC, positive CLDN18.2 expression was reported in nearly 60% patients, indicating its potential as a novel target for anti-tumor therapy. The preliminary Ph1 results of IBI389 in pts with CLDN18.2-positive PDAC who failed standard treatments were reported (link).

As of Jan 2024, a total of 64 CLDN18.2-positive PDAC pts were enrolled (stage IV: 84.4%). All patients received prior therapy with a median of 2 lines (range: 1 to 5).

Grade ≥3 TRAEs occurred in 54.7% pts. The most common grade ≥3 TRAEs were gamma-glutamyl transferase increased (20.3%), lymphocyte count decreased (9.4%) and nausea (7.8%). Cytokine release syndrome (CRS) related adverse events occurred in 51.6% pts with no grade ≥3 CRS occurred. TEAEs leading to dose interruption and treatment discontinuation occurred in 24 (37.5%) and 3 (4.7%) pts.

Preliminary efficacy of IBI389 was observed in pts with CLDN18.2 expression ≥10% (immunohistochemistry 2+/3+) at 600 μg/kg. As of Jan 2024, in the 23 evaluable pts, the ORR was 30.4%. DoR and PFS were not reached.

IBI389 showed manageable safety profiles in pts with advanced PDAC. Preliminary efficacy was observed, including in pts with relatively low expression of CLDN18.2.

IBI363 (PD-1/IL-2)

IBI363 in CRC (Poster)

Ph1 results of IBI363 in pts with advanced CRC were released (link). Pts with locally advanced or metastatic CRC who failed or intolerant to standard treatment were enrolled and received IBI363 intravenously at dose levels ranging from 100 ug/kg to 3 mg/kg QW, Q2W or Q3W.

As of Dec 2023, a total of 68 pts (61.8% with liver metastasis; 76.5% had ≥3 previous treatment; 27.9% previous immunotherapy) received IBI363 treatment, including 24 pts at 600 ug/kg Q2W and 20 pts at 1 mg/kg Q2W. 83.8% of the pts were microsatellite stable (MSS)/proficient mismatch repair (pMMR) and 16.2% had unknown microsatellite status. Median follow-up time was 5.3 months.

Grade ≥3 TEAEs was in 32.4% pts. Common TEAEs were arthralgia (35.3%), anemia (32.4%), pyrexia (22.1%) and hypoalbuminemia (20.6%). Grade ≥3 TRAEs were in 23.5% pts. Immune related AEs (irAEs) were reported in 32.4% pts including grade ≥3 irAEs in 5.9% pts. Serious TRAE were reported in 17.6% pts. TRAEs leading to treatment interruption and discontinuation were reported in 36.8% and 2.9% pts. No TRAE leading to death was reported.

In all evaluable pts (n=63), overall ORR was 12.7%. In pts with liver metastasis (n=38), ORR was 13.2%. In pts with PD-L1 CPS ≥1 (n=13), ORR was 30.8%, and DCR was 76.9%. The median DoR was not reached. A prospective cohort of CRC pts with PD-L1 CPS ≥1 has been initiated.

CMBI comments:

Promising efficacy and safety profiles of IBI363 in late-line CRC. IBI363 demonstrated much better early efficacy signals than other treatment options in CRC, with better tolerance. In the China FRESCO trial of fruquintinib vs placebo for 3L+ CRC, the ORR was 4.7% vs 0% (1.5% vs 0% in the FRESCO-2 trial), much lower than the 12.7% ORR in Innovent's IBI363 trial. Notably, the enrolled patients in IBI363 seemed to be more heavily pre-treated with 76.5% having ≥3 previous treatment, vs 68.3% patients having 2 or 3 lines of prior treatment in the FRESCO trial. Grade ≥3 TRAEs of IBI363 were observed in 23.5% patients, which was more tolerable compared to the 46.0% in fruquintinib's FRESCO trial and 36.0% in the FRESCO-2 trial. TRAEs leading to discontinuation were 2.9% with IBI363, compared to 25.1% (TEAEs) with fruquintinib in FRESCO trial and 20.4% (TEAEs) in FRESCO-2 trial. Serious TRAEs were reported in 6.1% of patients in the fruquintinib group vs 1.5% in the placebo group in the FRESCO trial, while IBI363 reported higher 17.6% serious TRAE rate. Additionally, in patients with PD-L1 CPS ≥1 (n=13), IBI363 demonstrated a promising ORR of 30.8%.

