Trinity Delta

HUTCHMED

Update

ASCO 2023: a growing body of evidence for fruquintinib

22 June 2023

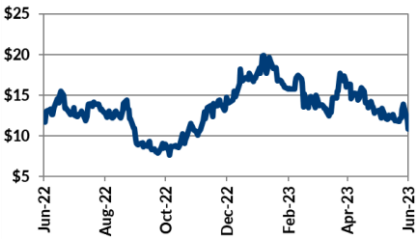
Several presentations on key HUTCHMED pipeline assets were featured at ASCO 2023. Notably for lead asset fruquintinib these included sub-group analyses from the global Phase III multi-regional FRESCO-2 study in metastatic colorectal cancer (mCRC), a key element of the recently accepted US and EU filings; real-world China data in 3,000+ patients, where it has been available as Elunate since 2018; and exploratory investigator-sponsored combination studies with PD-1 inhibitors and chemotherapy. Subject to a positive regulatory decision by the 30 November 2023 PDUFA goal date, fruquintinib will become the first HUTCHMED product to be launched outside China, partnered with Takeda ex-China. Our valuation remains US$5.5bn (US$32.01 per ADS), £4.6bn and HK$43.2bn (534p or HK$49.94 per share).

Year-end: December 31	2021	2022	2023E	2024E
Revenues (US$m)	356.1	426.4	726.1	607.2
Adj. PBT (US$m)	(337.1)	(410.4)	(78.6)	(205.3)
Net Income (US$m)	(194.6)	(360.8)	(27.2)	(149.2)
Earnings/ADS (US$)	(1.23)	(2.13)	(0.16)	(0.88)
Cash (US$m)	1,011.7	631.0	705.1	488.4
Adj. EBITDA (US$m)	(260.5)	(349.3)	(20.8)	(141.6)

Source: Trinity Delta Note: Adjusted PBT excludes exceptionals, Cash includes short-term investments, Adjusted EBITDA includes equity in earnings of equity investees.

- **Strengthening the fruquintinib evidence base** Data from both clinical trials (as monotherapy and in combination with anti-PD-1 agents) and in real-world settings further confirm fruquintinib's clean tolerability and safety profile, with FRESCO-2 sub-analyses pointing to consistent efficacy across a diverse and heavily pre-treated mCRC patient population. Encouraging data from investigator-sponsored studies, including in kidney cancer, could help inform the direction of future life-cycle management initiatives, which will be led ex-China by partner Takeda.
- **Fruquintinib filings accepted by FDA and EMA** The US FDA has granted Priority Review for fruquintinib in previously treated metastatic colorectal cancer (mCRC) and has assigned a PDUFA goal date of 30 November 2023. The European regulatory package has also been validated and accepted. Japan filing is expected in 2023. In China, we note that the NDA for fruquintinib's second indication, 2L gastric cancer in combination with chemotherapy, has also been accepted.
- **Clinical data from other assets at ASCO 2023** Data from exploratory studies of surufatinib in combination with a PD-1 inhibitor and/or chemotherapy in advanced solid tumours confirmed a tolerable safety profile and supports further development in combination, with the first China registration study, SURTORI-01 (+ toripalimab) underway in 2L advanced neuroendocrine carcinoma. First in human data were also published for FGFR-1/2/3 inhibitor HMPL-453, in patients with previously treated advanced cholangiocarcinoma containing FGFR2 fusions; these data support the ongoing enrolment of a China Phase II registration intent study cohort.
- **Valuation of $32.01/ADS or 534p/HK$49.94 per share** We value HUTCHMED at $5.5bn/£4.6bn/HK$43.2bn, equivalent to $32.01/ADS and 534p/ HK$49.94 per share. Further value should be unlocked with clinical, regulatory, and commercial execution, including through existing and new strategic partnerships. Our April 2023 Update details the underlying assumptions and valuation methodology.

Price (US ADS)	$10.82
(UK share)	181p
(HK share)	HK$19.74
Market Cap	$1.89bn
	£1.57bn
	HK$17.09bn
Enterprise Value	$1.28bn
	£1.06bn
	HK$12.31bn
Shares in issue (ADS)	173.2m
(shares)	866.2m
12 month range	$7.39-$21.28
	130.0p-337.46p
	HK$11.36-33.20
Free float	59.65%
Exchanges	NASDAQ
	AIM
	SEHK
Sector	Healthcare
Company codes	HCM
	HCM.L
	0013.HK
Corporate client	Yes



Company description

HUTCHMED is a Hong Kong headquartered biopharma focused on discovering, developing and commercialising innovative targeted therapeutics and immunotherapies to treat cancer and autoimmune diseases. It has a diverse pipeline of first-in-class/best-in-class selective oral TKIs in development for the China and global markets.