IBI363 in melanoma (Poster)

Data summary:

Despite great success of IO in advanced melanoma, there remains unmet clinical needs for IO resistant and cold tumors. IBI363 is a first-in-class PD-1/IL-2α-bias bispecific antibody fusion protein which could block PD-1 checkpoint and activate α-bias IL-2 to rejuvenate exhausted tumor-specific T cells. Ph1 results of IBI363 in pts with advanced melanoma were released (link). Pts with advanced melanoma who failed or intolerant to standard therapy were enrolled to receive IBI363 intravenously at different dose levels ranging from 100-2000 μg/kg QW/Q2W/Q3W.

As of Jan 2024, 67 pts were enrolled (59.7% had ≥2 prior treatment lines, 89.6% had prior IO). There were 17 pts with cutaneous melanoma, 22 pts with acral melanoma, 25 pts with mucosal melanoma and 3 pts with unknown primary melanoma.

TEAEs occurred in 63 (94.0%) pts. Grade ≥3 TEAEs and TRAEs occurred in 23.9% and 17.9% pts. Common TEAEs were arthralgia (34.3%), hyperthyroidism (29.9%), anemia (25.4%). TEAE leading to treatment discontinuation occurred in 1.5% pt. No pts had TEAEs leading to death.

In all evaluable pts (n=57), the ORR was 28.1% and DCR was 71.9%.

In pts had prior IO (n=52), ORR was 21.2% and DCR was 67.3%.

In 1 mg/kg Q2W pts had prior IO (n=25), ORR was 32.0% and DCR was 80.0%.

The DoR and PFS data were immature at the time of analysis.

In pts with advanced melanoma, IBI363 showed encouraging efficacy in different tumor subtypes and in pts with prior IO. The safety profiles were acceptable and manageable. Further clinical development of IBI363 in melanoma are ongoing both in China and overseas.

IBI363 in other solid tumors (Publication only)

Data summary:

IBI363 was well tolerated and showed encouraging efficacy in patients with advanced melanoma, NSCLC and CRC. The Ph1 results of IBI363 in patients with other solid tumors were released (link). Pts with advanced biliary tract cancer (BTC), head and neck squamous cell carcinoma (HNSCC), cervical cancer (CC) and ovarian cancer (OC) who failed or were intolerant to standard therapy were enrolled.

As of Jan 2024, 24 pts were enrolled including 13 pts with BTC, 3 pts with HNSCC, 4 pts with CC and 4 pts with OC. In the 18 efficacy evaluable patients, ORR was 22.2% and DCR was 77.8%.

In 11 evaluable pts with BTC, best overall response (BOR) was confirmed partial response (cPR) in 1 pt (600 μg/kg Q2W, IO-failed). ORR was 9.1% and DCR was 90.9%.

In 2 evaluable pts with HNSCC, 1 pt had cPR (600 μg/kg Q2W, IO-naïve, PD-L1 expression negative).

In 3 evaluable pts with CC, 1 pt had cPR (1000 μg/kg Q2W, IO-failed).

In 2 evaluable pts with OC, 1 pt had cPR (1000 μg/kg Q2W, platinum-resistant).

All cPR pts had previous 1-2 lines of treatments.

IBI363 showed promising and durable efficacy in pts with various solid tumors including refractory tumors such as BTC and IO or platinum-resistant tumors such as CC and OC.

IBI343 (CLDN18.2 ADC)

IBI343 in PDAC and BTC (Poster)

Data summary:

Prognosis for advanced pancreatic ductal adenocarcinoma (PDAC) and biliary tract cancer (BTC) remains poor, with limited treatment options available. Preliminary Ph1 NCT05458219 results of IBI343, a CLDN18.2 ADC in patients with advanced PDAC or BTC were released (link). Eligible pts who failed or were intolerant to standard treatment were enrolled. IBI343 were intravenously administered at 6 mg/kg or 8 mg/kg Q3W. In dose escalation, pts were enrolled regardless of CLDN18.2 expression. In dose expansion, pts were required to have CLDN18.2 expression ≥40%.

As of Dec 2023, 35 pts (1 pt in dose escalation and 34 pts in dose expansion) were enrolled from China and Australia (stage IV 91.4%, median 2 lines of prior treatment) including 28 PDAC pts and 7 BTC pts. Pts received IBI343 at 6 mg/kg (n=17) or 8 mg/kg (n=18).

In all pts, grade≥3 TRAEs occurred in 25.7% pts. Common TRAEs were anemia (42.9%), neutrophil count decreased (28.6%), nausea (25.7%), vomiting (25.7%) and white blood cell count decreased (22.9%). Serious TRAEs occurred in 11.4% pts. TRAEs leading to dose interruption and treatment discontinuation occurred in 20.0% pts and 2.9% pts respectively. No TRAE led to death.

As of Jan 2024, among 25 efficacy evaluable pts, PR was observed in 7 pts (5 PDAC and 2 BTC). The ORR was 28.0%. In evaluable pts at 6 mg/kg with CLDN18.2 expression ≥60% (1+/2+/3+, n=13), 5 pts had PR with ORR of 38.5%. Among 10 PDAC pts in this subgroup, ORR was 40%.

IBI343 was well tolerated with favorable safety profiles and encouraging efficacy in CLDN18.2-positive PDAC and BTC.

Hansoh (3692 HK, NR)

HS-20093 (B7-H3 ADC)

HS-20093 in pre-treated SCLC (Poster)

Data summary:

Results of the expansion doses of HS-20093 (B7-H3 ADC) in patients with SCLC from Ph1a/b ARTEMIS-001 study were released (link). The ARTEMIS-001 study consisted of dose escalation (1a) and expansion (1b) part. As of Nov 2023, 56 ES-SCLC pts pre-treated with platinum-based standard therapy were enrolled at the expansion dose of 8.0 mg/kg (n=31) or 10.0 mg/kg (n=25). Median prior lines of therapy was 2.0 (range: 1-6). All pts received platinum plus etoposide and 73.2% (41/56) received immunotherapy.

The most common grade≥3 TRAEs were neutropenia, leukopenia, lymphopenia, thrombocytopenia and anemia. 52 pts were efficacy evaluable (8.0 mg/kg: 31 pts; 10.0 mg/kg: 21 pts), and HS-20093 showed encouraging efficacy in relapsed ES-SCLC, with ORR of 58.1%/57.1%, mPFS of 5.6/NA months in the 8mg/10mg dose cohorts.

Figure 6: Ph1a/b results of HS-20093 in relapsed SCLC

	8.0 mg/kg Q3W (n=31)	10.0 mg/kg Q3W (n=21)
ORR, n (%), (95% CI)	18 (58.1%)* (39.1, 75.5)	12 (57.1%)# (34.0, 78.2)
DCR, n (%), (95% CI)	25 (80.6%) (62.5, 92.5)	20 (95.2%) (76.2, 99.9)
Median DOR, month, (95% CI)	4.3 (3.3, NA)	NA (3.1, NA)
Median PFS, month, (95% CI)	5.6 (3.4, NA)	NA (4.4, NA)
Median follow-up time, month, (95% CI)	4.8 (3.6, 5.6)	4.9 (4.1, 5.6)

*Fifteen pts were confirmed PRs, 3 pts are awaiting confirmation.

#Ten pts were confirmed PRs, 2 pts are awaiting confirmation. ORR: objective response rate, DCR: disease control rate, DOR: duration of response; PFS: progression free survival, CI: confidence interval, PR: partial response.

Source: Company data, CMBIGM

HS-20093 demonstrated promising antitumor activity and manageable safety in pts with previously-treated SCLC. Ph3 study is planned to compare the efficacy and safety of HS-20093 with standard-of-care chemotherapy in relapsed SCLC.

CMBI comments:

Promising early data in SCLC. In cross-trial comparison of the early trial results, for heavily pretreated SCLC patients, HS-20093's 58.1%/57.1% ORR and 5.6/NA months of mPFS were comparable to I-DXd's 52.4% ORR and 5.6 months of mPFS. Additionally, similar to Daiichi's other ADC drugs, I-DXd's adverse effect of ILD could be a concern.

Leading position in the global B7-H3 ADC development. I-DXd, developed by Daiichi Sankyo/MSD, is globally the first B7-H3 ADC drug that has entered Ph3 stage. I-DXd mono is currently evaluated in a Ph3 Ideate-2 study vs chemo for the treatment of 2L SCLC, and in several Ph2 studies for other solid tumors. Hansoh's HS-20093 ranks second globally in clinical development, which is currently assessed in Ph2 studies, with Ph3 studies in plan. Approximately 65% of all SCLC tumors have a moderate-to-high expression of B7-H3, which is associated with disease progression and short survival. With limited effective

treatment options beyond traditional chemotherapy and immunotherapy, later-line SCLC can be difficult to treat. HS-20093 represents a promising treatment option for this underserved patient population, in our view.

Potential broad indication coverage of HS-20093. Besides SCLC, HS-20093 is also in Ph2 studies for HNSCC, mCRPC, osteosarcoma, etc. The Ph2 results of HS-20093 in heavily-treated R/R osteosarcoma were released at 2024 ASCO meeting as well (link). HS-20093 exhibited promising antitumor activities with acceptable toxicity for heavily pretreated R/R osteosarcoma. We look forward to the further initiation of a Ph3 study of HS-20093 in relapsed SCLC in China, and the initiation of the global trials by GSK.