Analysts

Lala Gregorek
lgregorek@trinitydelta.org
+44 (0) 20 3637 5043

Philippa Gardner
pgardner@trinitydelta.org
+44 (0) 20 3637 5042

HUTCHMED: ASCO 2023 round-up

Data presented at the 2023 American Society of Clinical Oncology (ASCO) meeting further strengthen the clinical evidence base for fruquintinib, HUTCHMEDs highly selective and potent oral VEGFR 1/2/3 inhibitor. These included subgroup analyses from the highly positive global Phase III FRESCO-2 multi-regional clinical trial in mCRC, real world data from 3,000+ patients evaluated as part of the prospective China Phase IV study, as well as exploratory investigator-sponsored studies in several indications including as part of a combination. These data substantiate fruquintinib's clean safety and tolerability profile and its efficacy across a heavily pre-treated mCRC population, as well as the high comfort levels by Chinese oncologists in evaluating its potential outside mCRC. We note that data from these exploratory studies could also help inform future decisions on potential HUTCHMED (China) and/or Takeda (ex-China) run clinical studies to support label extensions. With fruquintinib under FDA Priority Review, a major catalyst is the approval decision anticipated by year-end (PDUFA goal date of 30 November 2023). Following approval, US launch by Takeda will mark an important milestone for HUTCHMED, as fruquintinib will be first of its internal assets to be marketed ex-China. We maintain our HUTCHMED valuation of US$5.54bn / £4.61bn / HK$43.19bn, equivalent to $32.01/ADS or 534p / HK$49.94 per share.

ASCO 2023: focus on fruquintinib

Further FRESCO-2 analyses, real world CRC data, and investigator run trials augment fruquintinib evidence base

Fruquintinib data presented at ASCO 2023 were wide-ranging, covering additional analyses from the global Phase III FRESCO-2 mCRC study, real world Phase IV data from Chinese mCRC patients, and data from investigator-sponsored studies. The data presented were consistent with already reported compelling evidence of fruquintinib's efficacy and clean safety profile in mCRC, and continue to support broad uptake in this highly refractory patient population, where there are limited current treatment options.

Full FRESCO-2 data also published in The Lancet

FRESCO-2, coupled with the China FRESCO trial, was one of the two Phase III pivotal trials underpinning the submitted regulatory dossiers, with both the US and EU filings recently accepted for review. Detailed FRESCO-2 data were first presented as a late breaker at the European Society of Medical Oncology (ESMO) 2022 (September 2022 Update), with the ASCO 2023 posters focused on new subgroup analyses and analysis of adverse events of special interest (AESI). Full FRESCO-2 data have also been published in The Lancet.

Fruquintinib OS and PFS in heavily pre-treated mCRC consistent across number of lines and type of prior therapy

Patients enrolled into FRESCO-2 were heavily pre-treated, with a median of four prior lines of therapy. The subgroup analysis explored fruquintinib's efficacy by number of prior line(s) of therapy (from ≤3 to ≥6) and by prior use of approved therapies (including anti-VEGF, anti-EGFR, TAS-102, and/or regorafenib [Stivarga]). These analyses found a clinically meaningful improvement in overall survival and progression free survival in the fruquintinib arm vs placebo (best supportive care) for all subgroups and prior therapies, which was also consistent with the intent to treat population. The safety profile and incidence of adverse events was also balanced between placebo and fruquintinib arms, and consistent across all subgroups. Median duration of exposure was longer with fruquintinib than with placebo (3.06 months vs 1.84 months), as expected given its 2.6 month

overall survival (OS) benefit. Further analysis of AESIs (hypertension, skin toxicity, thyroid dysfunction) indicated low rates of dose reduction (13.6% for fruquintinib vs 0.9% on placebo) and dose discontinuation (8.3% vs 6.1% respectively).

China real world data consistent with fruquintinib clinical studies

Real world data were also presented from a prospective Phase IV study of 3,005 Chinese patients from 96 sites who received at least one dose of fruquintinib. These data did not identify any new or significant safety signals, with results that were consistent with the fruquintinib safety profile seen in prior clinical studies.