Figure 7: Comparison of B7-H3 ADCs in SCLC

	HS-20093	I-DXd
Company	Hansoh/ GSK	Daiichi Sankyo/ MSD
mAb	B7-H3 mAb	MABX-9001a (B7-H3 mAb)
Linker	--	thioether (cleavable)
Payload	Topo I inhibitor	Deruxtecan (DXd, a DNA topo I inhibitor)
DAR	4	4
Trial ID	NCT05276609, Ph1	NCT04145622, Ph1/2
Dose	8 or 10mg/kg, Q3W	6.4-16.0mg/kg, Q3W
Patient number	52 (31 vs 21 in 8 or 10mg/kg)	21
Baseline	heavily pre-treated (median of two lines of prior therapy, 73.2% received prior immunotherapy)	heavily pre-treated (median of two lines of prior therapy, the majority were treated with platinum-based chemotherapy and immunotherapy)
ORR	58.1% (8mg), 57.1% (10mg)	52.4%
mDoR	4.3 months (8mg), NA (10mg)	5.9 months
mPFS	5.6 months (8mg), NA (10mg)	5.6 months
mOS	--	12.2 months
TEAE (Gr>=3)	--	36.4%
ILD	no ILD	one Gr2 treatment-related ILD or pneumonitis one Gr5 non-treatment-related COVID-19 pneumonia
Latest development	Ph2 pivotal in SCLC ongoing, Ph3 in plan (10mg/kg, Q3W)	Ph3 pivotal in SCLC ongoing (12mg/kg, Q3W)
Source	Link	Link

Source: PubMed, CMBIGM

Figure 8: Clinical trials of HS-20093 (B7-H3 ADC) conducted by Hansoh

Trial ID	Regimen	Indication	Stage	Start date	Completion date	Patient No.
NCT06052423/ ARTEMIS-007	mono	1L ES-SCLC	Ph2	2024-11-30	2027-06-30	50
NCT06007729/ ARTEMIS-006	mono	HNSCC and other solid tumors	Ph2	2023-08-23	2027-12-12	170
NCT06112704/ ARTEMIS-005	mono	Esophageal carcinoma	Ph2	2023-11-01	2026-12-31	220
NCT06001255	mono	mCRPC (2L+)	Ph2	2023-08-21	2025-12-31	120
NCT05830123/ ARTEMIS-002	mono	R/R osteosarcoma and other sarcomas	Ph2	2023-04-26	2027-12-31	170
NCT06332170/ ARTEMIS-101	+ adebrelimab (PD-L1) +/- chemo; + cetuximab +/- chemo; + enzalutamide (AR inhibitor)	Solid tumors	Ph1	2024-03-27	2028-05-30	610
NCT05276609/ ARTEMIS-001	mono	Solid tumors	Ph1	2022-03-11	2023-12-31	177

Source: PubMed, CMBIGM

Figure 9: Clinical trials of I-DXd (B7-H3 ADC)

Registration Num	Indication	Regimen	Sponsor	Trial Phase	First Posted	Completion Date	Participants Num
NCT06203210/IDeate-2	3L+ SCLC	mono vs chemo	Daiichi Sankyo	Ph3, pivotal	2024-01-12	2028-01-31	468
NCT05280470/IDeate-Lung01	ES-SCLC (with 1-3 prior lines of treatment)	mono	Daiichi Sankyo	Ph2, pivotal	2022-03-15	2025-06-20	180
NCT06330064	Multiple solid tumors	mono	Daiichi Sankyo	Ph2	2024-03-26	2028-07-01	260
NCT06362252/IDeate-Lung03	1L ES-SCLC	+atezolizumab +/-chemo	Daiichi Sankyo	Ph1/2	2024-04-12	2026-12-30	149
NCT04145622	Solid tumors	mono	Daiichi Sankyo	Ph1/2	2019-10-30	2027-03-01	250

Source: PubMed, CMBIGM

Figure 10: Global development of B7-H3 ADCs

Drug Name	Target	Action	Institute	Global Phase	CN Phase	US Phase
ifinatamab deruxtecan; DS-7300a;I-DXd;MK-2400	Top I;B7-H3	anti-B7-H3 ADC; camptothecin; Top I inhibitor	Merck & Co.; Daiichi Sankyo	PhIII	PhII	PhII
vobramitamab duocarmazine; MGC018	Top II;DNA; B7-H3	anti-B7-H3 ADC; anthracycline antibiotic; Top II inhibitor; DNA intercalator	MacroGenics	PhII/III	N/A	PhII
HS-20093	Top;B7-H3	anti-B7-H3 ADC; Top inhibitor	GSK; Hansoh	PhII	PhII	N/A
YL201	Top I;B7-H3	anti-B7-H3 ADC; camptothecin; Top I inhibitor	MediLink Therapeutics	PhII	PhII	PhI
7MW3711	Top I;B7-H3	anti-B7-H3 ADC; Top I inhibitor	Mabwell Bioscience	PhI/II	PhI/II	IND
DB-1311;BNT324	Top I;B7-H3	anti-B7-H3 ADC; Top I inhibitor	BioNTech; DualityBio	PhI/II	PhI/II	PhI/II
IBI129	B7-H3	anti-B7-H3 ADC	Innovent	PhI/II	PhI/II	N/A
IBI3001	EGFR;B7-H3	anti-B7-H3/EGFR ADC; anti-B7-H3/EGFR bispecific antibody	Innovent	PhI/II (Australia)	N/A	N/A
MHB088C	Top I;B7-H3	anti-B7-H3 ADC; Top I inhibitor	Minghui Pharma	PhI/II	PhI/II	N/A
BAT8009	Top I;B7-H3	anti-B7-H3 ADC; camptothecin; Top I inhibitor	Bio-Thera Solutions	PhI	PhI	N/A
MGC026	Top;B7-H3	anti-B7-H3 ADC; Top inhibitor	MacroGenics	PhI	N/A	PhI
mirzotamab clezutoclax;ABBV-155	Bcl-xl;B7-H3	anti-B7-H3 ADC; Bcl-xl inhibitor	AbbVie	PhI	PhI	PhI

Source: PubMed, CMBIGM. Notes: MacroGenics' MGC018 reported updated Ph2 data with 5 deaths, two of which were not drug-related, while the other three cases were still under investigation (link); Ph3 to start in 2025.

Hutchmed (13 HK, BUY, TP HK$34.31)

Fruquintinib (VEGF1/2/3 inhibitor)

Fruquintinib+sintilimab in pre-treated EMC (Poster)

Data summary:

Antiangiogenic therapy plus immunotherapy significantly improved PFS and OS as compared to chemotherapy among pts with previously treated advanced EMC per KEYNOTE-775 study. However, no combination immunotherapies are currently approved for EMC in China.

The results of fruquintinib (VEGFR inhibitor) plus sintilimab (PD-1) in treated advanced endometrial cancer (EMC) with pMMR status from an open-label, single-arm registrational Ph2 study (NCT03903705) were released (link).

As of Nov 2023, 98 previously treated advanced EMC pts with pMMR status were enrolled and received the fruquintinib + sintilimab combination treatment. All pts had previously received at least first-line platinum-containing therapy, and 22.4% pts had received bevacizumab. Detailed disease histories are summarized below.

Figure 11: Disease histories of the Ph2 study (N=98, n [%])

ECOG PS Score	0 vs 1	45 (45.9) vs 53 (54.1)
Histology	Endometrioid vs Serous vs Others	63 (64.3) vs 27 (27.6) vs 8 (8.2)
Prior surgery	Radical vs Palliative*	70 (71.4) vs 31 (31.6)
Prior pelvic radiotherapy	Y vs N	33 (33.7) vs 65 (66.3)
Prior treatment lines	1L vs ≥2L	68 (69.4) vs 30 (30.6)
Prior treatment	Platinum+taxane Bevacizumab-containing therapy	98 (100) 22 (22.4)
Platinum-free interval	<6m vs ≥6m	52 (53.1) vs 46 (46.9)

*Some pts underwent palliative surgeries after recurrence following radical surgery.

Source: Company data, CMBIGM

With the median follow-up time of 15.7m, among 87 efficacy evaluable pts, ORR was 35.6% (CR: 2/87 and PR: 29/87); DoR was not reached and the 9m-DoR rate was 80.7%.

Among 98 pts, the mPFS and OS was 9.5m and 21.3m respectively. Based on prior bevacizumab therapy (Yes vs No), ORR was 40.9% vs 30.3%, and mPFS was 13.8m vs 9.5m.

The most common ≥Grade 3 TEAEs included hypertension (18.4%), hypertriglyceridaemia (11.2%), and palmar-plantar erythrodysaesthesia syndrome (11.2%).

CMBI Comments:

Promising efficacy of fruquintinib plus sintilimab as a treatment option for pre-treated pMMR ECM in China. Keytruda+lenvatinib delivered 6.6 months of mPFS and 17.4 months of mOS for pMMR EMC patients pre-treated with at least one platinum-based chemotherapy (link), falling short compared with fruquintinib plus sintilimab's 9.5 months of mPFS and 21.3 months of mOS. The BLA of fruquintinib plus sintilimab for pre-treated EMC based on the above registrational Ph2 trial was filed in China in Apr 2024 with BTD and priority review status, and we expect the approval in end-2024/early-2025. In China, there were 82,000 new diagnosed EMC patients every year, and the standard systematic treatment for advanced EMC patients is platinum-based chemotherapy. Keytruda mono is recommended for pre-treated dMMR EMC patients and Keytruda+lenvatinib is

recommended for pre-treated pMMR EMC patients (link). However, Keytruda was not approved for EMC in China yet. We expect fruquintinib plus sintilimab to be the first antiangiogenic therapy and immunotherapy combination for EMC treatment in China. In the overseas market, I/O therapies have moved to 1L pMMR EMC treatment. Keytruda+chemo demonstrated an mPFS of 13.1 months (link) and the sBLA of Keytruda+chemo for 1L pMMR and dMMR EMC has been under FDA review since Feb 2024. Jemperli (PD-1) +chemo was approved in the US and EU in late 2023 for 1L dMMR (MSI-H) EMC.