Clean safety and tolerability profile, and MoA, support combination approaches

Fruquintinib's best-in-class profile, with high specificity and improved tolerability through more consistent target coverage, has been demonstrated in the clinical and real-world data obtained from an increasing patient sample size. This profile suggests low potential for drug-drug interactions, lending itself to combinations with other oncology therapies, and given potentially synergistic mechanisms of action, the combination with PD-1 checkpoint inhibitors is an area of interest.

Registration intent China ccRCC study in combination with PD-1 supported by Phase II data at ASCO 2023

Data from an open-label single arm Phase II trial in advanced clear-cell renal cell carcinoma (ccRCC) evaluating fruquintinib plus sintilimab (Tyvyt, Innovent Biologics) were presented at ASCO 2023. Both treatment-naïve (n=22) and previously treated (n=20) patients were enrolled, and at the 30 November 2022 data cut off, the confirmed objective response rates (ORR) were 68.2% and 60.0% respectively, and disease control rate was 95.5% and 85.0%. Median PFS had not been reached in treatment-naïve patients and was 15.9 months in previously treated patients. No new safety signals were observed. These data supported the initiation of a China Phase II/III trial in 2L ccRCC, which should complete recruitment during H223.

Other less specific VEGFR/PD-1 combinations in RCC have yielded mixed results

Other VEGFR/PD-1 combinations have been evaluated in RCC, although these have been multi-kinase inhibitors that are less specific to VEGFR. In the 2L ccRCC setting, cabozantinib (Cabometyx, Exelixis) plus atezolizumab (Tecentriq, Roche) recently showed no PFS or OS benefit to cabozantinib alone in the Phase III CONTACT-3 trial (mPFS was 10.6 months for the combination and 10.8 months for cabozantinib monotherapy) while being associated with significantly higher adverse events. We note that to date, the only VEGFR/PD-1 combination approved in RCC is lenvatinib (Lenvima, Eisai) plus pembrolizumab (Keytruda, Merck & Co) in 1L RCC which was approved in 2021 on the basis of the Phase III CLEAR study (mPFS of 23.9 months vs 9.2 months on sunitinib, Pfizer's Sutent).

Multiple investigator-sponsored studies across a broad range of settings

Other presentations at ASCO were centred on exploratory investigator-sponsored studies of fruquintinib in China and included its evaluation in earlier lines of mCRC (2L mCRC with microsatellite stable phenotype in combination with chemotherapy; >2L RAS/BRAF wild-type mCRC in combination with cetuximab), as monotherapy in other solid tumours (1L/2L unresectable metastatic soft tissue sarcoma; ≥2L biliary tract cancer), and in combination with chemotherapy (neoadjuvant therapy for gastric cancer).

ASCO 2023: focus on surufatinib combinations

Surufatinib also under evaluation in several investigator run trials

Similarly, there is a plethora of investigator-sponsored studies investigating surufatinib in various advanced solid tumours beyond its approved monotherapy indication of neuroendocrine tumours (both pancreatic and non-pancreatic NETs) in China where it is marketed as Sulanda. As surufatinib has a unique dual angio-immuno kinase profile, through its inhibition of VEGFR-1/2/3, FGFR-1, and CSF-

1R, there is strong rationale for its use as a multi-functional monotherapy; and given its clean safety and toxicity profile, potential use in combination with PD-1 checkpoint inhibitors or chemotherapy.

ASCO 2023 presentations cover monotherapy and various combinations…

Data at ASCO 2023 were from exploratory studies of surufatinib monotherapy (in 2L osteosarcoma/soft tissue sarcoma) and in combination with other agents, including the PD-1 inhibitors toripalimab (advanced or refectory thyroid cancer and advanced endometrial cancer cohorts from the open-label Phase II study: these cohorts had a 33.3% ORR, 93.3% Disease Control Rate [DCR] and median duration of response [mDoR] of 8.34 months and mPFS of 10.91 months for thyroid cancer, and a 28.6% ORR, 82.1% DCR, and mDoR of 5.65 months and mPFS of 5.42 months in EMC) and camrelizumab (plus chemotherapy in advanced metastatic pancreatic cancer and in 2L CRC: in the latter, of 12 evaluable patients, three achieved a Partial Response and nine achieved Stable Disease with a 100% DCR and a 7.2 month mPFS), and docetaxel (2L NSCLC). Promisingly, all studies confirmed a tolerable safety profile (including in combination with anti-PD-1 agents and chemotherapies), with encouraging anti-tumour activity.