Henlius (2696 HK,BUY, TP HK$20.33)

Serplulimab (PD-1)

Serplulimab+beva+chemo in 1L MSS CRC (Poster)

Data Summary:

Updated data of Ph2/3 study (NCT04547166) of serplulimab (PD-1) + HLX04 (bevacizumab biosimilar) + XELOX chemo (group A) vs bevacizumab + XELOX (group B) for 1L mCRC was presented (link), with an extended follow-up duration of 24.2 months.

In the Ph2 part, 114 patients were randomized 1:1 in the two groups. As of Dec 2023, continued improvements in PFS (16.8 vs 10.7 months; stratified HR 0.62, 95% CI 0.33–1.12) and DOR (19.4 vs. 12.6 months; stratified HR 0.33, 95% CI 0.13–0.85) were observed for group A vs group B.

55/112 (49.1%) of the patients in the efficacy evaluable set died; 24/55 (43.6%) patients in group A and 31/57 (54.4%) in group B. Median OS was not reached in group A, and 21.2 months in group B (stratified HR 0.75, 95% CI 0.43–1.30). Subgroup analysis showed similar trends towards an improved median OS for key subgroups including MSS (NR vs. 21.2 months; stratified HR 0.73, 95% CI 0.39–1.37), KRAS-mutant (21.9 vs. 18.2 months; unstratified HR 0.72, 95% CI 0.37–1.39), and liver metastasis (NR vs. 20.2 months; unstratified HR 0.75, 95% CI 0.40–1.41) patients. The estimated OS rate at 2 years was 53.7% vs 43.1%.

Grade ≥3 TRAEs was 69.1% vs 59.6%. Serplulimab/placebo-related deaths occurred in 2 (3.6%) patients in group A and 1 (1.8%) patient in group B.

With an extended follow-up duration, improved survival benefits demonstrated with the addition of serplulimab were maintained in the first-line treatment of mCRC, alongside a manageable safety profile. These results support serplulimab plus HLX04 and XELOX as a promising first-line treatment option for mCRC.

CMBI Comments:

Consistent benefit of serplulimab+beva+chemo in 1L CRC with longer follow-up. Previously, as of Jun 2023 with a median follow-up of 17.7 months (link), group A demonstrated 17.2 months of mPFS, vs 10.7 months in group B, HR 0.60 (CI 0.31-1.14), and the mOS was not reached in both groups, with HR of 0.77 (CI 0.41-1.45) in previous analysis. As of Dec 2023, with a longer follow-up of 24.2 months, continued improvements in PFS (16.8 vs 10.7 months; HR 0.62) were observed for group A vs B, and the mOS advantage of group A vs B was maintained (NR vs 21.2, HR 0.75).

Broad potential in the highly underserved large 1L CRC indication. Colorectal cancer (CRC) is the second most common cancer in China (link), while is highly underserved. 85% of CRC are cold tumors classified as MSS CRC (link), which currently has no I/O therapies available. Previously, I/O therapies only validated their benefits in MSI-H CRC patients. Recall that in CheckMate9X8 study, nivolumab + SoC failed to extend PFS vs SoC in 1L mCRC (mPFS 11.9 vs 11.9 months, link), and atezolizumab + SoC in AtezoTRIBE study only realized 13.1 months of mPFS vs 11.5 months with SoC in 1L MSS mCRC (HR 0.69, link). On the safety side, the addition of serplulimab was well-tolerated with a grade≥3 TRAEs rate of 69.1% vs 59.6% in the two groups. Serplulimab mono was approved in 2022 for MSI-H solid tumors, including mCRC. Serplulimab's above Ph2 study demonstrated the drug's potential to expand the label to include the highly underserved MSS CRC population. The Ph3 stage of the above Ph2/3 trial NCT04547166 recently completed first patient dose in May 2024. We expect Henlius to further initiate a Ph3 MRCT study in Asia evaluating serplulimab + HLX04 + chemo in 1L mCRC.

Akeso (9926 HK, BUY, TP HK$59.61)

Ivonescimab (AK112/SMT112, PD-1/VEGF bsAb)

AK112+chemo vs chemo in EGFR-TKI resistant nsq-NSCLC (Oral Abstract)

Data summary:

Results of a Ph3 study (HARMONi-A/NCT05184712) of AK112+chemo VS chemo in EGFR-TKI resistant EGFRm nsq-NSCLC were released (link). The primary endpoint was PFS.

Total 322 patients were randomized (161 to AK112+chemo, 161 to chemo). 86.3% versus 85.1% of patients had received the third generation EGFR-TKIs, 21.7% versus 23.0% of patients had brain metastases.

As of Mar 2023, with a median follow-up time of 7.89 months, the PFS was 7.06m in the AK112+chemo arm, vs 4.80m in the chemo arm, HR=0.46, P < 0.0001.

The ORR were 50.6% and 35.4%, respectively.

The prespecified subgroup analysis showed PFS benefit favoring patients receiving ivonescimab over placebo across almost all subgroups. For patients who progressed on the third-generation EGFR-TKIs therapy, the HR was 0.48, (95% CI 0.35-0.66). For those with brain metastases, the HR was 0.40 (0.22-0.73). For those with EGFR mutation of deletion 19, the HR was 0.48 (0.32-0.73); for individuals with T790M mutation positive, the HR was 0.22 (0.09-0.54).

Grade ≥3 TEAEs was 61.5% vs 49.1%, and the most common grade ≥3 TEAEs were chemotherapy related adverse events. Grade ≥3 immune-related adverse events occurred in 10 (6.2%) patients versus 4 (2.5%). Grade ≥3 VEGF blocking related adverse events occurred in 5 patients (3.1%) versus 4 patients (2.5%).

5.6% of patients discontinued ivonescimab due to adverse events (Summit news release, link).

CMBI comments:

Competitive profile for EGFR-TKI resistant NSCLC patients. In China, the approved combination therapy of sintilimab+bevacizumab+chemo delivered 7.2 months of mPFS (vs 4.2 months in the chemo arm) with an HR of 0.51. AK112+chemo's 0.46 HR represented a competitive profile. To note, the rate of patients with prior 3rd-generation EGFR TKI was 38% vs 86% in sintilimab's and AK112's trials, respectively. Additionally, AK112+chemo demonstrated strong HR results of 0.40 for patients with brain metastases vs HR of 0.84 in sintilimab's trial.

Wait for the results of the global trial in EGFR-TKI resistant NSCLC patients. In the Ph3 MARIPOSA-2 study, the combination of amivantamab (EGFR/MET bsAb) + chemo delivered a satisfying 6.3 months of mPFS (vs 4.2 months in chemo arm, HR=0.48) for 2L+ EGFR TKI-resistant patients post osimertinib, and the BLA is under FDA review. In comparison, in Akeso's China Ph3 study, among patients previously treated with 3rd-generation EGFR TKI, AK112+chemo delivery an HR of 0.48 vs chemo. For patients with brain metastases, AK112+chemo delivered an HR of 0.40, vs 0.52 HR of amivantamab+chemo. Recall that for OS, amivantamab+chemo vs chemo had an HR of 0.77 (95% CI 0.49-1.21), missing the significance of the secondary OS endpoint. In Akeso's China Ph3 study, AK112+chemo's OS endpoint had an HR of 0.80 (95% CI 0.59, 1.08) as of Dec 2023 (52% data maturity). Summit's global HARMONi-A trial in EGFR-TKI resistant NSCLC patients has co-primary endpoints of OS and PFS. For the grade>=3 TRAEs, the rate of AK112 + chemo was 54.0% (vs 42.9% in chemo), better than the 67% of amivantamab+chemo (vs 35% in chemo). The discontinuation rate of amivantamab+chemo in MARIPOSA-2 study was 18% vs AK112+chemo's 5.6% (link).

Eyes on readout of the H2H Ph3 trial of AK112 vs Keytruda in 1L PD-L1+ NSCLC. Akeso announced that the head-to-head Ph3 China study of AK112 mono vs Keytruda in 1L PD-L1>=1% NSCLC met the PFS superiority endpoint (link1, link2), with "HR significantly better than expected". In various subgroup patients such as TPS >=50% or 1-49%, nsq- or sq-NSCLC, with or without liver/brain metastases, significant PFS benefits were observed. We look forward to the detailed data release of the study at WCLC meeting in Sep this year. Summit is conducting a global Ph3 trial of AK112+chemo vs Keytruda+chemo in 1L sq-NSCLC. We think the detailed results of the China H2H study will give us better visibility of AK112's global potential in 1L sq-NSCLC.