… with HUTCHMED focussing on PD-1 combination in China

The China clinical development focus for surufatinib is largely on combinations with PD-1 checkpoint inhibitors, with the first registration study, SURTORI-01, underway in combination with toripalimab (Tuoyi, Shanghai Junshi) in 2L advanced neuroendocrine carcinoma (NEC).

Upcoming catalysts

All eyes on ex-China regulatory decisions on fruquintinib…with FDA up first

Our previous reports have explored HUTCHMED's development and commercial strategy (September 2022 Outlook), reviewed the pipeline (September 2022 Pipeline Review), and highlighted several of the key upcoming catalysts (April 2023 Update). The key near-term catalyst is the outcome of the FDA review of fruquintinib in Q423 which, if positive, would be the first HUTCHMED discovered and developed drug to be launched (by partner Takeda) outside China. This should be followed by a European EMA decision in 2024 following confirmation that the regulatory package has been accepted. The Japan PDMA submission is expected later this year. We believe that fruquintinib represents a material near-term opportunity ex-China.

Expected 2023 clinical progress includes key data from haem-oncology assets

Further clinical progress is anticipated during 2023, including the completion of recruitment of various registration-intent studies, including the savolitinib SAVANNAH non-small cell lung cancer trial. HUTCHMED's second wave of pipeline assets, including haem-oncology assets sovleplenib and amdizalisib, are under evaluation in potentially registrational studies which should read out in H223 which, if positive, could be followed by first China NDA filings in relapsed/refractory ITP (immune thrombocytopenia) for sovleplenib and 3L follicular lyphoma for amdizalisib.