Cadonilimab (AK104, PD-1/CTLA-4 bsAb)

AK104 + AK109 (VEGFR-2 mAb) + chemo in IO-resistant 2L GC (Rapid Oral Abstract)

Data summary:

PD-1 plus chemo has become standard first-line therapy for advanced G/GEJ patients. The results of a Ph1b/2 (NCT04982276) of AK104 + AK109 (VEGFR-2 mAb) + chemo in IO-resistant 2L GC were released (link). This study consisted of two parts: safety run-in (arms A, B and C, n = 6 each) and expansion (a randomized, double-blind Ph2 study). In expansion part of the study, pts were randomly assigned 1:1 to receive cadonilimab + pulocimab + paclitaxel (arm 1) or pulocimab + paclitaxel (arm 2). Doses of cadonilimab and pulocimab are both 10mg/kg, Q3W.

As of Oct 2023, a total of 77 pts were enrolled. In expansion part, 59 pts were randomly assigned to arm 1 (n = 29) and arm 2 (n = 30). With median follow-up of 7.3 months, among the 53 evaluable pts, ORR was 48.0% (12/25) for arm 1 vs 35.7% (10/28) for arm 2, mPFS was 6.8 vs 4.9 months, mDoR was not reached vs 4.0 months, 9-mo OS rate was 65.5% vs 34.0%.

Grade 3-4 TRAEs occurred in ≥10% pts were neutrophil count decreased (27.6% vs 33.3%), white blood cell count decreased (10.3% vs 26.7%) and blood pressure increased (13.8% vs 10.0%).

CMBI comments:

Promising results in 2L GC. AK104 + AK109 (VEGFR2 mAb) +chemo demonstrated promising efficacy for post-PD(L)-1 GC patients, with ORR of 48% (vs 36% of AK109+chemo), mPFS of 6.8 months (vs 4.9 months of AK109+chemo). Recall that for 2L GC patients, ramucirumab+chemo had 27% ORR and 4.1 months of mPFS in the RAINBOW-Asia trial (link), while fruquintinib+chemo had 42% ORR and 5.6 months of mPFS in the FRUTIGA trial (link). We see the potential of AK109 in combo with AK104 for the large IO-resistant GC patient population. Akeso has recently started a Ph3 trial (NCT06341335) of AK104 + AK109 (VEGFR2 mAb) + chemo in 2L GC patients post-PD(L)-1.

RemeGen (9995 HK, BUY, HK$41.72)

RC88 (mesothelin ADC)

RC88 in OC, nsq-NSCLC, CC (Poster)

Data summary:

RC88 is a first-in-class, antibody-drug conjugate (ADC) targeting mesothelin (MSLN) with the payload of Monomethyl auristatin E. Ph1/2 results of RC88 in ovarian cancer, nsq-NSCLC and cervical cancer who are MSLN-expressing and have failed after standard therapies were reported (link).

As of 19 Dec, 2023, 164 pts were enrolled. Dose escalation phase was completed, and 2.0 mg/kg and 2.5 mg/kg Q3W were expanded in Ph2.

In ovarian cancer cohort, 60 pts were enrolled and all with 2+ or 3+ MSLN expression. 42 (70%) were FIGO stage IV. 33 (55%) had prior bevacizumab, and 29 (48.3%) had prior PARPi. The number of previous lines of systemic therapy were 2-7. 54 (90%) pts were platinum-resistant. Among the 43 pts with tumor assessment, the ORR was 37.2% (16/43). In pts with prior 2-4 lines of therapies, the ORR was 45.5% (10/22) in 2.0 mg/kg and 33.3% (2/6) in 2.5mg/kg.

In nsq-NSCLC, 26 pts who progressed on previous systemic therapy were enrolled and 23 (88.4%) had received ≥ 2 lines of prior therapies. The ORR was 21.7% (5/23). Among the 15 pts without driver gene mutations, 11 (73%) had received prior chemotherapy+PD-(L)1 inhibitor. The ORR was 33.3% (5/15) with 1 CR.

In cervical cancer, 18 pts who progressed on previous systemic therapy were enrolled. In 17 pts with one post-baseline tumor assessment, 11 (64.7%) had received ≥ 2 lines of prior therapies; 12 (70.5%) had prior chemotherapy+PD-(L)1. The ORR was 35.3% (6/17).

40.2% were reported with ≥grade 3 TEAEs. 23 pts (14%) had SAE related to RC88. The most frequent TRAEs were white blood cell count decreased (46.3%), neutrophil count decreased (42.1%), anemia (34.1%), nausea (32.3%), and aspartate aminotransferase increased (31.1%). The overall safety profile was better in 2.0mg/kg than 2.5mg/kg, and therefore 2.0mg/kg was chosen as RP2D in further studies in China.

RC88 demonstrated tolerable safety and encouraging preliminary efficacy in MSLN-expressing solid tumors, warranting further investigations.

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