Exhibit 1: Summary of financials

Year-end: December 31 $'000s	2019	2020	2021	2022	2023E	2024E
INCOME STATEMENT						
Revenues	**204,890**	**227,976**	**356,128**	**426,409**	**726,078**	**607,183**
Cost of goods sold	(160,152)	(188,519)	(258,234)	(311,103)	(298,021)	(344,703)
Gross Profit	**44,738**	**39,457**	**97,894**	**115,306**	**428,058**	**262,480**
R&D expenses	(138,190)	(174,776)	(299,086)	(386,893)	(378,483)	(329,598)
Selling expenses	(13,724)	(11,334)	(37,827)	(43,933)	(54,464)	(63,767)
G&A expenses	(39,210)	(50,015)	(89,298)	(92,173)	(82,956)	(85,444)
Underlying operating profit	**(146,386)**	**(196,668)**	**(328,317)**	**(407,693)**	**(87,845)**	**(216,329)**
Other revenue/expenses	0	0	0	0	0	0
EBITDA	**(141,444)**	**(190,607)**	**(321,127)**	**(399,029)**	**(75,590)**	**(201,368)**
Operating Profit	**(146,386)**	**(196,668)**	**(328,317)**	**(407,693)**	**(87,845)**	**(216,329)**
Interest income/expense	3,914	2,449	1,484	8,947	12,235	14,054
Other income/expense	1,367	4,485	(10,217)	(11,676)	(3,000)	(3,000)
Profit Before Taxes	**(141,105)**	**(189,734)**	**(215,740)**	**(410,422)**	**(78,609)**	**(205,275)**
Adj. PBT	**(141,105)**	**(189,734)**	**(337,050)**	**(410,422)**	**(78,609)**	**(205,275)**
Current tax income	(3,274)	(4,829)	(11,918)	283	(2,945)	(3,209)
Equity in earnings of equity investees, net of tax	40,700	79,046	60,617	49,753	54,826	59,760
Net Income	**(103,679)**	**(115,517)**	**(167,041)**	**(360,386)**	**(26,729)**	**(148,724)**
Minority interests	(2,345)	(10,213)	(27,607)	(449)	(471)	(495)
Net income attributable to equityholders	**(106,024)**	**(125,730)**	**(194,648)**	**(360,835)**	**(27,200)**	**(149,219)**
EPS ($)	**(0.16)**	**(0.18)**	**(0.25)**	**(0.43)**	**(0.03)**	**(0.18)**
Earnings per ADS ($)	**(0.80)**	**(0.90)**	**(1.23)**	**(2.13)**	**(0.16)**	**(0.88)**
DPS ($)	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**
Average no. of shares (m)	665.7	697.9	792.7	847.1	845.2	845.2
Gross margin	*22%*	*17%*	*27%*	*27%*	*59%*	*43%*
EBITDA margin	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*
Underlying operating margin	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*
BALANCE SHEET						
Current assets	**317,022**	**530,740**	**1,212,076**	**839,888**	**935,850**	**767,891**
Cash and cash equivalents	121,157	235,630	377,542	313,278	387,408	170,692
Short-term investments	96,011	199,546	634,158	317,718	317,718	317,718
Accounts receivable	43,254	47,870	83,580	97,988	119,355	149,716
Inventories	16,208	19,766	35,755	56,690	57,155	75,551
Other current assets	40,392	27,928	81,041	54,214	54,214	54,214
Non-current assets	**148,100**	**193,378**	**160,585**	**189,557**	**224,965**	**225,004**
Property, plant & equipment	20,855	24,170	41,275	75,947	111,440	111,479
Intangible assets	3,387	3,534	3,543	3,222	3,137	3,137
Investments in equity investees	98,944	139,505	76,479	73,777	73,777	73,777
Other non-current assets	24,914	26,169	39,288	36,611	36,611	36,611
Current liabilities	**(113,101)**	**(158,397)**	**(311,658)**	**(353,903)**	**(410,557)**	**(393,998)**
Short-term debt	0	0	(26,905)	0	(360)	(839)
Accounts payable	(23,961)	(31,612)	(41,177)	(71,115)	(68,993)	(76,249)
Other current liabilities	(89,140)	(126,785)	(243,576)	(282,788)	(341,204)	(316,910)
Non-current liabilities	**(39,118)**	**(46,772)**	**(21,489)**	**(38,672)**	**(114,738)**	**(85,722)**
Long-term debt	(26,818)	(26,861)	0	(18,104)	(57,744)	(56,905)
Other non-current liabilities	(12,300)	(19,911)	(21,489)	(20,568)	(56,994)	(28,817)
Equity	**312,903**	**518,949**	**1,039,514**	**636,870**	**635,521**	**513,175**
CASH FLOW STATEMENTS						
Operating cash flow	**(80,912)**	**(62,066)**	**(204,223)**	**(268,599)**	**85,502**	**(198,886)**
Net income	(103,679)	(115,517)	(167,041)	(360,386)	(26,729)	(148,724)
Non-cash adj & other operating cash flow	6,662	24,178	(69,640)	33,083	37,635	41,340
Change in working capital	16,105	29,273	32,458	58,704	74,596	(91,501)
Investing cash flow	**119,028**	**(125,441)**	**(306,320)**	**296,588**	**(47,663)**	**(15,000)**
CAPEX	(8,565)	(7,949)	(16,401)	(36,664)	(47,663)	(15,000)
Change in short term investments	118,904	(103,535)	(434,612)	316,440	0	0
Investment in an equity investee	8,689	(13,957)	144,693	16,812	0	0
Financing cash flow	**(1,493)**	**296,434**	**650,028**	**(82,763)**	**36,292**	**(2,831)**
Proceeds from equity	(95)	297,896	660,501	(47,993)	0	0
Increase in loans	(116)	0	0	(9,170)	40,000	(360)
Other financing cash flow	(1,282)	(1,462)	(10,473)	(25,600)	(3,708)	(2,471)
Net increase in cash	**36,623**	**108,927**	**139,485**	**(54,774)**	**74,130**	**(216,717)**
Exchange rate effects	(1,502)	5,546	2,427	(9,490)	0	0
Cash at start of year	86,036	121,157	235,630	377,542	313,278	387,408
Cash at end of year	**121,157**	**235,630**	**377,542**	**313,278**	**387,408**	**170,692**
Net cash at end of year	**190,350**	**408,315**	**984,795**	**612,892**	**647,022**	**430,666**

Source: Company, Trinity Delta Note: Adjusted PBT excludes exceptionals, Cash includes short-term investments.

Philippa Gardner pgardner@trinitydelta.org
+44 (0) 20 3637 5042

Lala Gregorek lgregorek@trinitydelta.org
+44 (0) 20 3637 5043

Franc Gregori fgregori@trinitydelta.org
+44 (0) 20 3637 5041

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More information is available on our website: www.trinitydelta.org